CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202258Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Secondary Review – Clinical Pharmacology Team Leader

Date	April 20, 2011
From	Sarah Robertson, Pharm.D.
Subject	Secondary Clinical Pharmacology Review
NDA #	202-258
Applicant	Merck
Date of Submission	11/15/10
PDUFA Goal Date	5/13/11
Proprietary Name / Established (USAN) names	VICTRELIS / Boceprevir
Dosage forms / Strength	200 mg capsules
Proposed Indication(s)	Treatment of chronic hepatitis C (CHC) genotype 1 infection in combination with pegylated interferon alpha and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy with standard-of-care.
Recommendation:	Approval, with PMRs and revisions to the proposed label

I concur with the final conclusions and recommendations of the primary clinical pharmacology reviewer, Dr. Ruben Ayala, as outlined in his review of the NDA (4-15-11). Several *in vitro* study reports were submitted late in the review cycle, and thus, were not included in Dr. Ayala's review. Those studies are summarized individually in this review.

In brief, the *in vitro* experiments outlined in this review demonstrated that boceprevir is not a substrate of hepatic transporters OATP1B1 and OATP1B3. Boceprevir inhibited OATP1B1-mediated uptake of [^{3}H]-pitavastatin *in vitro* in a concentration-dependent fashion, with an IC_{50} value of 18 (± 2.4) μM. However, boceprevir is unlikely to be a clinically significant inhibitor of OATP1B1 *in vivo*, based on the unbound C_{max}/IC_{50} ratio (0.04). Boceprevir inhibited the ATP-dependent BCRP-mediated uptake of [^{3}H]-methotrexate in a concentration-dependent fashion (IC_{50} 81 ± 28 μM). However, inhibition of BCRP is not likely to be clinically relevant based on the unbound C_{max}/IC_{50} ratio (<0.01). Boceprevir did not inhibit the ATP-dependent uptake of an MRP2 substrate at concentrations up to 100 μM.

Boceprevir did not inhibit UGT2B7 in human liver microsomes (IC_{50} >100 μM), as measured by glucuronidation of AZT. There was a trend of increasing UGT1A1 inhibition with increasing SCH503034 concentrations. However, SCH503034 had an IC_{50} >100 μM, indicating that boceprevir is unlikely to be a clinically relevant inhibitor of UGT1A1 *in vivo*.

With the submission of these *in vitro* study reports, no further *in vitro* experiments are considered necessary for describing the metabolic and transporter specificity or modulating potential of boceprevir. As outlined in Dr. Ayala's review, the NDA for boceprevir is approvable from a clinical pharmacology perspective. However, the NDA contained insufficient information regarding potential drug interactions with boceprevir. The following PMRs are recommended:

- Conduct an *in vivo* drug-drug interaction trial between boceprevir and an oral contraceptive containing a progesterone component other than drospirenone.
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and methadone.
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and a sensitive substrate of p-glycoprotein (e.g. digoxin).
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and a selective serotonin reuptake inhibitor (SSRI) (e.g. escitalopram).

PK-008 – Uptake of SCH503034 into MDCKII Cells Stably Expressing Human OATP1B1, OATP1B3, or Rat Oatp1b2

Study initiated March 28, 2011 at Merck Research Laboratories, Rahway, NJ.

Objective:

To determine the uptake of SCH503034 into MDCKII cells expressing human OATP1B1, OATP1B3, and rat Oatp1b2 transporters.

Materials:

MDCKII cells transfected with cDNA encoding for human OATP1B1, OATP1B3, and rat Oatp1b2 transporters were treated with 10 mM sodium butyrate to increase OATP expression prior to study start. The cells were dislodged with trypsin EDTA and re-suspended in Hank's Balanced Salt Solution (HBSS) containing 10 mM Hepes. Cells were then transferred to 96-well plates at a density of 0.6×10^6 cells per well.

On the day of the study, the uptake reaction was initiated by adding [^{14}C]-SCH503034 (1 μM) to the 96-well plates along with the respective positive control substrates: [^{3}H]-$E_2$17βG (1 μM) for OATP1B1 and Oatp1b2, and [^{3}H]-CCK8 (1 μM) for OATP1B3. Cells were incubated with the probes for an unspecified time at 37ºC. The reactions were stopped by adding ice-cold PBS. At the end of the reaction, cells were centrifuged for 1 minute at 3000 rpm at 4ºC, and washed three times with PBS. The cell pellets were suspended in scintillation fluid containing 50% acetonitrile. Cell pellets were processed for radioactivity counting using a LS6500 Multipurpose Scintillation Counter.

The study was conducted in triplicate.

Results:

The uptake of [^{14}C]-SCH503034 by MDCKII-OATP1B1, MDCKII-OATP1B3, and MDCKII-rat Oatp1B2 cell lines was not significantly greater than uptake in MDCKII control cell lines (Figures 5, 6, and 7). Results suggest that SCH503034 is not a substrate of these three transporters.

In contrast, uptake of control substrates [^{3}H]-$E_2$17βG and [^{3}H]-CCK8 (1 μM) was significantly greater in MDCKII-OATP1B1, MDCKII-OATP1B3, and MDCKII-rat Oatp1B2 cell lines relative to MDCKII control cell lines (figures not shown). Results indicated the presence of functional transporters in the cell lines used in this study.

Figure 1 Time course of 1µM of [^{14}C]-SCH503034 uptake into stably transfected MDCKII-OATP1B1 cells

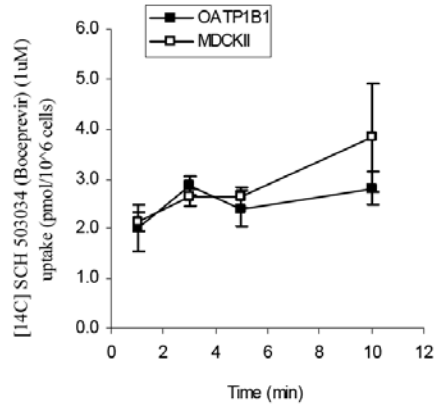


Figure 2 Time course of 1 µM [^{14}C]-SCH503034 into stably transfected MDCKII-OATP1B3 cells

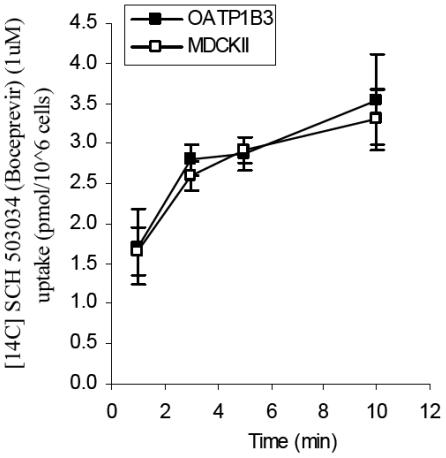
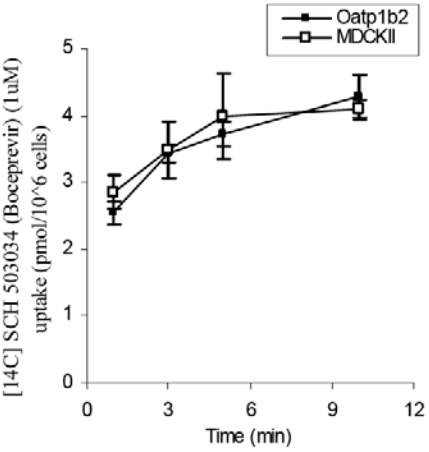


Figure 3 Time course of 1 µM [^{14}C]-SCH503034 into stably transfected Rat Oatp-1b2-MDCKII cells



Conclusion:

SCH503034 is not a substrate of human OATP1B1, OATP1B3, and rat Oatp1b2. The study was adequately controlled using control substrates and non-transfected cell lines. The experiment appears to have been adequately designed to meet the study objectives.

PK-005 – SCH503034 inhibition of OATP1B1

Study initiated March 15, 2011 at Merck Research Laboratories, Rahway, NJ

Objective:

To determine the inhibitory effects of SCH503034 on OATP1B1-mediated transport of [^{3}H]-pitavastatin in MDCKII cells.

Methods:

To increase OATP1B1 expression, MDCKII cells transfected with OATP1B1 were treated with 10 mM sodium butyrate 24 hours prior to the experiment. The cells were dislodged with trypsin EDTA and re-suspended in Hank's Balanced Salt Solution (HBSS) containing 10 mM Hepes (pH 7.4). Cells were then transferred to 96-well plates at a density of 0.4 X 10^6 cells per well.

On the day of the experiment, cells were incubated with [^{3}H]-pitavastatin at 0.1 μM along with SCH503034 at concentrations ranging from 0 to 50 μM. Cells were incubated at 37ºC for an unspecified time, at which point the reaction was stopped by adding ice-cold phosphate buffered saline (PBS). At the end of the reaction, cells were centrifuged for 1 minute at 3000 rpm at 4ºC, and washed three times with PBS. The cell pellets were suspended in scintillation fluid containing 50% acetonitrile. Cell pellets were processed for radioactivity counting using a LS6500 Multipurpose Scintillation Counter.

The experiment was conducted in triplicate.

Data analysis:

OATP1B1-mediated uptake of [^{3}H]-pitavastatin was calculated by subtracting the rate of pitavastatin uptake in MDCKII-OATP1B1-expressing cells from that observed in MDCKII cells.

The percent control was calculated using the equation:

% Control = (Ri/Ro) X 100, where Ri= rate of uptake in the presence of inhibitor, and Ro= rate of uptake in the absence of inhibitor.

Results:

Uptake of [^{3}H]-pitavastatin into MDCKII-OATP1B1 cells decreased in the presence of SCH503034 in a concentration-dependent fashion (figure 1). The IC_{50} value of SCH503034 was 18 ± 2.4 μM (figure 2).

Figure 4 Mean inhibitory effects of SCH503034 on the uptake of 0.1 µM [^{3}H]-pitavastatin in OATP1B1 stably transfected MDCKII cells.

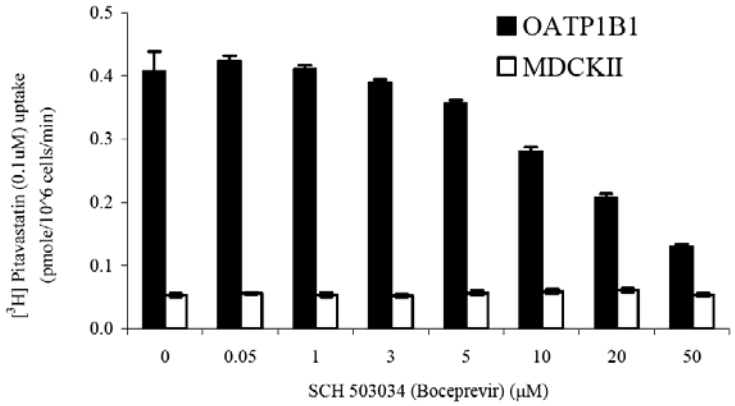
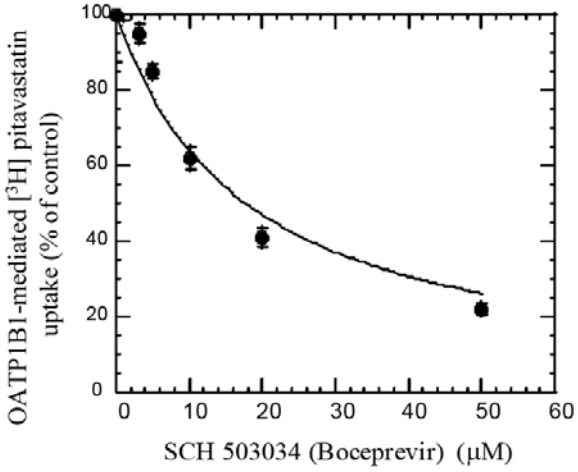


Figure 5 SCH503034 inhibition of OATP1B1-mediated 0.1 µM [^{3}H] pitavastatin uptake (% control).



Discussion/Conclusion:

SCH503034 inhibited the OATP1B1-mediated uptake of [^{3}H]-pitavastatin in a concentration dependent fashion with an IC_{50} value of 18 ± 2.4 µM. However, an *in vivo* drug interaction between SCH503034 and a substrate of OATP1B1 is unlikely based on the I_u/IC_{50} ratio (below). Of note, the study did not utilize a positive control OATP1B1 inhibitor.

Mean C_{max} = 1680 ng/mL or 3.23 µM
Plasma protein binding = 77%
Unbound [I] = 0.74 µM
IC_{50} = 18 µM
[I]/IC_{50} ratio = 0.04

PK-013 – SCH503034 inhibition of BCRP and MRP2

Study initiated March 31, 2011 at Merck Research Laboratories, Rahway, NJ

Objectives:

To determine the inhibitory effects of SCH503034 on BCRP and MRP2 as measured by the uptake of [^{3}H]-methotrexate and [^{14}C]-EA-SG by each transporter, respectively.

Methods:

BCRP

The inhibitory effect of SCH503034 on BCRP was evaluated by monitoring the uptake of [^{3}H]-methotrexate into membrane vesicles (Sf9) containing BCRP. All uptake reactions were conducted in 8-strip tubes. Each tube contained the following ingredients:

- 0, 0.1, 1, 10, 25, 100, or 250 µM of SCH503034.
- 20 µL of [^{3}H] methotrexate (final concentration of 10 µM).
- 10 µL of membrane vesicles (Sf9) containing BCRP (2 mg protein/mL) at 20 µg per tube.
- 1 µM (final concentration) of the positive control Ko143 dissolved in transport buffer consisting of 0.25 M sucrose, 10 mM Tris-HCl buffer (pH 7.4), and 10 mM $MgCl_2$.

MRP2

The inhibitory effect of SCH503034 on MRP2 was evaluated by monitoring the uptake of [^{14}C]-EA-SG into membrane vesicles (Sf9) containing MRP2. All uptake reactions were conducted in 8-strip tubes. Each tube contained the following ingredients:

- 0, 0.1, 1, 10, 25, 100, or 250 µM of SCH503034.
- 20 µL of [^{14}C] EA-SG (final concentration of 1 µM).
- 10 µL of membrane vesicles (Sf9) containing MRP2 (2 mg protein/mL) at 20 µg per tube.
- BSP (positive control) at a final concentration of 100 µM dissolved in transport buffer consisting of 0.25 M sucrose, 10 mM Tris-HCl buffer (pH 7.4), and 10 mM $MgCl_2$.

BRCP and MRP2

Prior to study start, all tubes were pre-incubated for 3 minutes at 37ºC. The reactions were initiated by adding 20 µL of ATP-regenerating reagent or 20 µL of transport buffer per tube. The ATP-regenerating reagent consisted of final concentrations of 5 mM ATP, 10 mM creatine phosphate, and 100 µg/mL creatine phosphokinase. All tubes were incubated for 5 minutes at 37ºC.

After 5 minutes of incubation, the reactions were stopped by adding 200 µL of ice-cold stop buffer consisting of 0.25 M sucrose, 0.1 M NaCl, and 10 mM Tris-HCl buffer (pH 7.4). Test tube contents were transferred to pre-wetted 96-well glass filter (1.0 µm) plates, and subsequently filtered by vacuum. Filters were collected and washed five times with 200 µL ice-cold stop buffer. The filters were dried at room temperature and then placed into scintillation vials along with 25 µL of liquid scintillation. Radioactivity was determined by liquid scintillation counting.

The experiment was performed in triplicate.

Data analysis:

BCRP- and MRP2-mediated uptake of [^{3}H]-methotrexate and [^{14}C]-EA-SG, respectively, was calculated by subtracting the uptake of both drugs in the absence of ATP from the uptake of both drugs in the presence of ATP.

Percent control was calculated using this equation:

% Control = (Ri/Ro) X 100, where Ri= ATP-dependent uptake in the presence of inhibitor, and Ro= uptake of probe in the absence of inhibitor.

Results:

BCRP

SCH503034 inhibited the ATP-dependent uptake of [^{3}H]-methotrexate by BCRP in a concentration-dependent fashion (figures 8 and 9). The IC_{50} value was 81 µM for boceprevir. In contrast, K0143 inhibited the uptake of [^{3}H]-methotrexate by BCRP with an IC_{50} = 1 µM (figure not shown).

Figure 6 Mean inhibitory effect of SCH503034 on uptake of 10 µM [^{3}H]-methotrexate into membrane vesicles containing human BCRP in the presence and absence of ATP

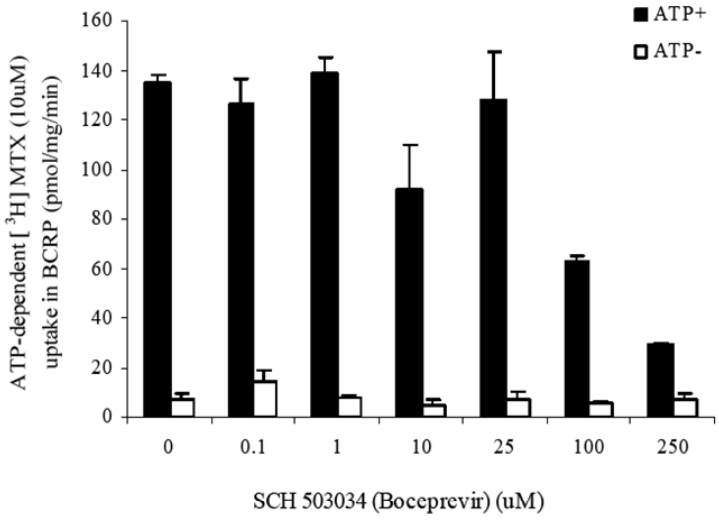
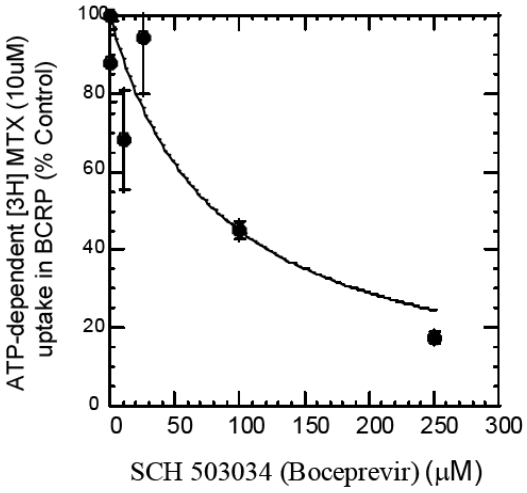


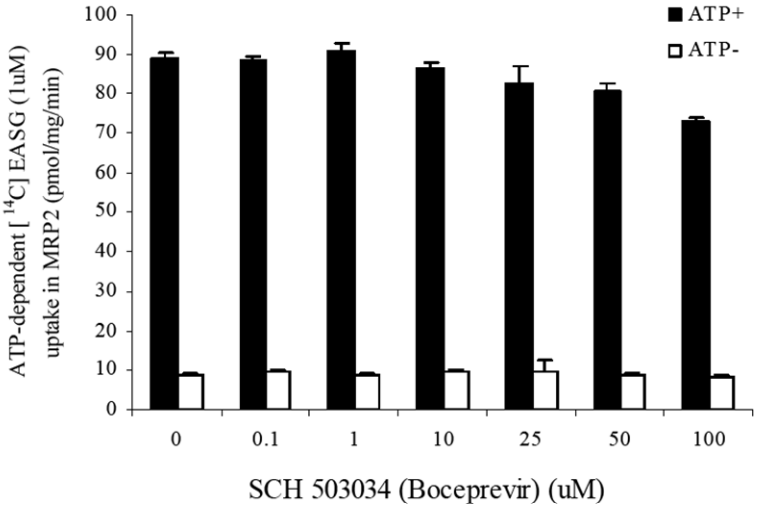
Figure 7 SCH503034 inhibition of ATP-dependent 10 µM [^{3}H]-methotrexate uptake (% control)



MRP2

SCH503034 did not significantly inhibit the ATP-dependent uptake of [^{14}C] EA-SG by MRP2 (figure 10). In contrast, BSP inhibited the MRP2-mediated uptake of [^{14}C]-EA-SG at 100 µM (figure not shown).

Figure 10 Mean inhibitory effect of SCH503034 on uptake of 1 µM [^{14}C] EA-SG into membrane vesicles containing human MRP2 in the presence and absence of ATP



Conclusion:

SCH503034 inhibited the ATP-dependent uptake of [^{3}H]-methotrexate mediated by BCRP in a concentration-dependent fashion (IC_{50} = 81 ± 28 µM). However, the inhibition of BCRP is not likely to be clinically relevant at mean C_{max} levels (~3.23 µM) delivered by boceprevir 800 mg TID.

Mean C_{max} = 1680 ng/mL or 3.23 µM
IC_{50} = 81 µM
Plasma protein binding = 77%
Unbound [I] = 0.74 µM
[I]/IC_{50} ratio = 0.009

SCH503034 did not inhibit the ATP-dependent uptake of [^{14}C]-EA-SG mediated by MRP2 at concentrations up to 100 µM (IC_{50} >100 µM).

The study was appropriately controlled using positive control inhibitors which demonstrated inhibition of BCRP and MRP2. The experiment appears to have been adequately designed to address study objectives.

PK-006 – Effect of SCH503034 on UGT2B7-Mediated 3'-Azido-3"-Deoxythimidine (AZT) Glucuronidation in Human Liver Microsomes

Study initiated March 24, 2011 at Merck Research Laboratories, Rahway, NJ.

Objective:

To determine the inhibitory effects of SCH503034 on UGT2B7-mediated AZT glucuronidation.

Methods:

Pooled human liver microsomes (0.5 mg/mL) were incubated in a 0.2 mL reaction mixture for 20 minutes at 37ºC. The reaction mixture consisted of 750 µM of AZT, 0.78 to 100 µM of SCH503034, 8 mM of $MgCl_2$, 5 mM of UDPGA, 25 µg/mL of alamethicin, and 50 mM of potassium phosphate buffer (pH 7.4). Diclofenac was used as a positive control inhibitor at concentrations ranging from 0.78 to 100 µM.

After 20 minutes of incubation, the reactions were terminated by (b) (4) as the internal standard. Samples were centrifuged for 30 minutes at 4ºC. The supernatant was collected and analyzed using LCMS.

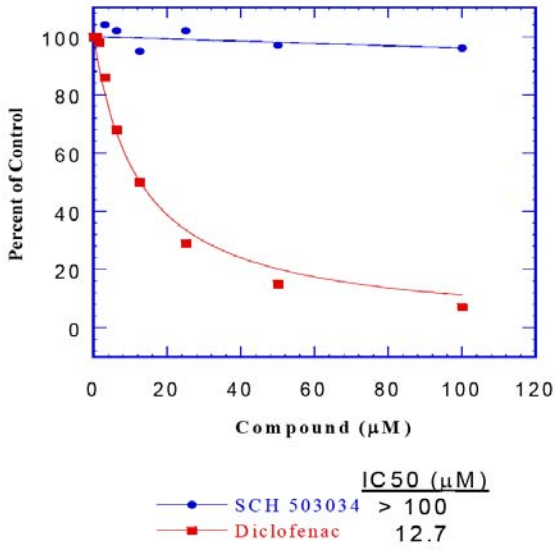
Data analysis:

Non-linear regression was used to calculate the IC_{50} values of boceprevir relative to diclofenac inhibitory values.

Results:

SCH503034 did not inhibit UGT2B7 in human liver microsomes at concentrations of up to 100 µM. In contrast, the positive control, diclofenac, had an IC_{50} value of 12.7 µM.

Figure 8 Effect of SCH503034 on UGT2B7-mediated AZT glucuronidation in human liver microsomes[1]



[1]IC_{50} values were determined in duplicate (n=2) for both SCH503034 and diclofenac.

Discussion/Conclusion:

SCH503034 did not inhibit UGT2B7 in human liver microsomes (IC_{50} >100 µM) as measured by UGT2B7-mediated glucuronidation of AZT. The study appears to have been adequately designed to address study objectives.

PK-007 – Effect of SCH503034 on UGT1A1-Mediated Estradiol 3-Glucuronidation in Human Liver Microsomes

Study initiated March 24, 2011 at Merck Research Laboratories, Rahway, NJ.

Objective:

To determine the inhibitory effects of SCH503034 on UGT1A1-mediated estradiol 3-glucuronidation.

Methods:

Pooled human liver microsomes (0.5 mg/mL) were incubated at 37ºC for 20 minutes with a chemical mixture containing 20 µM of estradiol and 0.78 to 100 µM of SCH503034. The mixture also contained 81 mM Hepes buffer (pH 7.0), 9 mM $MgCl_2$, 5 mM UDPGA, and 25 µg/mL alamethicin. Nicardipine was the positive control inhibitor at concentrations ranging from 0.78 to 100 µM.

After 20 minutes of incubation, the reactions were terminated by (b) (4) as the internal standard. Samples were centrifuged for 30 minutes at 4ºC. Supernatant was collected and analyzed by LCMS.

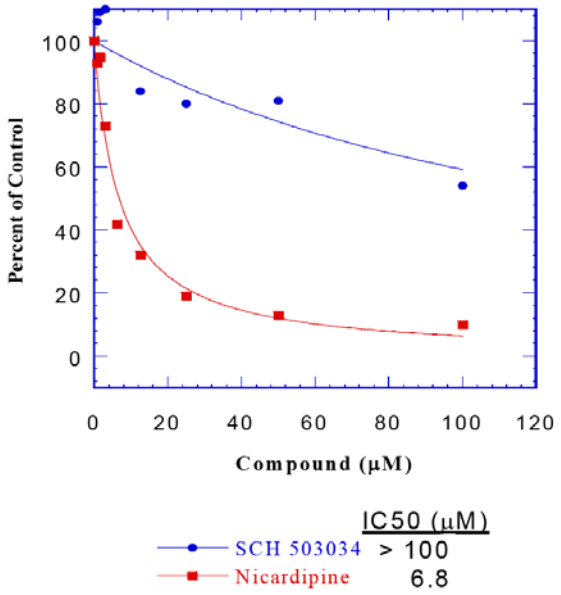
Data analysis:

Non-linear regression was used to calculate the IC_{50} values of boceprevir relative to nicardipine inhibitory values.

Results:

There was a trend of increasing UGT1A1 inhibition with increasing SCH503034 concentrations. However, SCH503034 had an IC_{50} >100 µM. In contrast, the positive control, nicardipine, had an IC_{50} value of 6.8 µM.

Figure 9 Effect of SCH503034 on UGT1A1-mediated Estradiol 3-glucuronidation in Human Liver Microsomes[1]



[1]IC_{50} values were determined in duplicate (n=2) for both SCH503034 and nicardipine.

Discussion/Conclusion:

SCH503034 did not inhibit estradiol 3-glucuronidation in human liver microsomes (IC_{50} >100 µM). There was a trend of increasing UGT1A1 inhibition with increasing SCH503034 concentrations. Boceprevir-mediated inhibition of UGT1A1 is not likely to be clinically relevant at mean C_{max} levels (~3.23 µM) delivered by the therapeutic dose of 800 mg TID.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH M ROBERTSON
04/21/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	202258
Submission date:	November 15, 2010
Brand Name:	VICTRELIS
Generic Name:	Boceprevir
Reviewer:	Ruben Ayala, Pharm.D.
Team Leader:	Sarah Robertson, Pharm.D.
Pharmacometrics Reviewer:	Jeffry Florian, Ph.D.
Pharmacometrics Team Leader:	Pravin Jadhav, Ph.D.
Genomics Reviewer:	Shashi Amur, Ph.D.
Genomics Team Leader:	Michael Pacanowski, Pharm.D., M.P.H.
OCP Division:	Division of Clinical Pharmacology 4
OND Division:	DAVP
Sponsor:	Merck/Schering-Plough
Relevant IND(s):	IND69027
Submission Type; Code:	Original NDA (NME)
Formulation; Strength(s):	(b) (4) SLS-containing; 200 mg capsules
Dosing Regimen:	800 mg TID
Indication:	Treatment of HCV infection in treatment naive or treatment experienced adult patients who have received pegylated interferon with ribavirin.

Table of Contents

1. Executive Summary

Boceprevir is a new molecular entity, direct-acting antiviral for the treatment of chronic hepatitis C infection. Boceprevir directly inhibits the NS3/4A protease that facilitates viral propagation in HCV infected cells. Boceprevir consists of two diastereomers, SCH534128 and SCH534129. In plasma, the diastereomer ratio (2:1) favors the active diastereomer SCH534128.

Boceprevir is intended for use in combination with pegylated interferon and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in adult patients with compensated liver disease who are previously untreated or who failed previous treatment with standard of care.

The proposed dosing regimen for boceprevir is 800 mg orally three times daily (TID) with food delivered as 200 mg capsules. The proposed treatment duration depends on response to therapy (i.e. response-guided therapy, RGT) as follows.

1. Treat all patients with pegylated interferon and ribavirin for the first 4 weeks.

2. Add boceprevir 800 mg TID to pegylated interferon alpha and ribavirin at week 5.

3. **In patients who are previously untreated**:

- If virus levels (HCV-RNA) are undetectable at weeks 8 and 24, then discontinue the three-drug regimen at week 28.

- If HCV-RNA is detectable at week 8 but undetectable at week 24, then continue the three-drug regimen until (b) (4), and then administer pegylated interferon and ribavirin alone until week 48.

- If HCV-RNA is detectable at week 24 (regardless of week 8 response), then discontinue the three-drug regimen.

(b) (4)

1.1 Recommendations

The NDA for boceprevir is acceptable from a Clinical Pharmacology perspective. Post-Marketing Requirements (PMRs) and Post-Marketing Commitments (PMCs) are recommended, as outlined below in Section 1.2.

Longer treatment duration of boceprevir (e.g. 32 or 44 weeks) is recommended for treatment-naïve patients who are late responders to treatment (i.e. HCV RNA detectable at Week 8 and undetectable at Week 24). Either of the following two options outlined below would be acceptable.

Early Responder (Weeks 8 and 24 undetectable)	PR4/BOC-PR24
Late Responder (Week 8 detectable, Week 24 undetectable)	Option 1: PR4/BOC-PR44
	Option 2: • PR4/BOC-PR32/PR12 in patients with >1.0 log10 decrease in viral load at week 4 • PR4/BOC-PR44 in patients with ≤1.0 log10 decrease in viral load at week 4

PR=pegylated interferon alpha + Ribavirin. BOC=Boceprevir

1.2 Phase 4 Commitments

The NDA for boceprevir has insufficient information regarding potential drug-drug interactions with commonly coadministered medications and sensitive substrates of p-glycoprotein. The Applicant should conduct the following clinical trials as PMRs:

- Conduct an *in vivo* drug-drug interaction trial between boceprevir and an oral contraceptive containing a progesterone component other than drospirenone.
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and methadone.
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and a sensitive substrate of p-glycoprotein (e.g. digoxin).
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and a commonly used selective serotonin reuptake inhibitor (SSRI) (e.g.

escitalopram).

The following clinical trial should be conducted as a PMC:

- Conduct a trial evaluating shorter treatment durations of pegylated interferon and ribavirin with and without boceprevir in patients with the IL28B rs12979860 C/C genotype.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The NDA contains several clinical trials. This document only reviews ten Phase 1 trials in healthy subjects, two Phase 1 trials in HCV-infected patients, one Phase 2 trial in HCV-infected patients, and two Phase 3 trials in HCV-infected patients. These trials are summarized in detail in Section 2.2.1.

Key results from the NDA review:

- Boceprevir should be administered with food.
- Dose adjustment of boceprevir is not necessary in patients with various degrees of renal or hepatic impairment.
- Dose adjustment of boceprevir is not necessary based on age, gender, race, or body weight.
- Boceprevir may be coadministered with inhibitors of aldoketo reductase (AKR) enzymes.
- Boceprevir is a strong inhibitor of CYP3A4; thus, sensitive substrates of CYP3A4 with a narrow therapeutic index should not be coadministered. Other CYP3A4 substrates should be used with caution.
- Boceprevir is a substrate of CYP3A4; thus, moderate and strong inducers of CYP3A4 should not be co-administered due to the potential for loss of efficacy. Boceprevir may be coadministered with strong inhibitors of CYP3A4 and P-gp, but patients should be monitored closely because increased levels of boceprevir may increase the risk of anemia.
- Boceprevir is a substrate for P-gp and may be an inhibitor of P-gp, based on *in vitro* study results. A drug interaction trial was not conducted to assess the effect of boceprevir on a sensitive P-gp substrate (e.g. digoxin).

- Oral hormonal contraceptives may not be as effective during concomitant boceprevir therapy due to decreases in ethinyl estradiol concentrations. The Applicant plans to conduct an additional oral contraceptive drug interaction trial to better characterize the effect of boceprevir on the PK of oral contraceptives.

- An FDA exposure-response analysis of limited Phase 3 data revealed (1) lack of evidence of an exposure-response relationship between boceprevir C_{trough} or AUC with antiviral activity, and (2) an upward trend of increasing anemia with increasing boceprevir exposures (AUC).

- Treatment-naive patients who respond late to therapy may benefit from an additional 8 weeks of triple therapy with boceprevir and SOC. We recommend that treatment-naïve patients with detectable HCV-RNA at treatment week 8 but undetectable at week 24 receive 32 weeks of boceprevir plus SOC followed by 12 weeks of SOC alone, instead of 28 weeks of triple therapy, followed by 20 weeks of SOC alone.

- HCV-infected patients with IL28B genotype C/T and T/T had higher SVR rates in the boceprevir arms relative to SOC alone. In contrast, patients with C/C genotype had similar SVR rates in the boceprevir arms relative to the control arm.

The following section highlights clinical pharmacology, biopharmaceutics, and the *in vitro* characteristics of boceprevir.

Drug Product

The Applicant plans to commercialize boceprevir as 200 mg capsules in a (b) (4) formulation containing (b) (4) sodium lauryl sulfate.

Boceprevir is a racemic mixture of two diastereomers: SCH534128 and SCH534129. Boceprevir capsules contain a diastereomer ratio of 1:1. In plasma, the diastereomer ratio converts to a stable ratio of 2:1, in favor of SCH534128. SCH534128 is the active stereoisomer of boceprevir.

Pharmacokinetic Properties

Single dose:

The mean maximum systemic concentrations occur within ~3 hours postdose. The mean terminal $t_{1/2}$ of boceprevir is ~2-4 hours following single doses.

With single dosing, boceprevir exposures increase proportionally to dose from 200 mg to 400 mg, but increase less than dose proportionally with doses greater

than 400 mg.

The mean apparent clearance (CL/F) and mean apparent volume of distribution (Vd/F) values following a single 800 mg dose of boceprevir were 208 ± 86.4 L/hr and 1170 ± 819 L, respectively.

Multiple doses (TID regimen):

Boceprevir has a mean half-life of ~2-4 hours that allows steady-state concentrations to be reached within 1 day of TID dosing. The steady-state accumulation ratio ranges from 0.8 to 1.5 with multiple doses relative to single dose, at the therapeutic dose (800 mg TID).

With multiple dosing, boceprevir steady-state exposures increase linearly and proportionally to dose from 200 mg to 800 mg TID, but increase less than dose proportionally with doses greater than 800 mg TID.

Boceprevir exposures are similar between healthy subjects and HCV-infected patients.

ADME Properties

Absorption:

The absolute bioavailability of boceprevir is unknown.

Food increases the mean exposures (AUC) of boceprevir by ~50% relative to fasting conditions, regardless of fat content or dosing relative to mealtime (immediately before, during, or immediately after a meal). A high fat meal resulted in ~10-15% higher AUC relative to a low-fat meal. The effect of pH on the absorption of boceprevir is unknown.

Distribution:

The mean steady-state apparent volume of distribution of boceprevir is large (~772 liters or 11 L/kg), suggesting that boceprevir distributes extensively into tissues. In animals, liver concentrations of boceprevir were 11 to 49-fold higher relative to concentrations in blood. In humans, liver concentrations of boceprevir are unknown.

In humans, the blood-to-plasma partitioning ratio of boceprevir is 0.33, suggesting that boceprevir remains largely in plasma, and partitions minimally into cellular components of blood.

The plasma protein binding of boceprevir is low (~77%). The protein(s) responsible for binding boceprevir were not identified.

Metabolism:

Boceprevir is primarily metabolized by the enzyme aldo-keto reductase. *In vitro*, AKR1C2 and AKR1C3 are responsible for producing M28, M30, and M31, the most abundant circulating metabolites in plasma. In the mass balance trial, the sum of M28, M30, and M31 accounted for ~18% of the radioactive dose of ^{14}C-boceprevir recovered in feces.

Boceprevir is also partially metabolized by CYP3A. *In vitro* experiments with human liver microsomes and SUPERSOMES™ revealed that CYP3A4 metabolizes boceprevir to form minor metabolites including M11, M14, M15, M16, M21, and M23. In the mass balance trial, the sum of these metabolites accounted for ~8% of the radioactive dose of ^{14}C-boceprevir recovered in feces.

Elimination:

The mean apparent total clearance (CL/F) of boceprevir is 157 L/hr (2.2 L/hr/kg). Clearance values were similar throughout clinical trials with boceprevir.

Boceprevir undergoes hepatic and renal elimination, but most elimination occurs hepatically. In the mass balance trial, investigators recovered ~88.2% of the total dose of radioactivity in feces (78.9%) and urine (9.3%). Approximately 10% and 32% of the total radioactivity recovered in feces and urine, respectively, was unchanged boceprevir. The radioactivity in feces and urine was quantifiable up to 168 hours and 12 hours post dose, respectively.

Exposure-Response Relationship

There is lack of evidence for an exposure-response (E-R) relationship between boceprevir C_{trough} or AUC and efficacy in the Phase 3 trials. Exposure-response analyses were conducted with sparse PK data obtained from HCV-infected patients in the two pivotal Phase 3 trials, including treatment-naïve (n=67, P05216) and previous treatment failures (n=49, P05101). A shallow and non-significant relationship was identified between boceprevir exposure and sustained virologic response (SVR). Results indicate that higher boceprevir exposures than those delivered with boceprevir 800 mg TID may not result in greater efficacy. However, the current dataset is limited by small patient numbers and does not allow us to explore the possibility that subsets of the treatment population may have an exposure-response efficacy relationship.

Exposure-Safety Relationship

A non-significant upward trend of increasing incidence of anemia (Hgb <10 g/dL) was observed with increasing boceprevir exposures (AUC_T) in the Phase 3 PK population. Similar relationships were identified between C_{trough} or C_{max} and incidence of anemia. Model predicted incidence of anemia for the median boceprevir AUCτ (4.3 µg·hr/mL) was 48%. The predicted incidence of anemia at the lowest and highest exposure quartiles (3.2 and 6.3 µg·hr/mL) was 43% and 58%, respectively. Higher doses of boceprevir are anticipated to further increase the incidence of anemia without an expected benefit in efficacy, as described above.

A significant relationship between incidence of anemia and ribavirin exposures (AUC_T) was observed in the Phase 3 PK population (n=167; p<0.0001). This result is not unexpected, given ribavirin's known affect on anemia, with an observed incidence rate of ~30% of HCV-infected patients receiving SOC. Indeed, a similar E-R relationship is observed if the analysis is limited to patients receiving only SOC (n=51; p-value=0.001) in the Phase 3 trials.

Ribavirin demonstrated a steeper E-R safety relationship with incidence of anemia compared to boceprevir. Therefore, an appropriate strategy to manage anemia is to dose reduce ribavirin with no accompanying dose reduction for boceprevir. The ribavirin label already recommends modifying the dose of ribavirin if severe adverse reactions, such as anemia, develop during combination therapy with ribavirin and peg-interferon.

Boceprevir does not prolong the QT or QTc interval at 800 mg TID or 1200 mg TID, according to results from a multiple dose thorough QTc trial conducted in healthy subjects.

Intrinsic factors

Dose adjustment of boceprevir is not necessary in subjects with any degree of hepatic impairment. In the hepatic impairment trial, subjects with moderate and severe liver impairment experienced 32% and 45% higher exposures (AUC) of boceprevir relative to healthy subjects. Higher boceprevir exposures may increase the risk of anemia, but the risk may be mitigated by decreasing the dose of ribavirin. Of note, boceprevir is proposed for use only in patients with compensated liver disease (i.e. patients with normal hepatic function or Child-Pugh category A impairment). Pegylated interferon and ribavirin are contraindicated in patients with Child-Pugh categories B and C.

Dose adjustment of boceprevir is not necessary in patients with any degree of

renal impairment. In the renal impairment trial, subjects with end stage renal disease on hemodialysis experienced 10% lower boceprevir exposures relative to healthy subjects. The clearance of boceprevir was similar between healthy subjects and ESRD subjects before and after hemodialysis (range 178 – 193 L/hr). According to the E-R analysis, a 10% decrease in boceprevir exposures is clinically irrelevant and does not pose an efficacy concern. Moreover, hemodialysis did not affect the PK of boceprevir in ESRD subjects. Therefore, a compensatory dose of boceprevir is not recommended following hemodialysis.

Boceprevir exhibits high intersubject pharmacokinetic variability. The following table summarizes the ranges of intersubject variability observed across clinical trials.

Table 1 Range of intersubject PK variability of boceprevir across clinical trials in healthy subjects and HCV-infected patients.

	C_{max}	AUC	C_{min}
Range of Intersubject Variability (%CV)	11 – 87	9 – 53	26 - 104

The source of intersubject PK variability is unknown. A population PK analysis revealed that age, gender, race, body weight, and health status (healthy vs. HCV-infected) do not affect the pharmacokinetics of boceprevir.

The intrasubject PK variability is currently unknown.

Pharmacogenomics

A genetic variant near the gene encoding interferon-lambda-3 (IFN λ-3, IL28B rs12979860 C>T) is a strong predictor of response to pegylated interferon and ribavirin. In a retrospective subset analysis of the Phase 3 trials, treatment-naïve subjects with the CT and TT genotypes had lower SVR rates than subjects with the CC genotype following treatment with pegylated interferon and ribavirin with or without boceprevir (see Section 2.3.2.7). The prevalence of the rs12979860 genotypes in treatment-naïve subjects was as follows: white CC 32%, CT 53%, TT 15%; black CC 17%, CT 43%, TT 40%.

Extrinsic factors

Boceprevir is a substrate and strong inhibitor of CYP3A4, a substrate and potential inhibitor of p-glycoprotein, and a substrate of AKR.

The Applicant conducted four, multiple-part clinical trials to evaluate potential drug interactions between boceprevir and various probe substrates and inhibitors of CYP3A4 and AKR. The goal of one of these trials was to identify an agent that would increase the steady-state C_{min} of boceprevir to a clinically relevant extent by inhibiting its metabolism via CYP3A4 and/or AKR. Investigators tested diflunisal, ritonavir, and clarithromycin as potential PK "boosters." None of these inhibitors increased boceprevir C_{min} by a clinically relevant extent. A second trial investigated the effects of ketoconazole and ibuprofen on the PK of boceprevir. The Applicant also evaluated the effect of boceprevir on the PK of CYP3A4 substrates. The following drug-drug interactions with boceprevir were notable.

- Ketoconazole increased the AUC of boceprevir by 2.3-fold relative to boceprevir alone. According to the exposure-response analysis, a doubling of boceprevir exposure is anticipated to increase the incidence of anemia by an additional 20% from the expected incidence (49%) at the median boceprevir AUC following 800 mg TID.

  In the Phase 3 trials, investigators allowed the use of azole antifungals and some subjects received ketoconazole with boceprevir. However, there is insufficient information to make a definitive conclusion regarding the safety of the combination, as only 8 subjects received ketoconazole and boceprevir concomitantly. Further, drug levels of boceprevir were unavailable during the period of co-administration.

- Efavirenz decreased the C_{min} of boceprevir by 44% relative to boceprevir alone. A decrease in boceprevir trough levels may affect the clinical efficacy of boceprevir. Data obtained during boceprevir monotherapy in Phase 2 trials indicate HCV-RNA decreases correlate best with boceprevir trough concentrations, as opposed to C_{max} or AUC. In addition, exposure-response data from two small Phase 2 trials evaluating different boceprevir regimens in combination with PegIFN in previous non-responders identified a moderate positive correlation between boceprevir trough levels and reduction of viral load. The model estimated an EC_{50} value of 98 ng/mL, which is similar to the in vitro IC_{50} for boceprevir (~100 ng/mL). The model predicted similar viral decreases with boceprevir trough levels between 100 and 200 ng/mL. However, the model had limitations that complicate the interpretation of the exposure-response relationship between boceprevir trough levels and antiviral activity.

  In Phase 3 clinical trials, HCV-infected patients had a median boceprevir C_{min} of 200 ng/mL following multiple boceprevir doses of 800 mg TID. In the presence of efavirenz, the median C_{min} of boceprevir may decrease by 44% from 200 to 112 ng/mL. At this lower trough level, boceprevir retains antiviral activity as predicted by the exposure-response analysis. However, patients with initial C_{min} values below 200 ng/mL may fall below the threshold of activity (~100 ng/mL) predicted by the exposure-response analysis. Given

that efavirenz is a moderate inducer of CYP3A4, we expect even lower boceprevir trough levels in the presence of stronger inducers of CYP3A4 such as rifampin, phenytoin, and others.

- Boceprevir increased the AUC and C_{max} of midazolam by 5- and 2.5-fold, respectively, relative to midazolam alone. This result confirms that boceprevir is a strong inhibitor of CYP3A4. Therefore, boceprevir should not be co-administered with sensitive substrates of CYP3A4 with a narrow therapeutic index. Other CYP3A substrates should be used with caution.

- Boceprevir increased the C_{max}, AUC, and C_{min} of drospirenone (DRSP) by ~2-fold relative to oral contraceptive alone. Drospirenone is a synthetic progestin found in the oral contraceptive Yaz®. Based on a consultation obtained from the Division of Reproductive and Urologic products (DRUP), there are no safety data indicating that a two-fold increase in the C_{max} and AUC of DRSP increases the risk of adverse events; however, DRUP is concerned about this magnitude of increase. The principal potential safety concerns for drospirenone are thromboembolism and hyperkalemia. DRUP recommended drospirenone be listed as a contraindication in the boceprevir label.

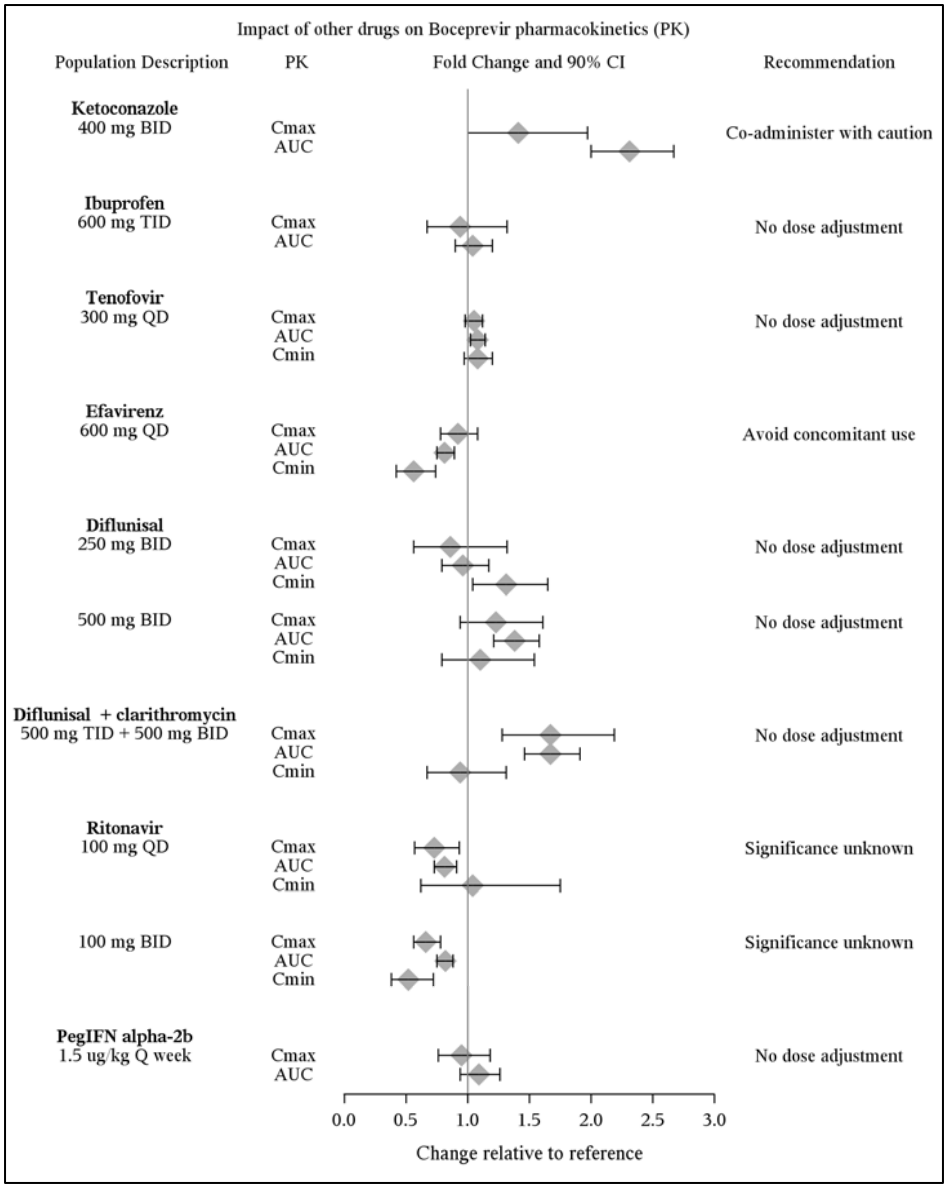
  DRUP indicated that the drug-drug interaction trial with drospirenone had several limitations, which may affect the reliability of the trial results; in addition, results for drospirenone cannot be directly extrapolated to other progesterone components. The Applicant has agreed to conduct an additional DDI trial with an oral contraceptive containing a different progesterone, such as norethindrone.

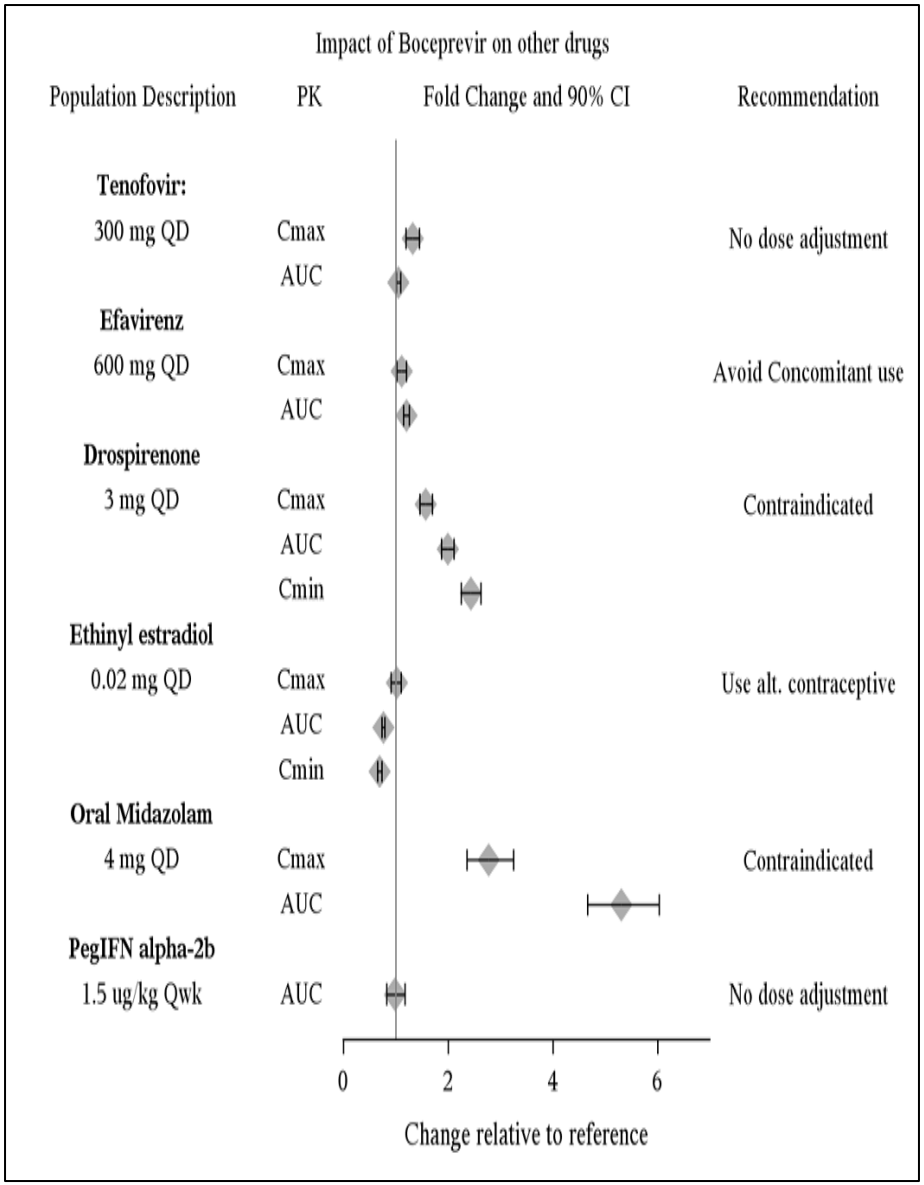
  Boceprevir decreased the AUC of ethinyl estradiol by 24% relative to oral contraceptive alone. Generally, contraceptive efficacy is attributed to progestin more than the estrogen component. However, loss of efficacy due to lower ethinyl estradiol exposure cannot be ruled out, since efficacy may be affected by the relative proportions of the estrogen and progestin components and their effects on cervical mucus, ovulation, and endometrial lining changes. It is unknown whether recommending a minimum ethinyl estradiol dose may ameliorate the concern and DRUP does not favor making such a recommendation. At this time, it is appropriate to state that the effect of decreased EE exposure on oral contraceptive efficacy is unknown, and that efficacy may be impaired.

  I agree with DRUP's recommendation that women of child-bearing potential should not rely on the use of hormonal contraceptives as an effective method of contraception during boceprevir therapy. Instead, patients should use two alternative effective methods of contraception, including barrier methods and IUDs.

The figures below display the results from all the drug-drug interaction trials conducted with boceprevir. The plots display geometric mean ratios with their respective 90% confidence intervals.

Figure 1 Summary of results from the drug-drug interaction trials between boceprevir and various probes. Figure A displays the effect of probes on the PK of boceprevir. Figure B displays the effect of boceprevir on the PK of the probes. The symbol (♦) represents the geometric mean ratio with its respective 90% confidence interval.





List of Abbreviations

ADME	Absorption, distribution, metabolism, excretion
AKR	Aldo-keto reductase
ARB	Angiotensin II receptor blocker
AUC	Area under the concentration-time curve
AUCinf or AUCI	Area under the concentration-time curve from zero to infinity
AUCt	Area under the concentration-time curve from zero to the last timepoint
AUCtf	Area under the concentration-time curve from time zero to the time of the final quantifiable sample
BA	Bioavailability
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics classification system
BID	Bis in die; twice a day
BMI	Body mass index
BOC	Boceprevir
CL/F	Apparent clearance
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
COC	Combined oral contraceptive
COX-2	Cyclooxigenase-2
CP	Child-Pugh Classification System
C_{trough}	Trough concentration
CsA	Cyclosporin A
CV	Coefficient of variability
CYP	Cytochrome P450
DAVP	Division of Antiviral Products
DDI	Drug-drug interaction
Δ	Change
DRSP	Drospirenone
DRUP	Division of Reproductive and Urologic products
EC_{50}	Half maximal effective concentration
EE	Ethinyl estradiol
E_{max}	Maximum effect
EOT	End of treatment
E-R	Exposure-response
ESRD	End stage renal disease
FDA	Food and Drug Administration
g or gm	Grams
g/dL	Grams per deciliter
H or Hr	Hour

HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation
IFN	Interferon
IL28B	Interleukin 28B
IND	Investigational new drug
kg	Kilogram
Ki	Inhibition constant
$K_{O/W}$	Octanol-water partition coefficient
IC_{50}	Half maximal inhibitory concentration
IU	International units
L	Liter
LC-MS/MS	Liquid chromatography/mass spectrometry/mass
LS means	Least-squares means
µCi	Microcurie
mL	Microliter
ms	millisecond
ng/mL	Nanograms per mililiter
N	Number
NS3/4A	Non structural polypeptide 3/4A
NDA	New drug application
NME	New molecular entity
NNT	Number needed to treat
OAT1, OAT3, OATP1B1, OATP1B3	Organic anion transporter
OCP	Office of Clinical Pharmacology
OND	Office of New Drugs
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEG	Pegylated interferon
PegIFN	Pegylated interferon
P-gp	P-glycoprotein
PK	Pharmacokinetics
PM	Pharmacometrics
PPK	Population pharmacokinetics
PR	Pegylated interferon and ribavirin; same as SOC
PR48	Pegylated interferon + ribavirin for 48 weeks; SOC
PR Lead-in	Initial 4-week treatment with Pegylated interferon + ribavirin
Q	Every
QWk	Every week
QD	Quaque die; every day
QID	Quater in die; four times a day

QT	Measure between Q wave and T wave in the heart's electrical cycle
QTc	Corrected QT
QTcI	Corrected QT interval
RBV	Ribavirin
RGT	Response-guided therapy
RNA	Ribonucleic acid
RPM	Rotations per minute
SC	Subcutaneous
SCH503034	Boceprevir (Sum of both diastereomers)
SCH534128	Active diastereomer
SCH534129	Inactive diastereomer
SCH629144	Boceprevir metabolite (sum of 4 diastereomers SCH783004, SCH783005, SCH783006, and SCH733007)
SLS	Sodium lauryl sulfate
SOC	Standard of care; same as PR
SSRI	Selective serotonin reuptake inhibitor
SVR	Sustained virologic response
SVR24	Sustained virologic response 24 weeks after end of treatment
$t_{1/2}$	Half-life
TID	Ter in die; three times a day
T_{max}	Time after administration of a drug when the maximum plasma concentration is reached
TW	Treatment week
µg	Microgram
UGT	Uridine 5'-diphospho-glucuronosyltransferase
µM	Micromolar
USP	United States Pharmacopeia
Vd/F	Apparent volume of distribution
vs.	Versus
w/w	Weight in weight

2. Question Based Review

2.1. General Attributes of the Drug

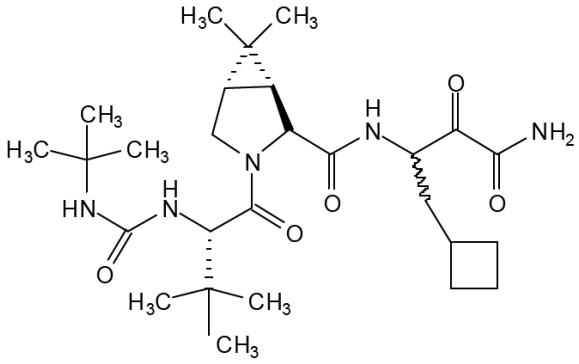
2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Boceprevir is a serine protease inhibitor of the NS3/4A HCV protease. The drug product is a white to off-white amorphous powder with the following characteristics.

Molecular formula: $C_{27}H_{45}N_5O_5$

Molecular weight: 519.7 g/mol

Chemical Structure:



Chemical name: (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(S)-carboxamide.

***In vitro* solubility:** Boceprevir is soluble in most organic solvents (>100 mL), but slightly soluble in aqueous media (~1.5 mg/mL in water).

Partition coefficient: Boceprevir has a log intrinsic equilibrium partition coefficient in octanol/water ($K_{O/W}$) of 3.0.

Biopharmaceutical Classification: BCS 4, low solubility and low permeability.

Drug product: The Applicant plans to commercialize boceprevir in 200 mg capsules formulated with (b) (4) sodium lauryl sulfate (SLS). The proposed commercial formulation is the same as the formulation used in the Phase 3 pivotal trials, (b) (4) The following table lists the capsule ingredients.

Table 2 Composition of boceprevir's capsule

Component	Quality Standard	Clinical Image	Commercial Image
Boceprevir	In-House	200.0 mg	200.0 mg
Microcrystalline Cellulose	NF	(b) (4)	
Lactose Monohydrate (b) (4)	NF		
Pregelatinized Starch	NF		
Croscarmellose Sodium	NF		
Sodium Lauryl Sulfate	NF		
Magnesium Stearate	NF		
(b) (4) Hard Gelatin Capsule[a]	-	(b) (4)	Red cap/Yellow body
Capsule Fill Weight		400.0 mg	400.0 mg

NF = National Formulary

[a] (b) (4)

Boceprevir capsules contain a 1:1 mixture of two steroisomers, SCH534128 and SCH534129. In plasma, the stereoisomer ratio changes to 2:1, favoring the active stereoisomer SCH534128 over inactive SCH534129. The plasma ratio remained constant in a variety of conditions during clinical trials with boceprevir. For instance, SCH534128 exposures were 2-times higher than SCH534129 exposures during boceprevir single dose, multiple doses, under fed and fasting conditions, in the presence of concomitant drugs, or in subjects with hepatic or renal dysfunction.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Boceprevir prevents viral replication by directly inhibiting the non-structural protein 3 (NS3/4A) protease of the hepatitis C virus. NS3/4A protease cleaves long polypeptides that serve as precursor components for creating functional viral proteins. Boceprevir binds to and forms a stable, covalent, reversible bond with the active site of NS3/4A. This binding prevents the cleavage and subsequent formation of functional proteins that are essential for hepatitis C viral propagation.

The Applicant is seeking an indication for boceprevir for the treatment of chronic hepatitis C genotype 1 infection, in combination with peg-interferon alpha and ribavirin, in adult patients (≥18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dose of boceprevir is 800 mg by mouth three times daily (7 to 9 hours apart) with food. Clinicians must co-administer boceprevir with pegylated interferon-alpha and ribavirin. Boceprevir monotherapy is not recommended, because it may lead to development of viral resistance.

The Applicant proposes a 4-week "lead-in" period with SOC alone before adding boceprevir to therapy.

The following section outlines the proposed treatment recommendation for boceprevir.

Treatment naive subjects:

1. Initiate therapy with pegylated interferon-alpha and ribavirin for 4 weeks (Treatment weeks 1 to 4).

2. Add boceprevir 800 mg orally three times daily (7 to 9 hours apart with food) to pegylated interferon alpha and ribavirin regimen at treatment week (TW) 5. Depending on the patient's HCV-RNA levels at (b) (4) use the following response-guided therapy (RGT) guidelines to determine duration of treatment.

Table 3 Duration of therapy using response-guided therapy in previously untreated HCV subjects.

(b) (4)

Treatment experienced subjects (previously failed SOC):

1. Initiate therapy with pegylated interferon-alpha and ribavirin for 4 weeks (Treatment weeks 1 to 4).

2. Add boceprevir 800 mg orally three times daily (7 to 9 hours apart with food) to pegylated interferon alpha and ribavirin regimen at treatment week (TW) 5. Depending on the patient's HCV-RNA levels at (b) (4) use the

following RGT guidelines to determine duration of treatment.

Table 4 Duration of therapy using response-guided therapy in subjects who have failed previous therapy

2.2. General Clinical Pharmacology

2.2.1 What are the design features and results of the clinical pharmacology and clinical studies used to support dosing or claims?

The following table lists important *in vitro* studies and clinical trials evaluated in this Clinical Pharmacology review.

Table 5 Summary of *in vitro* experiments and clinical trials evaluated for this review.

Study ID	Brief Description
***In vitro* Experiments**	
03208	Substrate of CYP450 and AKR
03368	Plasma protein binding
04061	Interconversion of boceprevir stereoisomers in plasma
DM27292	Metabolism in the presence of COX-2 inhibitors
DM27352	Inhibitor of CYP450 enzymes
DM27368	Inducer of CYP450 enzymes
DM27866	Substrate or inhibitor of p-glycoprotein
Clinical trials	
P03533	Phase 1, formulation effect, food effect (low fat vs. fasted), and DDI trial with ibuprofen and ketoconazole in healthy subjects.
P03588	Phase 1, ADME in fed healthy subjects.
P03747	Phase 1, hepatic impairment trial in fasted healthy subjects and subject with various degrees of hepatic impairment.
P04133	Phase 1, single dose, dose proportionality, food effect and timing (low fat vs. fasted) trial in healthy subjects.
P04486	Phase 1, multiple dose and DDI trial with diflunisal in fed healthy subjects
P04488	Phase 1, rising multiple and single-dose, ethnicity sensitivity (Caucasian vs.

	Japanese) and food effect (high fat vs. low fat vs. fasted) trial in healthy subjects.
P04624	Phase 1, DDI with diflunisal, ritonavir, and clarithromycin trial in healthy subjects.
P05579	Phase 1, renal impairment trial in fed hemodialysis-dependent ESRD subjects and matched subjects with normal renal function.
P05880	Phase 1, DDI trial with midazolam, efavirenz, tenofovir, and drospirenone and ethinyl estradiol in fed healthy subjects.
P04489	Phase 1, thorough QTc trial in fed healthy subjects.
P03516	Phase 1 Rising Multiple Dose Assessment of the Safety, Tolerance, Pharmacokinetics, and Pharmacodynamics of Boceprevir in HCV-Infected Genotype-1 Patients Who Were Non-Responders to Interferon-α.
P04487/P04531	Phase 1, multiple dose trial evaluating TID and QID boceprevir regimens in combination with peg-interferon in previous nonresponders.
P03659	Phase 2, randomized, placebo-controlled, dose-ranging, multi-site, double-blind, trial of boceprevir with SOC or placebo in adult, HCV-1 peginterferon alfa/ribavirin non-responder patients.
P05216 (HCV SPRINT-2)	Phase 3, double blind, placebo-controlled trial to examine the efficacy and safety of boceprevir 800 mg TID dosed with SOC backbone in 1097 treatment-naive patients.
P05101 (RESPOND-2)	Phase 3, double-blind, placebo-controlled trial to examine the efficacy and safety of boceprevir in 403 patients with previous treatment failure

The following section describes the crucial results from the Phase 1, Phase 2, and Phase 3 clinical trials conducted in HCV-infected patients that support the proposed dose and indication for boceprevir. The Phase 1 trial tested boceprevir in the original formulation. The Phase 2 and 3 trials tested the proposed commercial formulation of boceprevir.

A Phase 1 Rising Multiple Dose Assessment Trial (P03516) of the Safety, Tolerance, Pharmacokinetics, and Pharmacodynamics of Boceprevir in HCV-Infected Genotype-1 Patients Who Were Non-Responders to Interferon-α (n=92).

Trial P03516 had a randomized, third-party blind, placebo-controlled, multiple-dose design in HCV-infected genotype 1 patients who were previous interferon-nonresponders. The trial aimed to determine the correlation between the dosing regimen of boceprevir monotherapy and the change in viral load (HCV-RNA) for various boceprevir doses and schedules. Six groups (n=7 to 12 per group) received 14 days of boceprevir monotherapy. As shown in Table 6 below, the highest reduction in viral load was observed with the group administered boceprevir at 400 mg TID with food.

Table 6 Mean (SD) maximal viral load drop from baseline and mean (CV%) $AUC_{(tau)}$ following boceprevir administration for 14 days.

	BOC 100 mg BID (n=12)	BOC 200 mg BID (n=12)	BOC 400 mg BID (n=11)	BOC 400 mg TID (n=10)	BOC 400 mg BID With Food (n=12)	BOC 400 mg TID With Food (n=7)
Maximal Viral Load Drop (Δlog10)	-0.43 (0.40)	-0.96 (0.54)	-0.98 (0.57)	-1.69 (0.62)	-1.44 (0.79)	-1.91 (0.76)
AUC(τ) (ng·hr/mL)	700 (33)	1390 (28)	1640 (32)	1990 (16)	3620 (35)	2990 (33)

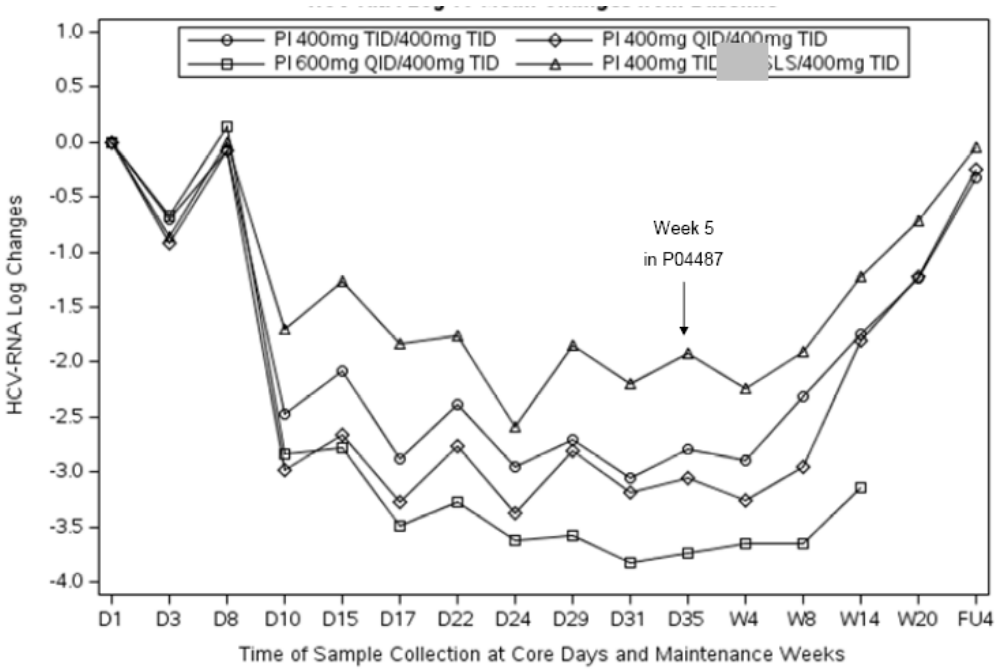
A Phase 1b Multiple Dose Trial (P04487/P04531) Evaluating TID and QID Boceprevir Regimens in Combination with Peg-Interferon in Previous Nonresponders

Trial 04487 (core protocol) evaluated the safety, PK and antiviral activity of the new and original formulations of boceprevir administered 400 mg TID, 400 mg QID and 600 mg QID, in combination with once weekly peg-interferon for 5 weeks in previous nonresponder patients. The objective of 04531 (maintenance protocol) evaluated longer-term (≥20 weeks) safety and activity of the 400 mg TID dose in combination with peg-interferon. Thirty subjects completed the initial 5-week core protocol and 29 went on to enter the maintenance protocol.

The PK-related objectives in these two studies were to examine the relationship between dosing frequency of boceprevir in combination with peg-interferon and change in HCV-RNA. All subjects received peginterferon alfa-2b starting on Day 1, and started on treatment with boceprevir (400 mg TID – original formulation, 400 mg QID – original formulation, 600 mg QID – original formulation, 400 mg TID – current formulation) starting on Day 8. Subjects received 400 mg TID (original formulation) and peginterferon alfa-2b for 20 weeks in P04531.

The mean log_{10} changes from baseline in HCV-RNA showed the greatest maximal declines for boceprevir at either 400 or 600 mg QID (4.05 and 4.18 [Δlog10 HCV-RNA], respectively) (Figure 51). The mean maximum change in HCV-RNA was lower for both TID dosing arms.

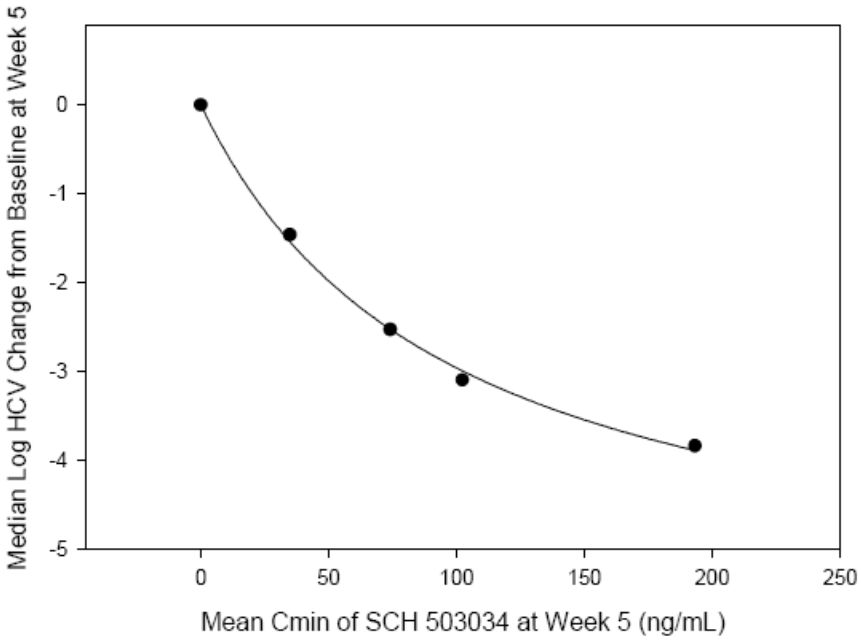
Figure 2 HCV-RNA Log_{10} Mean Change from Baseline Over Time for Four Boceprevir Treatment Arms from P04487/P04531.



Source: Sponsor's study-report-phase-1-2-pk-pd.pdf, page 16

C_{trough} was chosen as the PK parameter to further examine the PK/PD relationship between boceprevir and antiviral activity in combination therapy given the somewhat stronger association with maximal HCV-RNA than other PK parameters in prior analyses. The relationship between mean C_{trough} at Week 5 for each C_{trough} quartile and median log_{10} HCV-RNA change at Week 5 is presented in Figure 3 below. There was a consistent moderate positive correlation between boceprevir C_{trough} and reduction in viral load. The line represent curve fit by a simple E_{max} (maximum log10 HCV decline from baseline) model. The model estimated E_{max} value (Week 5) (in this case, maximum log HCV-RNA decline from baseline) was -5.86 (±0.316) and effective concentration (EC_{50}) was 97.8 (±11.3) ng/mL, which is similar to the in vitro IC_{50} for boceprevir (~100 ng/mL). The model predicts a similar decrease in viral load between C_{trough} of 100-200 ng/mL, and the sponsor selected a dose and dosing frequency to target that range.

Figure 3 Relationship Between Boceprevir C_{trough} at Week 5 and Early Responsiveness to Combination Treatment With Boceprevir and Peginterferon alfa-2b (log HCVRNA change from baseline at Week 5).



Source: *Sponsor's study-report-phase-1-2-pk-pd.pdf, page 18*

A Phase 2 Dose finding trial (P03659) in HCV-infected patients who were previously non-responders to pegylated interferon and ribavirin (n=357).

Trial P03659 had a randomized, double-blinded, placebo-controlled, open-label, design. The dose-ranging trial evaluated the safety and efficacy of boceprevir administered at four doses in combination with SOC to HCV genotype 1 non-responder patients who never achieved undetectable HCV-RNA during their previous course of SOC. The primary efficacy endpoint was SVR24 weeks after the end of treatment. All patients received a single dose of pegylated interferon alpha 2b at 1.5 µg/kg SC for 1 week. This initial treatment was followed by pegylated interferon alpha 2b (1.5 µg/kg SC QW) plus double-blinded treatment with either boceprevir (100, 200, or 400 mg TID) or boceprevir placebo plus either ribavirin (800-1400 mg/day) or ribavirin placebo, for an additional 24 or 48 weeks.

Investigators amended the trial twice before its completion. Amendment 1 added an additional treatment arm with African American (Arm 7) patients who received pegylated interferon alpha 2b (1.5 µg/kg SC QW) for 1 week, followed by pegylated interferon alpha 2b plus boceprevir 800 mg TID for 24 weeks (no ribavirin). Amendment 2 switched all patients from their initial boceprevir dose to receive boceprevir 800 mg TID. Ribavirin was also added to groups who were initially receiving ribavirin placebo. The Data Review Advisory Board

recommended amendment 2 because an interim analysis showed that patients receiving low doses of boceprevir had poor antiviral response, and those receiving ribavirin placebo started developing viral resistance to boceprevir.

Amendment 2 complicated the interpretation of sustained virologic response and viral relapse rates within each cohort. The addition of ribavirin and changes in boceprevir dosing altered the original length of therapy (24 weeks) assigned to all patients. The mean overall length of newly assigned therapy ranged from 1.9 to 26.9 weeks with mean duration of 19.3 weeks. Of note, no patients received more than 24 weeks of boceprevir 800 mg TID with SOC. Therefore, differences in treatment length complicated the identification of a boceprevir dose that produced the best antiviral response.

Due to boceprevir dosing modifications, data analysis focused on treatment responses observed during boceprevir therapy rather than on post-treatment measures (i.e. SVR 24). The lowest HCV-RNA response rate, based on the last sample value taken on-treatment prior to the safety amendment, was observed in the patients treated with PEG/BOC 100 mg TID (4.2%, 2/48). The two higher-dosed arms had similar response rates: the PEG/BOC 200 mg TID arm had a response rate of 14.3% (7/49) and the PEG/BOC 400 mg TID arms (arms 4/6) had a response rate of 13.4% (13/97). In contrast, arm 5 (PEG/RBV/BOC 400 mg TID) had a response rate of 34.7% (17/49), which was more than two times as high as that of the PEG/BOC 400 mg TID arms without RBV.

The Applicant conducted a population PK (PPK) analysis to evaluate sparse PK of boceprevir from patients in this trial along with PK data from six Phase 1 trials. The PPK analysis demonstrated a less than dose-proportional increase in C_{max}, C_{min}, and AUC of boceprevir from the 100 mg TID to 800 mg TID dose groups. In addition, dose-proportional assessment using power-law model on Phase 1 data showed that boceprevir C_{max}, C_{trough}, and AUC were less than dose-proportional and fairly overlapped from 800 mg and 1200 mg. Therefore, dose escalation above 800 mg TID will not substantially increase trough concentrations and associated efficacy since C_{trough} has good association with viral load drop.

Overall, results from this trial showed that (1) the addition of boceprevir to SOC is safe; (2) boceprevir has antiviral activity in patients who were previously non-responders to SOC alone; (3) ribavirin must be part of HCV treatment with boceprevir; and (4) doses of boceprevir above 800 mg TID may not produce higher exposures or significant increases in efficacy.

A Phase 2 Safety and Efficacy Trial (P03523) of Boceprevir in Previously Untreated Patients Infected with Chronic Hepatitis C Genotype 1 (n=595).

Trial P03523 had a randomized, open-label design and evaluated the safety and efficacy of boceprevir when added to SOC in treatment-naive patients. Patients received boceprevir 800 mg TID combined with SOC for treatment durations of

28 weeks versus 48 weeks, with and without a 4-week lead-in of SOC (PR lead-in) before the addition of boceprevir. The trial also assessed lower doses of ribavirin (arm 7).

The addition of boceprevir to SOC significantly increased the end of treatment responses and SVR rates in both the 28- and 48- week regimens relative to SOC alone. The following table summarizes the virologic response and relapse rates observed across patient cohorts.

Table 7 Virologic Response (Undetectable HCV-RNA) and Relapse Rates.

	Arm 1[a] P/R 48 wk n=104	Arm 2 P/R/B 28 wk n=107	Arm 3 P/R Lead-in P/R/B 28 wk n=103	Arm 4 P/R/B 48 wk n=103	Arm 5 P/R Lead-in P/R/B 48 wk n=103	Arm 6 P/R/B 48 wk n=16	Arm 7[b] P/Low-Dose R/B 48 wk n=59
EOT n (%)	53 (51.0)	84 (78.5)	79 (76.7)	76 (73.8)	81 (78.6)	9 (56.3)	28 (47.5)
SVR[c] n (%)	39 (37.5)	58 (54.2)	58 (56.3)	69 (67.0)	77 (74.8)	8 (50.0)	21 (35.6)
Difference vs Arm 1	--	16.7%	18.8%	29.5%	37.3%	--	--
95% CI	--	3.5%, 30.0%	5.5%, 32.2%	16.5%, 42.5%	24.7%, 49.8%	--	--
P value	--	0.0126	0.0048	<.0001	<.0001	NA	NA
Relapse[d,e] n/N (%)	12/51 (23.5)	24/81 (29.6)	18/76 (23.7)	5/73 (6.8)	2/79 (2.5)	1/9 (11.1)	6/27 (22.2)
Difference vs Arm 1	--	6.1%	0.2%	-16.7%[f]	-21.0%[f]	NA	NA

B = boceprevir; CI = confidence interval; EOF = End of Follow-up; EOT = End of Treatment; FW = Follow-up Week; HCV-RNA = hepatitis C virus-ribonucleic acid; NA = not applicable; P = peginterferon alfa-2b 1.5 µg/kg QW; QW = once weekly; R = ribavirin 800 to 1400 mg/day; SVR = sustained virologic response.

a: 36 Arm 1 crossover subjects were considered nonresponders for EOT and SVR and were excluded from Relapse.

b: Ribavirin 400 to 1000 mg/day weight based.

c: SVR: The last available value in the period at and after FW 24. If there is no such value, the FW 12 value was carried forward.

d: Relapse rates were calculated based on subjects with undetectable HCV-RNA at EOT and not missing EOF data.

e: One subject in Arm 2 had undetectable HCV-RNA at FW 24 that became detectable after FW 24. This subject was not considered a sustained virologic responder.

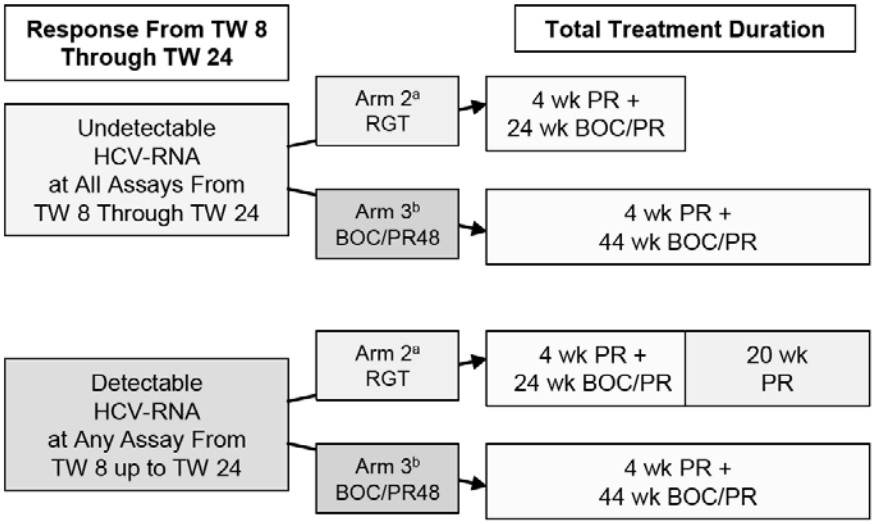
f: Relapse rate was significantly less than relapse rate in Arm 1: Arm 4 vs Arm 1 (P=0.0079 [95% CI -29.7%, -3.7%]) and Arm 5 vs Arm 1 (P=0.0002 [95% CI -33.1%, -8.9%]).

Overall, results from this trial support (1) the use of a 4-week SOC lead-in period prior to the addition of boceprevir; (2) the use of a treatment week 8 assessment of early virologic response to guide treatment duration, and (3) the need for full-dose ribavirin therapy along with peginterferon and boceprevir.

A Phase 3 Safety and Efficacy Trial (SPRINT-2, P05216) of Boceprevir in Previously Untreated Patients Infected with Chronic Hepatitis C Genotype 1 (n=1097).

Trial SPRINT-2 had a randomized, double-blind, placebo-controlled design. The trial enrolled 1097 treatment-naive patients infected with HCV genotype 1. The trial tested two treatment arms containing boceprevir 800 mg TID (dosing interval every 7-9 hours) with SOC given to subjects for 28 weeks or 48 weeks, with a 4-week lead-in period with SOC only. The control arm consisted of treatment with SOC alone for 48 weeks.

The treatment arm containing boceprevir plus SOC for 28 weeks was designated as response guided therapy (RGT). Several previous clinical trials with SOC in genotype 1 HCV-infected patients suggested that some patients with early on-treatment responses may be effectively treated with less than 48 weeks of therapy with SOC. In this trial, total treatment duration was either 28 or 48 weeks, based on viral load decline (HCV-RNA) at weeks 8 and 24, as depicted in the figure below.



a: Arm 2 (RGT) subjects: treatment duration assigned per IVRS.
b: Includes Arm 3 (BOC/PR48) subjects treated >28 weeks.

Results from SPRINT-2 demonstrated that boceprevir given in combination with SOC increased SVR rates to 63% in the RGT arm and 66% in the 48-week combination arm relative to the control group receiving SOC only (38%). The following table summarizes the efficacy results from this trial.

Table 8 Sustained virologic response across cohorts.

	Control	Experimental	
	PR48 n=363	RGT n=368	BOC/PR48 n=366
SVR, n (%)	137 (37.7)	233 (63.3)	242 (66.1)
Δ SVR	--	25.6	28.4
95%CI for Δ	--	18.6, 32.6	21.4, 35.3
P-value	--	<.0001	<.0001
EOT (Undetectable HCV-RNA), n (%)	191 (52.6)	261 (70.9)	277 (75.7)
Relapse, n/N (%)	39/176 (22.2)	24/257 (9.3)	24/265 (9.1)

The efficacy of RGT relative to 48-week treatment with SOC and boceprevir was assessed in early responder (Wk 8 undetectable) and late responder (Wk 8 detectable) patients. Although not statistically significant, SVR was numerically higher in Arm 3 than in RGT Arm 2 in subjects who were late responders (see Table 9 below). Further analyses of these data indicate treatment-naïve subjects that are late responders may benefit from receiving a longer duration of triple therapy (i.e. 32 or 44 weeks of boceprevir + PR), rather than discontinuing boceprevir at Week 28, as proposed by the Sponsor. See Sect. 2.2.4.4 for further details.

Table 9 Sustained virologic response, end of treatment response, and relapse rates in boceprevir-containing arms among early responders and late responders in SPRINT-2

Virologic Response	Arm 2 (RGT) SVR n/N (%)	Arm 3 Boc/PR48 SVR n/N (%)	Treatment Difference Arm 2-Arm 3 [95% CI two sided]
Overall	233/368 (63.3)	242/366 (66.1)	2.8 [-9.8, 4.1]
*Early Responders	156/161 (96.9)	155/161 (96.3)	0.6 [-3.8, 5.2]
#Late Responders	45/68 (66)	55/73 (75)	-9.2 [-24.4, 6.3]

*Early Responders: Undetectable HCV RNA treatment Week 8 through 24 (In RGT arm, early responders received BOC/PR through Week treatment Week 28).
#Late Responders: Detectable HCV RNA Week 8, but undetectable by Week 24 (In RGT arm, late responders received 28 weeks BOC/PR, followed by 20 weeks of PR for total of 48 weeks.
Subjects were discontinued for futility at Week 24 in all treatment arms if HCV RNA was detectable.

Source: Biostatistics reviewer, Dr. Wen Zeng.

Overall, results from this trial showed (1) the addition of boceprevir to SOC significantly increased the SVR rate relative to SOC alone in treatment naive patients; and (2) the RGT arms produced similar SVR rates compared to 48-

weeks of SOC with BOC in early responder patients; and (3) late responder patients may benefit from a longer duration of boceprevir in combination with SOC.

A Phase 3 Safety and Efficacy Trial (RESPOND-2, P05101) of Boceprevir in Patients Infected with Chronic Hepatitis C Genotype 1 who failed previous treatment with SOC (n=403).

Trial RESPOND-2 had a randomized, double-blind, placebo controlled design. The trial enrolled 403 subjects who demonstrated interferon responsiveness but had previously failed treatment with pegylated interferon alpha and ribavirin (i.e. relapsers and partial responders, but not null responders). The trial tested two boceprevir-containing arms, a RGT arm which included 36 weeks of boceprevir and either 36 weeks or 48 weeks of SOC depending on treatment response at weeks 8 and 12, and fixed duration of 48 weeks of combination with SOC. Both arms had a 4-week lead-in with SOC alone. The control arm consisted of treatment with SOC alone for 48 weeks.

Boceprevir given in combination with SOC resulted in SVR rates of 59% in the RGT arm and 66% in the 48-week arm versus 21% the control group. The following table summarizes the efficacy results from this trial.

Table 10 Sustained virologic response in previous treatment failures, RESPOND-2

	Control	Experimental	
	PR48 n=80	RGT n=162	BOC/PR48 n=161
SVR, n (%)	17 (21.3)	95 (58.6)	107 (66.5)
Δ SVR[c]	--	37.4	45.2
95%CI for Δ	--	25.7, 49.1	33.7, 56.8
P-value	--	<0.0001	<0.0001
EOT (Undetectable HCV-RNA), n (%)	25 (31.3)	114 (70.4)	124 (77.0)
Relapse, n/N (%)	8/25 (32.0)	17/111 (15.3)	14/121 (11.6)

SVR rates for the two boceprevir arms were compared for early responders (undetectable at Week 8) and late responders (detectable at Week 8) to evaluate the utility of RGT compared to 48 weeks of boceprevir plus SOC in early and late responder patients. In both patient groups, RGT produced similar SVR rates relative to 48-weeks of boceprevir plus SOC (see Table 11 below).

Table 11 Sustained virologic response, end of treatment response, and relapse rates in boceprevir-containing arms among early responders and late responders, RESPOND-2.

Virologic Response	Arm 2 (RGT) SVR n/N (%)	Arm 3 Boc/PR48 SVR n/N (%)	Treatment Difference Arm 2-3 [95% 2-sided CI]
Overall	96/162 (59.3)	107/161 (66.5)	-7.2 [-17.7, 3.5]
Early Responders#	62/68 (91.2)	68/70 (97.1)	-6.0 [-15.6, 2.2]
Late Responders*	27/34 (79.4)	29/40 (72.5)	6.9 [-14.0, 26.7]

#Early Responders: Subjects with undetectable HCV RNA (<10 IU/mL) Weeks 8 through 12 (In RGT arm received a total of 32 weeks boceprevir/PR after 4-week lead-in treatment with PR.)
*Late Responders: Subjects with detectable HCV RNA (> 10 IU/mL) at Week 8 but undetectable at Week 12 (In RGT arm received a total of 32 weeks boceprevir/PR after 4-week lead-in treatment with PR, followed by an additional 12 weeks PR).
In the Boc/PR48 arm, all subjects, both early and late responders received 44 weeks Boc/PR after 4 week lead-in treatment with PR.

Overall, results from this trial showed (1) the addition of boceprevir to SOC significantly increased the SVR rate relative to SOC alone in treatment experienced patients; and (2) supports the use of response guided therapy for early responders (36 weeks of BOC plus SOC in patients with undetectable virus at week 8); and (3) 32 weeks of triple therapy followed by 12 weeks of SOC is sufficient for late responders in this patient population.

2.2.2 What is the basis for selecting the response endpoint or biomarker and how was it measured in clinical pharmacology and clinical studies?

Sustained virological response (SVR) is the best predictor of a long-term response to treatment of chronic hepatitis C. SVR is defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks after discontinuation of therapy. The primary endpoint in the pivotal trials with boceprevir was SVR rates at 24 weeks after treatment discontinuation. Investigators measured HCV RNA levels in serum by collecting bi-weekly blood samples from patients in the trials.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

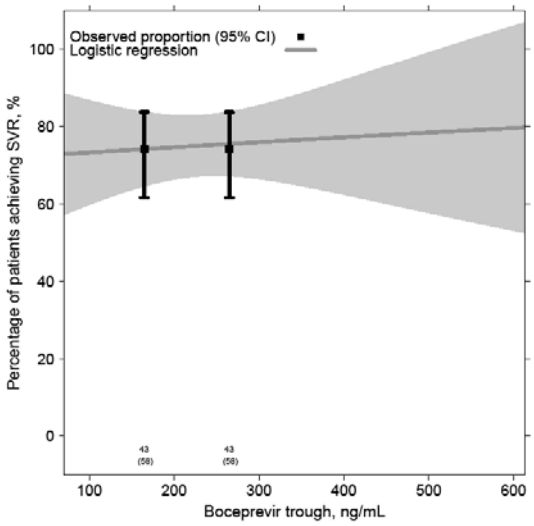
Yes, the Applicant appropriately identified and measured boceprevir in plasma. Boceprevir is a racemic mixture of two diastereomers: SCH534128 and SCH534129. In plasma, the diastereomer ratio converts to 2:1 in favor of the active diastereomer SCH534128. The Applicant also measured boceprevir's metabolite SCH629144 in plasma. Refer to Section 2.6 (Analytical Section).

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

There is no evidence of an exposure-response relationship between boceprevir $C_{trough,}$ C_{max} (not shown), or AUC (not shown) and efficacy based on Phase 3 data. The exposure-response analysis included data only from subjects who received boceprevir in the two Phase 3 trials (P05216, treatment naïve, n=67 and P05101 previous treatment failures, n=49). The analysis excluded patients receiving only standard of care. Analysis results identified a shallow and non-significant relationship between boceprevir exposure and SVR as shown in Figure 4. Similar trends in the exposure-response relationship for efficacy are observed if the patients are separated based on Phase 3 trial. These results indicate that higher exposures to boceprevir are not expected to result in greater efficacy; however, the possibility of subsets of the treatment population having an exposure-response efficacy relationship with respect to boceprevir cannot be excluded due to the limited number of Phase 3 patients with boceprevir exposure data available.

Figure 4 Percentage of Patients Achieving SVR from P05101 and P05216 versus Boceprevir Trough Concentration.

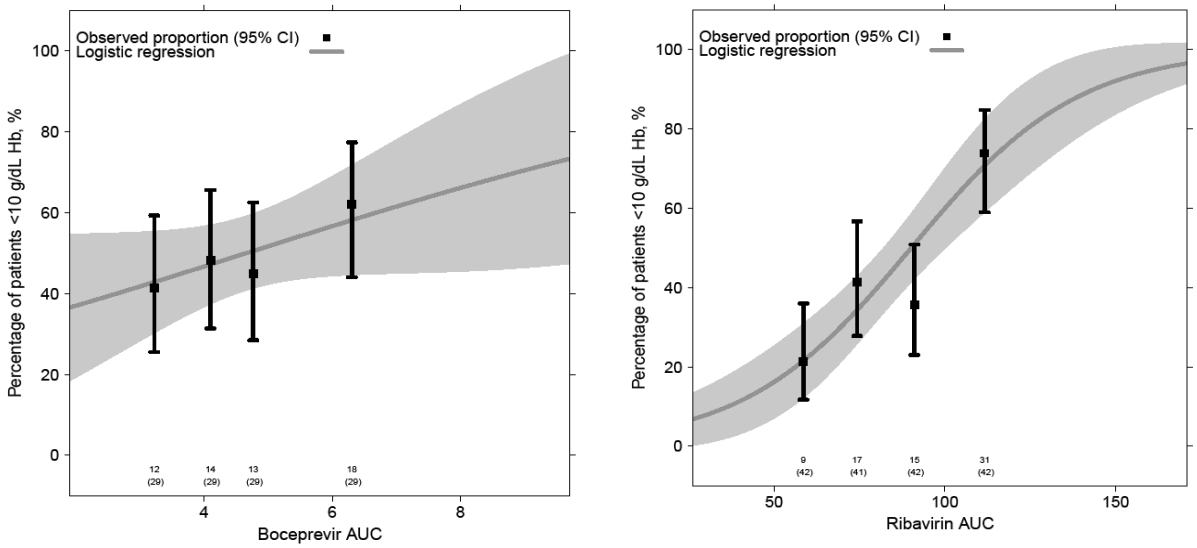


2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

A non-significant (p-value=0.11) upward trend of increasing incidence of anemia (lab hemoglobin measurement <10 g/dL) was observed with respect to increasing boceprevir AUC_T in the Phase 3 population (Figure 5 below, left). Boceprevir AUC_T was used as the PK parameter for exposure-response safety analysis as exposure over time is commonly employed as a predictor of progressive adverse events; however, similar relationships were identified between C_{trough} or C_{max} and incidence of anemia. Model predicted incidence of anemia for the median boceprevir exposure (4.3 µg·hr/mL) was 48%. The predicted incidence of anemia at the lowest and highest exposure quartiles (3.2 and 6.3 µg·hr/mL) was 43% and 58%, respectively. Higher doses of boceprevir (>800 mg TID) are anticipated to further increase the incidence of anemia without an expected benefit in efficacy.

In contrast, a significant relationship between incidence of anemia and ribavirin AUC_T was identified (Figure 5 below, right). The results are not unexpected given ribavirin's known effect on anemia, with an observed incidence of about 30% of patients who receive SOC. The relationships between ribavirin exposure and efficacy and ribavirin exposure and safety may explain why higher SVR rates were observed in subjects who developed anemia in the Phase 3 trials. The Applicant has proposed to dose reduce ribavirin as a strategy for managing on anemia with no accompanying dose reduction in boceprevir. The Applicant's recommendation is appropriate based on the E-R analysis results, and concurs with the recommendation in the ribavirin label.

Figure 5 Percentage of Patients with anemia from P05101 and P05216 observed with steady-state boceprevir exposures (AUC, left) and ribavirin (AUC, right).



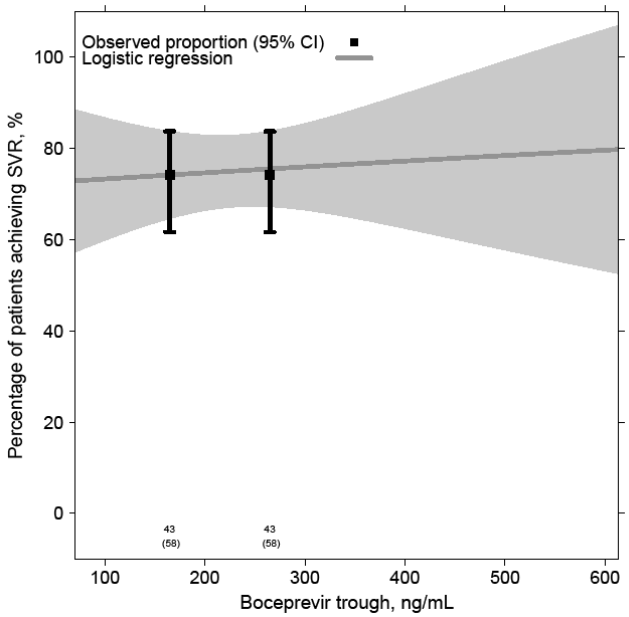
2.2.4.3 Does this drug prolong the QT or QTc interval?

A thorough QTc trial (P04489) in healthy subjects evaluated the effect of boceprevir on the baseline-corrected QTc based on the individual correction method (QTcI). The trial had a 4-way crossover design with placebo, an active control (moxifloxacin), a therapeutic dose, and a supratherapeutic dose of boceprevir. Investigators randomized subjects to receive all four treatments. Each subject served as his or her own control. Thirty six subjects received oral doses of boceprevir 800 mg TID, boceprevir 1200 mg TID, moxifloxacin 400 mg QD, and placebo QD for 5 days. Subjects received each treatment alone in four periods separated by a 7-day washout period. Trial results revealed that boceprevir does not prolong the QT or QTc interval at 1200 mg TID or 800 mg TID relative to placebo. The largest upper bound of the 2-sided 90% CI for the mean difference post-dose between boceprevir (800 mg and 1200 mg TID) and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

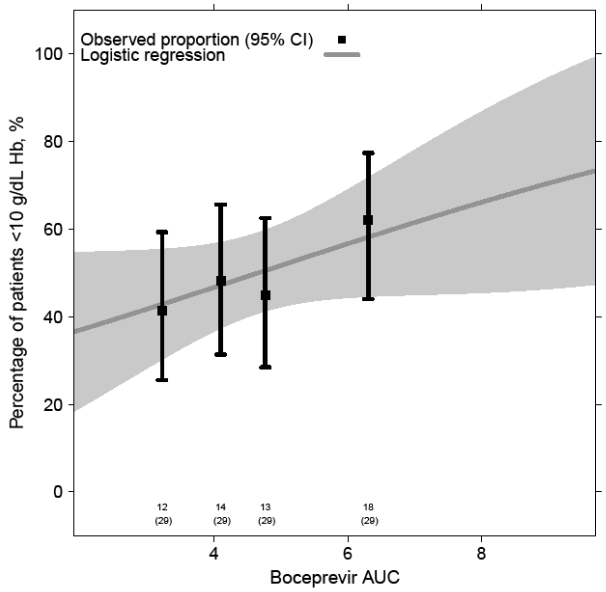
The proposed therapeutic dose of boceprevir, 800 mg TID, is consistent with known exposure-response relationships for efficacy and safety. The efficacy exposure-response relationship for boceprevir is flat over the administered dose, and higher exposures of boceprevir will not result in an appreciable increase in percentage of patients achieving SVR (figure 6 below).

Figure 6 Percentage of patients achieving SVR from P05101 and P05216 versus boceprevir trough concentration.



In contrast, an increasing rate of anemia was observed with increasing boceprevir exposure implying that higher boceprevir doses would lead to increased incidence of anemia (figure 7 below).

Figure 7 Percentage of Patients with anemia from P05101 and P05216 observed with steady-state boceprevir exposures (AUC).



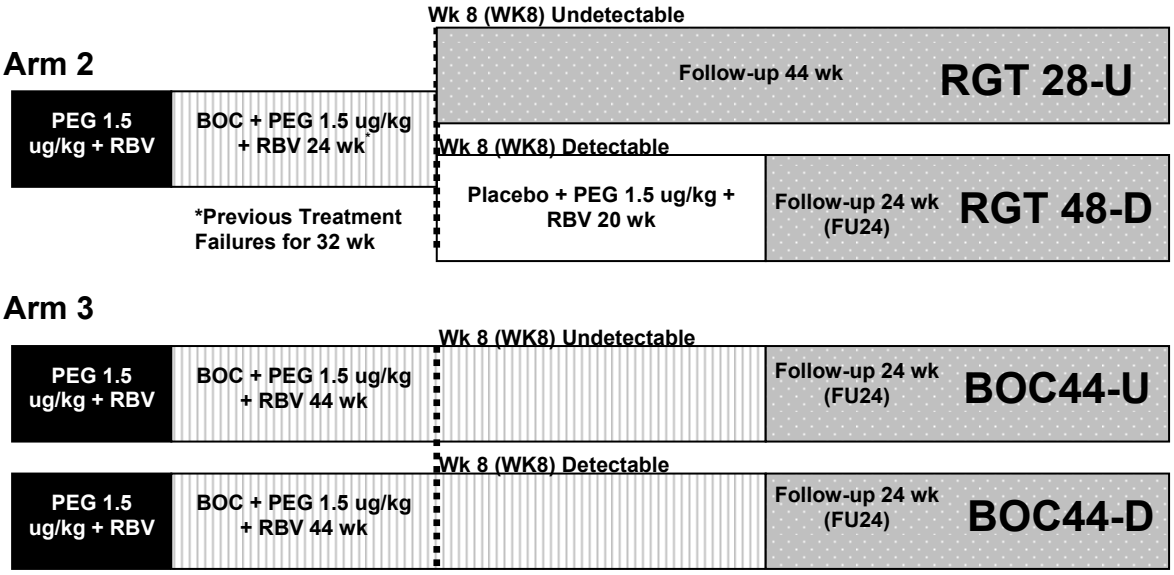
The therapeutic dose of boceprevir is appropriate, but the dosing schedule for treatment naïve should be revised to extend the duration of boceprevir treatment in late responders (i.e. patients with a detectable HCV RNA at Week 8, but undetectable at Week 24).

Response-guided therapy results in almost similar treatment outcome for patients with undetectable viral load at week 8, after receiving SOC alone or SOC with boceprevir. Among treatment naïve patients who had detectable viral load at week 8, patients treated with SOC over the last 20 weeks had lower response rate compared to patients receiving boceprevir and SOC over the last 20 weeks.

During Phase 3 development, the Applicant pursued two different boceprevir treatment arms: (1) a response-guided therapy (RGT) arm; and (2) a 48-week active treatment arm with boceprevir and SOC (triple therapy). In the RGT treatment arm, treatment-naive patients finished treatment at week 28, while previous treatment failure subjects finished treatment at week 36. Both groups finished treatment at weeks 28 and 36 only if their viral loads were undetectable at week 8. Otherwise, these patients received SOC treatment for the entire treatment duration of 48 weeks (20 additional weeks for treatment naïve and 12 weeks for previous treatment failures). In the 48-week active treatment arm, patients received 48 weeks of combination treatment regardless of initial viral response.

This study design compares two different treatments with respect to early viral response. The RGT treatment arm contains two different treatment options, different in the duration of therapy, and based on the viral response at week 8. For treatment naïve subjects, those patients with undetectable viral load at week 8 through week 24 will receive 28 weeks of treatment and will be referred to as RGT 28-U (i.e. response-guided therapy treated for 28 weeks and undetectable at week 8). Similarly, patients in the RGT arm with detectable viral load at one visit between week 8 through week 20 will be referred to as RGT 48-D (response-guided therapy treated for 48 weeks with detectable viral load at week 8). Analogous treatment groups can be selected from patients receiving triple therapy (BOC44 – U: patients undetectable at week 8 who received boceprevir for 44 weeks; BOC44 – D: patients detectable at week 8 who received boceprevir for 44 weeks). This allows a comparison between patients eligible for shorter therapy durations (RGT 28-U versus BOC44-U) in addition to the impact of triple versus SOC treatment over the last 20 weeks of treatment in later viral responders (RGT 48-D versus BOC44-D). A schematic of the treatment arms, and the grouping described above is shown in the figure below.

Figure 8 Schematic of Active Boceprevir Treatment Arms from Phase 3 With Subsequent Divisions to Permit Comparison of Treatments for Patients With Undetectable and Detectable Viral Load at Week 8.



The Pharmacometrics reviewer investigated the percent of patients undetectable for each of the above treatment arms, comparing treatment groups with patients that had undetectable or detectable viral load at week 8.

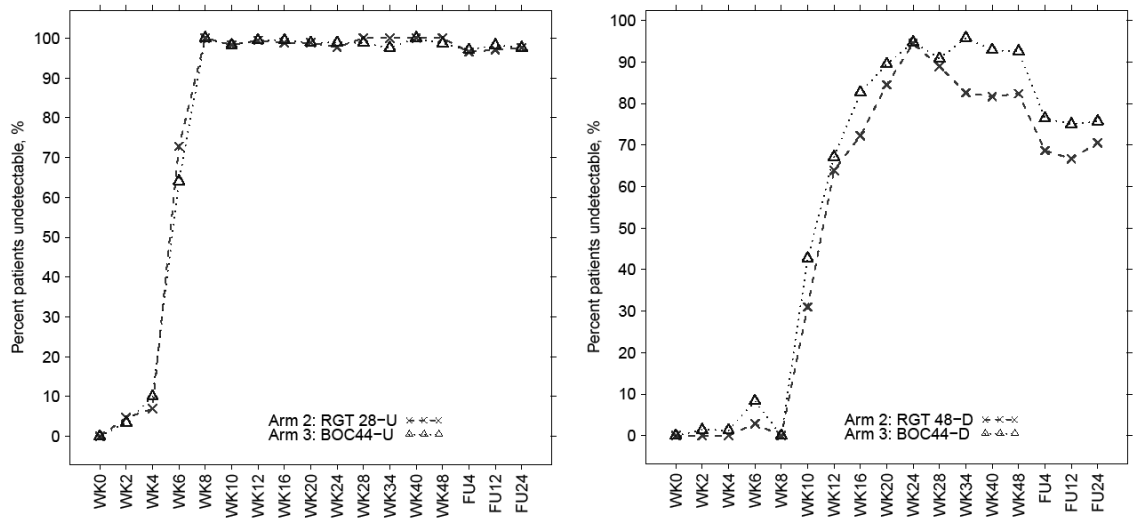
In the Response Guided Therapy (RGT) arm, SOC naive early responders (undetectable HCV RNA at weeks 8 through 24) received 28 weeks of treatment (Arm 2 early responders) and late responders (detectable HCV RNA during at least one time point between week 8 through week 20 but undetectable at week 24) received 20 weeks of additional SOC after triple therapy was stopped at week 28 (Arm 2 late responders). In the same study, patients received 44 weeks triple therapy irrespective of initial response. For comparison, patients that correspond to Arm 2 early and late responders were identified (Arm 3 early responders: early responders who received boceprevir for 44 weeks; Arm 3 late responders: late responders who received boceprevir for 44 weeks).

From this analysis, any patient that discontinued treatment prior to week 28 was removed from the analysis, as all patients received the same treatment during this period. After the end of 28 weeks of treatment, there were four groups of patients based on whether the viral load was detectable at week 8- Arm 2 early responders (N=161), Arm 2 late responders (N=68), Arm 3 early responders (N=161) and Arm 3 late responders (N=73).

For early responders, no difference in the percentage of patients with undetectable viral load was observed on treatment or during follow-up from Arm

2 or Arm 3 (SVR: 97% and 96%, respectively) (Figure 9, left). In contrast, late responders showed a numerical difference in SVR (66% for Arm 2 vs 75% for Arm 3). Further, there was a difference in the percentage of patients with detectable viral load beyond week 28. This time point also corresponds to switching late responders in Arm 2 to receive SOC only. Also, a greater percentage of late responders receiving triple therapy for the remainder of treatment in Arm 3 were undetectable at the end-of-treatment (93%) compared to patients receiving SOC (Arm 2 late responders: 82%), though this resulted in a modest increase in SVR between the two groups (Arm 2 late responders: 66% n= 45 (68); Arm 3 late responders: 75% n= 55 (73)) (Figure 9, right). This difference appears to represent virologic breakthrough while on PR after stopping boceprevir, which was not seen on triple therapy. These results indicate that SOC naive patients with detectable viral load at week 8 may benefit from receiving boceprevir in addition to SOC over the last 20 weeks of treatment. Therefore, the sponsor's proposed duration for SOC naive early responders is acceptable; (b) (4)

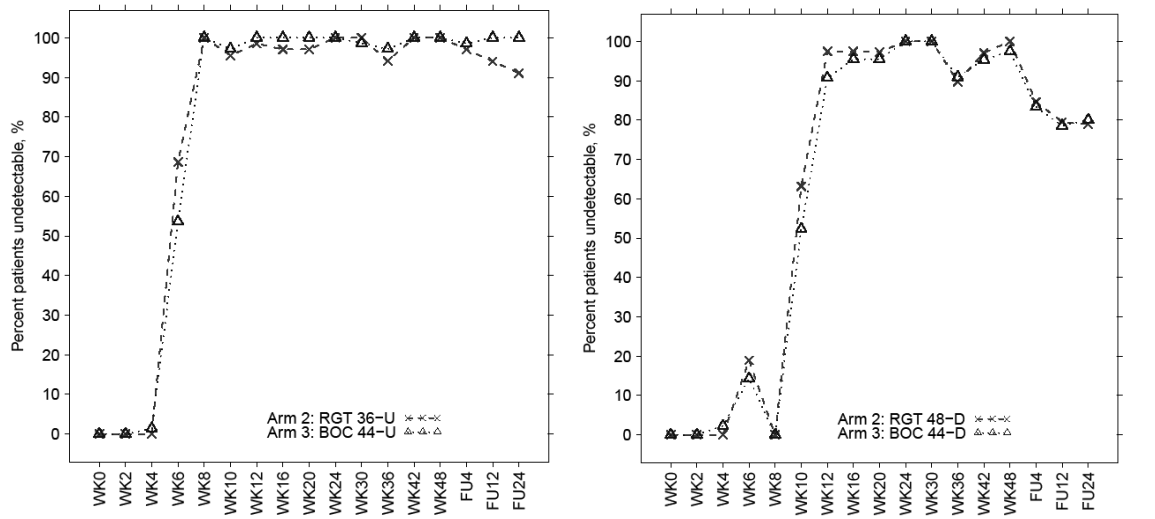
Figure 9 Percentage of Treatment Naïve Patients with Undetectable Viral Load at Different Treatment Time Points for With Undetectable (Left) or Detectable (Right) Viral Load at Week 8.



A similar analysis was performed for the treatment arms in P05101 evaluating boceprevir in previous SOC failures. In this population, patients in the Arm 2 (RGT) received therapy for 36 weeks, and SOC for the remaining 12 weeks if viral load was detectable at week 8 (i.e., late responder). The early and late response categories were based on week 8 and week 12 assessments. As before, any patient that discontinued treatment prior to treatment divergence, in this case week 36, was removed from the analysis (Arm 2 early responder: n = 74; Arm 2 late responder: n=72; Arm 3 early responder: n=84; Arm 3 late

responder: n=70). For early responders, no difference in the percentage of patients with undetectable viral load was observed on treatment with a slight separation in SVR between treatment groups (Arm 2 early responder: SVR 86% n=64 (74); Arm 3 early responder: SVR 88% n=74 (84)) (Figure 10, left). There was no difference in response rate for late responders if treated with SOC or boceprevir with SOC for the remaining 12 weeks of treatment (Figure 10, right). In fact, the RGT arm (shorter boceprevir treatment) resulted in higher SVR compared to longer boceprevir treatment. Therefore, the sponsor's proposed treatment durations for previous SOC failures who are early responders and late responders are acceptable.

Figure 10 Percentage of Previous Treatment Failures with Undetectable Viral Load at Different Treatment Time Points for With Undetectable (Left) or Detectable (Right) Viral Load at Week 8.



(b) (4)

, the data from SOC naive and previous failures was bridged to derive treatment duration in late responders. The rationale for bridging the data stems from the following set of observations.

- Week 4 response (lead-in) to SOC in late responders was similar to that of response in potential SOC failures (Figure 39).

- Week 4 response to SOC was similar for patients irrespective of first (naïve) or second (previous failures) round of treatment with SOC (Figure 40).

If late responders (potential SOC failures) are similar to previous SOC failure population, data from SOC failures can be leveraged to inform treatment duration in SOC naive late responders. An empirical data supports RGT (32 or 44 weeks of boceprevir) for previous relapsers and partial responders. However, there is no empirical data supporting RGT for null responders.

One option is to treat all late responders that include potential null responders, if treated with SOC, with 44 weeks of boceprevir. However, for this option the potential partial responders and relapsers, who might be benefited wit RGT will receive 44 weeks of boceprevir treatment.

Other option is to identify potential null, partial responder and relapser population based on lead in phase (week 4 response) to leverage all available data. A classification and regression tree (CART) analysis was performed on the SOC patients from Arm 1 of P05216 to determine the viral load decline at week 4 that best predicts a null responder SOC treatment outcome. A total of 363 patients were included in the SOC treatment arm, 329 of which had week 4 and week 12 data on change in viral load data available. Please note that week 12 results are used to define null responder status. The results suggest that a week 4 viral load decline ≤1.03 $\log_{10}$ is an appropriate cut point for selecting null responders. Approximately, 83 patients in the SOC arm had viral load decline ≤1.03 $\log_{10}$ at week 4. Of those 83 patients, 60 patients were eventually identified as null responders (85% sensitivity and 72% positive predictive value). In contrast, among 246 patients who had viral load decline >1.03 $\log_{10}$, only 4% were null responders.

Based on the above analyses, the following treatment regimens are recommended for SOC naive late responders.

	Week 4 response	**Treatment duration**
	Option 1[1]	
Late responders	-	PR4/BOC-PR44
	Option 2[2]	
Late responders	> 1.0 $\log_{10}$	PR4/BOC-PR32/PR12
	≤ 1.0 $\log_{10}$	PR4/BOC-PR44

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

<u>Single dose pharmacokinetics of boceprevir in healthy subjects</u>:

The mean maximum plasma concentrations of boceprevir occur at ~3 hours post

[1] Option 1: Treat late responders as potential SOC failures where potential partial responder and relapser population will receive longer therapy but will cover for null responder population.
[2] Option 2: Treat late responders as potential SOC failures, however, identify potential SOC null responders using week 4 response of ≤1.0 log10 such that potential relapser and partial responder population receives appropriate treatment duration by leveraging data from previous treatment failure patients.

dose. The mean terminal elimination half-life of boceprevir is approximately 2-3 hours.

The table below summarizes the single dose pharmacokinetics of boceprevir observed in trial P04488. The trial enrolled six healthy Caucasian subjects who received single doses of boceprevir for 4 days with a Western high fat meal.

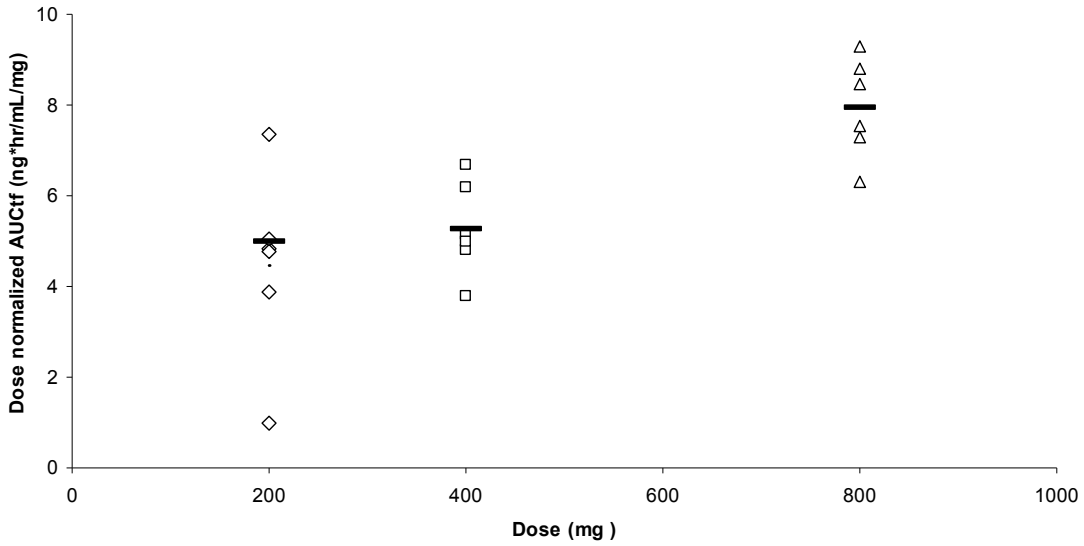
Table 12 Single dose pharmacokinetics of boceprevir in healthy subjects

Dose (mg)	C_{max} (ng/mL)	AUC_{tf} (ng*hr/mL)	t_{max} (h)	$t_{1/2}$ (h)
	Mean (CV%)	Mean (CV%)	Median (Min, Max)	Mean (CV%)
200	339 (36)	994 (25)	3.0 (1.5 – 6.0)	2.1 (29)
400	698 (24)	2100 (20)	3.0 (2.0 – 3.0)	1.9 (37)
800	1710 (18)	6350 (14)	3.5 (2.5 – 4.0)	3.0 (31)

AUC_{tf} = Area under the concentration-time curve from zero to the time of the final quantifiable sample.

Single dose pharmacokinetics of boceprevir increased proportionally to dose from 200 mg to 400 mg. Boceprevir exposures increased disproportionally from 400 mg to 800 mg. The following figure displays individual and mean dose normalized AUC_{tf} of boceprevir following a single dose of boceprevir across cohorts.

Figure 11 Dose proportionality of boceprevir exposures (AUCtf/dose) following a single dose of 200 mg, 400 mg, and 800 mg administered with a high fat meal to healthy Caucasian subjects (P04488).



Multiple dose (TID) pharmacokinetics of boceprevir in healthy subjects:

Boceprevir exposures (C_{max} and AUC_{tf}) are similar following single and multiple (TID) dosing, but some PK parameters are different. For instance, the half-life of boceprevir was approximately 1 to 2 hours longer during multiple dosing relative to single dosing. On the other hand, the mean t_{max} of boceprevir was similar with both dosing regimens.

Boceprevir exposures reach steady-state within one day of TID dosing with minimal accumulation (R= 0.8 to 1.5). In clinical trials (P04488 and P04489), single and multiple (TID) 800 mg doses of boceprevir produced mean AUC values of 5440 ng*hr/mL (AUC_{inf}) and 5320 ng*hr/mL (AUC_{0-8h}), respectively.

The table below summarizes the multiple dose pharmacokinetics of boceprevir following doses of 200 mg to 800 mg in trial P04488. The trial enrolled six healthy Caucasian subjects who received multiple doses of boceprevir for 14 days with low fat meals. Of note, data from the 1200 mg TID cohort is from the thorough QT trial (P04489).

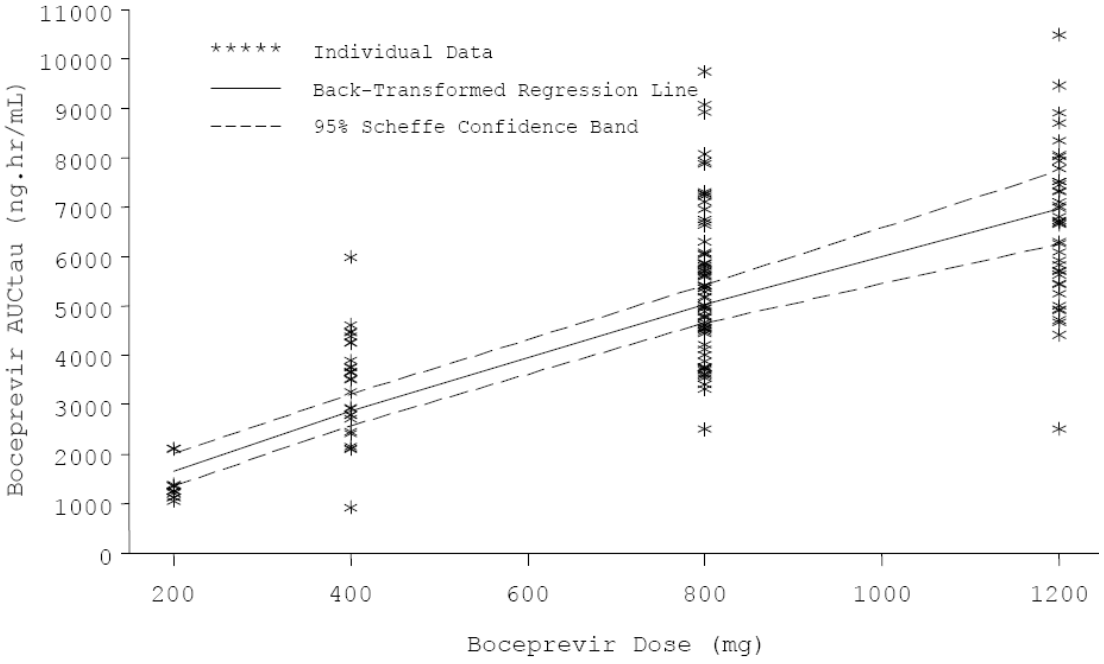
Table 13 multiple dose pharmacokinetic parameters of boceprevir following TID doses of boceprevir for 14 days in healthy Caucasian subjects.

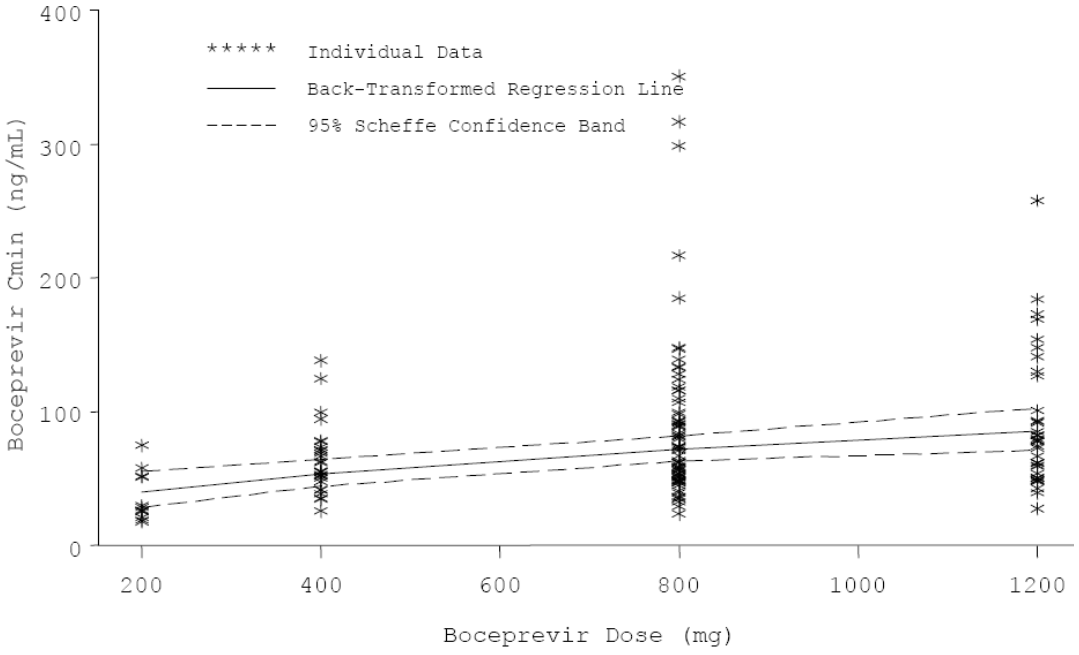
Dose (mg)	n	C_{max} (ng/mL)	AUC_{0-8h} (ng*hr/mL)	t_{max} (h)	$t_{1/2}$ (h)
		Mean (CV%)	Mean (CV%)	Median (Min, Max)	Mean (CV%)
200	6	505 (26)	1330 (30)	2.3 (1.0 – 3.0)	3.5 (29)
400	4	881 (22)	2620 (12)	3.0 (1.5 – 4.0)	5.1 (32)
800	6	1680 (35)	4830 (32)	2.0 (1.0 – 3.0)	10.2 (98)
1200	34	1940 (24)	6500 (22)	2.4 (1.0 – 4.0)	3.0 (73)

Steady-state boceprevir exposures (AUC) increased approximately proportional to dose from 200 mg to 800 mg TID, but increased sub proportionally to dose from 800 mg to 1200 mg TID. The mean AUC of boceprevir following a 1200 mg TID dose was only 32% higher than the mean AUC obtained with 800 mg TID. These results suggest that boceprevir bioavailability may decrease at higher doses.

The figures below display the dose proportionality of the mean AUC_{tau} and C_{min} of boceprevir dosed TID to fed healthy subjects across phase I trials.

Figure 12 Dose Proportionality Assessment for AUC Following Administration of Boceprevir TID to Fed Healthy Subjects (Combined Phase I Studies)





Source: Sponsor's study-report-phase-1-2-pk-pd.pdf, page 23

Pharmacokinetics of boceprevir's metabolite (SCH629144) in healthy subjects:

Plasma exposures (C_{max} and AUC) of SCH629144 are ~4-times higher (range 2.5 - 5.4) than boceprevir exposures, and exposure accumulates with repeat dosing. SCH629144 does not confer antiviral activity against HCV. The table below summarizes the single dose and multiple dose PK parameters of SCH629144 in humans.

Table 14 Mean PK parameters of SCH629144 following single 800 mg dose and multiple 800 mg TID dose across three clinical trials in healthy subjects.

Trial	Dose (mg)	n	C_{max} (ng/mL)	AUC_{0-8h} (ng*hr/mL)	t_{max} (h)	$t_{1/2}$ (h)
			Mean (CV%)	Mean (CV%)	Median (Min, Max)	Mean (CV%)
P05579	800	6	2750 (52)	15700* (51)	4.0	4.2 (24)
P05880	800 TID	12	6480 (33)	32500 (33)	3.5 (3.0 – 6.0)	-
P04489	800 TID	31	5160 (30)	23200 (37)	3.3 (2.0 – 4.0)	4.4 (29)

*AUC_{tf}

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

In Phase 1 trials (P04488 and P04487), HCV-infected patients had similar boceprevir PK profiles to healthy subjects. In the Phase 2 population PK (PPK) analysis for P03659, health status had no significant effect on CL/F or Vd/F. The Phase 3 PPK analysis revealed an effect of health status on central volume (ΔOFV: -19.7); however, the effect was well within the range of estimated inter-individual and intra-individual variability in boceprevir exposure and was therefore not considered clinically relevant.

No apparent difference was noted in PK between subjects infected with genotype 1 versus genotype 2/3 (studies P03516, P03527, and P03648), and the Phase 3 PPK analysis indicated no significant difference in boceprevir PK between treatment-naïve and treatment-experienced patients.

The Applicant did not provide metabolite information in the PPK analysis.

2.2.5.3 What are the characteristics of drug absorption?

The time to maximum concentration in healthy subjects is approximately 3 hours.

Food increases the absorption of boceprevir. Three clinical trials (P03533,

P04133, and P04488) evaluated the effect of food on the PK of boceprevir. In these trials, investigators tested 400 mg and 800 mg doses of boceprevir using the proposed commercial formulation under fed and fasted conditions. Results from the trials revealed that food increases the exposures (AUC) of boceprevir up to 65% (range 33.2% [P04488] to 65% [P03533]) relative to boceprevir administered in the fasted state. For more information on food effect, refer to Section 2.4.1.

The absolute bioavailability of boceprevir is unknown. In a mass balance trial in humans (P03588), investigators recovered 79% of radioactivity in feces and 9% of radioactivity in urine. Of the radioactivity recovered in feces, 10% consisted of unchanged boceprevir and the rest consisted of boceprevir metabolites. These results suggest that most of the radioactivity was absorbed into the circulation, and subsequently excreted into feces.

Boceprevir is a substrate of p-glycoprotein, based on an *in vitro* Caco-2 experiment (DM27866). Of note, boceprevir saturated its own efflux ratio with increasing concentrations, with maximal saturation occurring at 100 uM. For more information on boceprevir and p-glycoprotein, refer to Section 2.4.2.4.

Investigators did not evaluate the effect of pH on the pharmacokinetics of boceprevir in a clinical trial.

2.2.5.4 What are the characteristics of drug distribution?

Across clinical trials, boceprevir maintained a mean apparent volume of distribution (Vd/F) of ~772 liters or 11 L/kg, indicating extensive distribution. In animals, boceprevir distributes to the liver, where tissue concentrations range from 11 to 49-times higher relative to plasma concentrations (Study DM27192). Other reservoir tissues for boceprevir are the bladder walls, kidneys, and prostate gland of animals. In humans, the liver concentrations of boceprevir and its diastereomers are unknown.

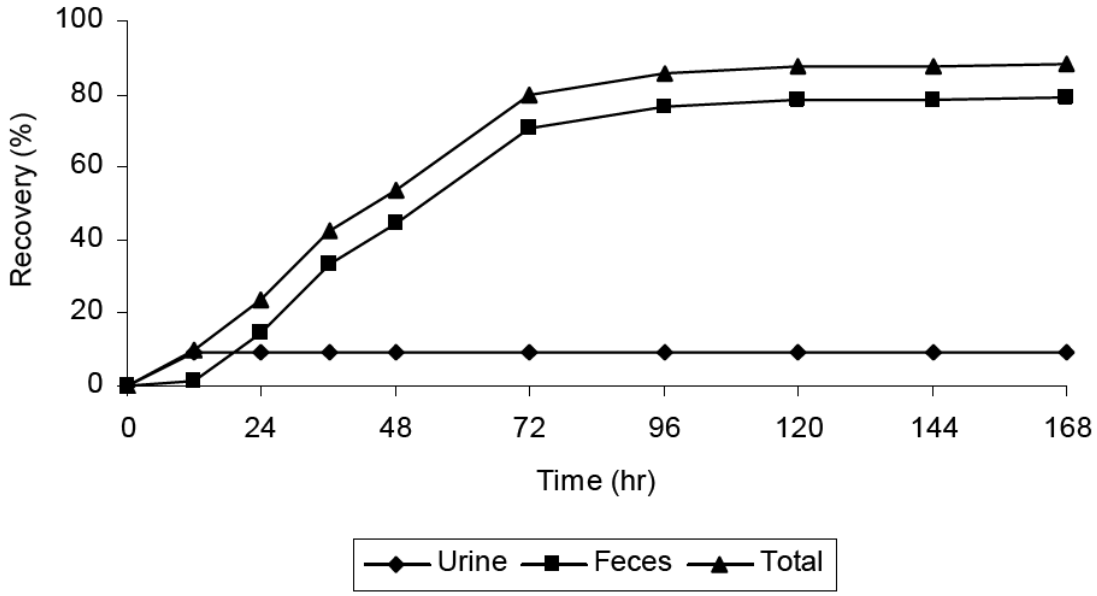
Boceprevir is not highly bound to proteins in human plasma. In the renal impairment trial (P05579), investigators assessed boceprevir plasma protein binding in healthy and in renally impaired subjects. The plasma protein binding in healthy and renally impaired subjects was 73.6% and 81.6%, respectively. Likewise, the *in vitro* plasma protein binding of boceprevir ranges from 68.6 to 81.7% (Study 03368).

Boceprevir remains mainly in plasma with minor partitioning in blood. In the mass balance trial (P03588), the blood-to-plasma partition ratio was 0.33, suggesting that boceprevir remains mostly in plasma and partitions minimally into the cellular components of blood.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Boceprevir undergoes hepatic and renal elimination, but most elimination occurs hepatically. In the mass balance trial (P03588), subjects received a single dose of boceprevir 800 mg with 125 µCi of ^{14}C-boceprevir, formulated as an oral suspension. Investigators recovered ~88.2% of the total dose of radioactivity in feces (78.9%) and urine (9.3%). The radioactivity in feces and urine was quantifiable up to 168 hours and 12 hours post dose, respectively. The following figure displays the mean cumulative excretion of radioactive ^{14}C-boceprevir in feces and urine.

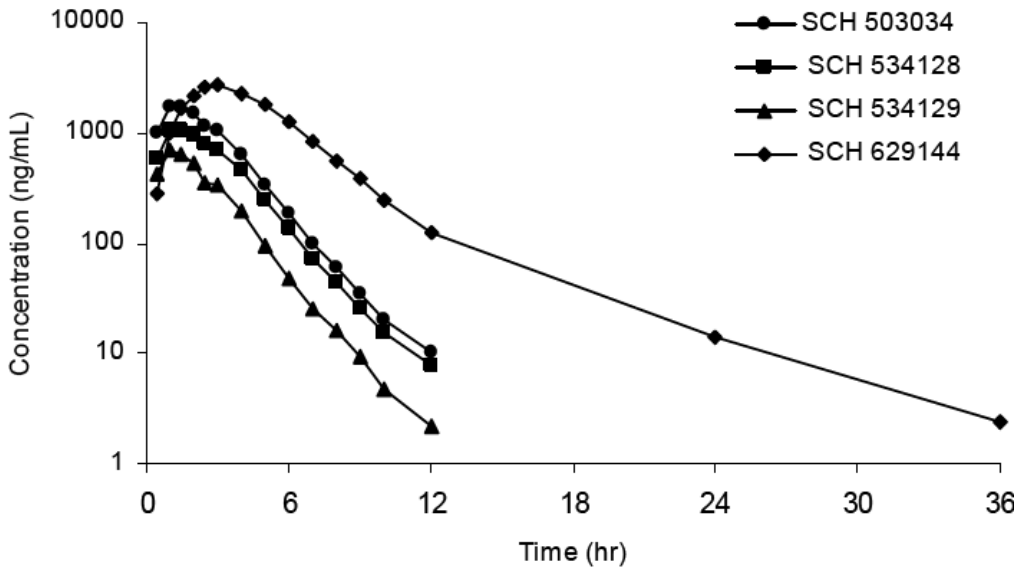
Figure 13 Mean cumulative excretion of radioactivity in feces and urine following a single 800 mg oral dose of ^{14}C-boceprevir (125 µCi) administered as an oral suspension to six healthy subjects



Boceprevir is extensively metabolized in the liver. Only 10% of the total radioactivity recovered in feces consisted of unchanged boceprevir (SCH534128 + SCH534129). The rest of the radioactivity in feces was comprised of boceprevir metabolites. In contrast, 32% of the total radioactivity recovered in urine was unchanged boceprevir and the rest was comprised of boceprevir metabolites.

The following figure shows the mean plasma concentrations of boceprevir (SCH503034), SCH 629144, SCH 534128, and SCH 534129 following a single oral dose of ^{14}C-SCH 503034 in an oral suspension.

Figure 14 Mean plasma boceprevir (SCH503034), SCH534128, SCH534129, and SCH629144 concentrations following a single 800-mg oral dose of ^{14}C-boceprevir administered as a suspension in (b) (4) (w/w) SLS in Ora-Sweet Sugar-free syrup to healthy male subjects.



The following table summarizes the mean pharmacokinetic parameters following a single 800 mg oral dose of ^{14}C-boceprevir. Of note, the mean AUC value of SCH629144 is ~2-fold higher than the AUC of boceprevir (SCH503034). SCH629144 has no antiviral properties against HCV.

Table 15 Mean (CV%) pharmacokinetic parameters of boceprevir (SCH503034), SCH534128, SCH534129, and SCH629144 following a single 800 mg oral dose of ^{14}C-boceprevir administered as a suspension in (b) (4) (w/w) SLS/Ora-Sweet Sugar-free syrup to healthy male subjects.

	Plasma SCH 503034		Plasma SCH 534128		Plasma SCH 534129		Plasma SCH 629144	
	Mean (n=6)	(CV)	Mean (n=6)	(CV)	Mean (n=6)	(CV)	Mean (n=6)	(CV)
Cmax (ng/mL)	1860	(22)	1140	(21)	726	(25)	2790	(34)
Tmax (hr)[a]	1.25	(1.0-2.0)	1.25	(1.0-2.0)	1.0	(1.0-2.0)	3.0	(2.5-4.0)
t½ (hr)	1.60	(30)	1.68	(18)	1.97	(44)	-	-
AUC(tf) (ng·hr/mL)	5680	(27)	3730	(28)	1940	(28)	14200	(43)
tf (hr)	11.7	(7)	11.7	(7)	10.3	(13)	28.0	(22)
Cmax/Dose (ng/mL/mg/kg])	168	(18)	103	(21)	64.9	(17)	257	(40)
AUC(tf)/Dose (ng·hr/mL/[mg/kg])	513	(29)	338	(32)	174	(26)	1310	(50)
Cmax Ratio[b]	-	-	-	-	-	-	1.52	(28)
AUC(tf) Ratio[c]	-	-	-	-	-	-	2.47	(21)

Mean (CV) subject weight = 73.4 (15) kg; Mean (CV) weight-adjusted dose = 11.1 (15) mg/kg

CV = coefficient of variation; SLS = sodium laurel sulfate

a: Tmax is reported as median (range).

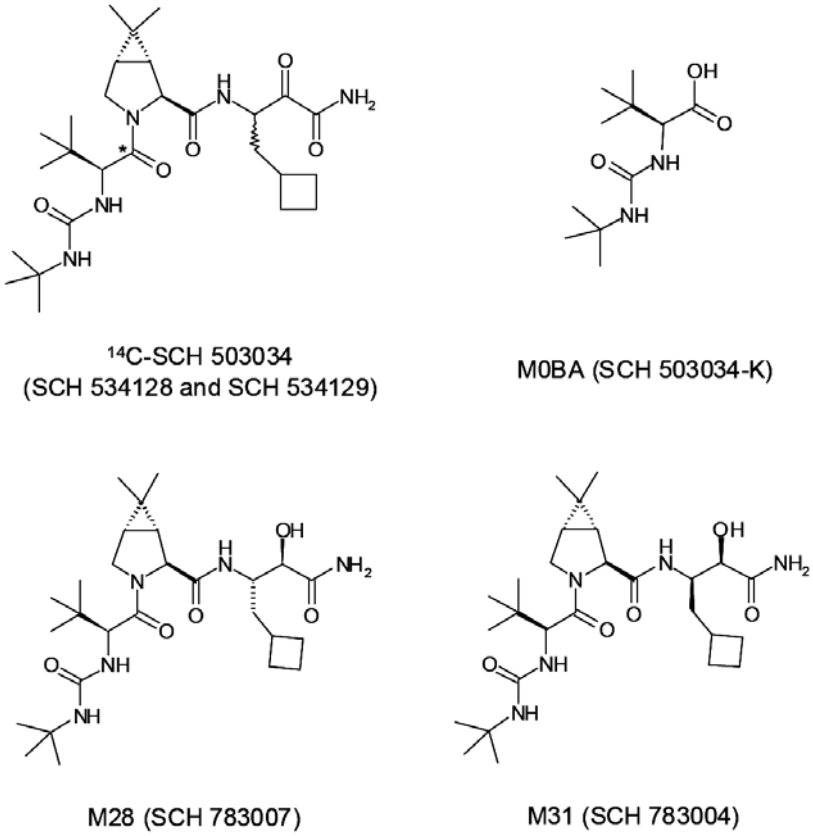
b: Cmax ratio of SCH 629144:SCH 503034

c: AUC(tf) ratio of SCH 629144:SCH 503034

2.2.5.6 What are the characteristics of drug metabolism?

The primary metabolite, SCH629144, is comprised of four different stereoisomers: SCH783004 (M31), SCH783005, SCH783006 (M30), and SCH783007 (M28). SCH783007 (M28) and SCH783005 are derived from SCH534128, and SCH783004 (M31) and SCH783006 (M30) from SCH534129. The following figure displays the major metabolites of boceprevir in plasma.

Figure 15 Structures of major circulating metabolites following single 800 mg oral dose of ^{14}C-boceprevir administered as a suspension in (b) (4) SLS in Ora-Sweet SF syrup to healthy male subjects (P03588)



In vitro, AKR1C2 and AKR1C3 produce the majority of boceprevir metabolites. AKR1C2 preferentially metabolizes SCH534129 to produce M31. AKR1C3 preferentially metabolizes SCH534128 to produce M28. *In vivo*, the most abundant circulating metabolites are M28, M30, and M31. Combined, these three metabolites account for approximately 46% to 70% of the circulating radioactivity in plasma at 2 and 6 hours post- ^{14}C-boceprevir dose. AKR1C2 and 1C3 are expressed in the liver as well as prostate and mammary glands. Thus, conversion of boceprevir to the stereoisomers of SCH629144 may occur in extra-hepatic issues.

CYP3A4 produces oxidative metabolites including M11, M14-16, M21, and M23. These metabolites account for approximately 22.5% of the circulating radioactivity in plasma at 2 and 6 hours post- ^{14}C-boceprevir dose.

Sodium Lauryl Sulfate (SLS), a component in the proposed commercial formulation of boceprevir, metabolizes boceprevir to produce M0BA. M0BA (SCH503034-K) is a product of the hydrolytic cleavage of boceprevir by SLS in

the gut. M0BA accounted for 13% and 19% of the circulating radioactivity in the 2-hour and 6-hour plasma samples, respectively. Of note, these percentages of M0BA were observed with the oral suspension of ^{14}C-boceprevir used in the mass balance trial. The proposed commercial capsules of boceprevir delivers less than 8% of circulating M0BA relative to boceprevir (Trial P05880).

2.2.5.7 What are the characteristics of drug excretion?

The mean apparent total clearance (CL/F) of boceprevir is 157 L/hr (2.2 L/hr/kg). Clearance values were similar throughout clinical trials with boceprevir.

Boceprevir undergoes hepatic and renal elimination, but most elimination occurs hepatically. In the mass balance trial, investigators recovered ~88.2% of the total dose of radioactivity in feces (78.9%) and urine (9.3%). Approximately 10% and 32% of the total radioactivity recovered in feces and urine was unchanged boceprevir. The radioactivity in feces and urine was quantifiable up to 168 hours and 12 hours post dose, respectively.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Refer to Section 2.2.5.1.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

In trial P04487, mean boceprevir AUC_{τ}, C_{max}, C_{min}, and T_{max} were similar over repeated dosing of boceprevir in HCV genotype-1 subjects under fed conditions. Subjects in P04487 received subcutaneous PEG2b 1.5 µg/kg on Day 1 Week 1, and then received one of the following boceprevir treatments in combination with subcutaneous PEG2b 1.5 µg/kg QW for the following 4 weeks: Treatment A (400 mg TID), Treatment B (400 mg QID), Treatment C (600 mg QID), or Treatment D (400 mg TID).

Table 16 Mean (CV%) Pharmacokinetic parameters of boceprevir following administration of boceprevir (400 mg or 600 mg, TID or QID, original or commercial formulation) Co-administered with Peg interferonalpha-2b (1.5 µg/kg weekly) in Fed HCV genotype 1 subjects

	Treatment A			Treatment B			Treatment C			Treatment D		
Parameter	Week 2-Day 1 (n=10)	Week 3-Day 3 (n=10)	Week 5-Day 3 (n=10)	Week 2-Day 1 (n=7)	Week 3-Day 3 (n=7)	Week 5-Day 3 (n=7)	Week 2-Day 1 (n=6)	Week 3-Day 3 (n=6)	Week 5-Day 3 (n=6)	Week 2-Day 1 (n=6)	Week 3-Day 3 (n=6)	Week 5-Day 3 (n=6)
AUC(τ) (ng·hr/mL)	2760 (36)	3090 (26)	3060 (36)	2820 (46)	3400 (41)	3000 (35)	3170 (61)	3600 (20)	3120 (27)	2930 (32)	3610 (25)	3520 (39)
Cmax (ng/mL)	1020 (46)	894 (33)	1060 (44)	1080 (42)	1310 (28)	1370 (34)	1260 (48)	1250 (27)	1210 (44)	971 (23)	1150 (28)	1010 (35)
Cmin (ng/mL)	253 (68)	235 (49)	157 (44)	401 (61)	444 (57)	580 (82)	489 (34)	510 (26)	649 (44)	213 (104)	143 (60)	169 (40)
Tmax[a] (hr)	4.50 (1.00-6.00)	4.00 (2.50-6.00)	2.50 (1.00-5.00)	2.50 (1.50-4.00)	2.50 (2.00-4.00)	2.00 (0.00-5.00)	3.00 (2.50-5.00)	2.75 (1.50-4.00)	2.50 (1.50-5.00)	3.50 (1.00-6.00)	3.00 (1.00-4.00)	3.00 (2.00-6.00)

Treatment A: Boceprevir 400 mg TID for 4 weeks [Week 2 to 5], 100 mg capsules, original formulation with PEG2b 1.5 µg/kg SC QW for 5 weeks

Treatment B: Boceprevir 400 mg QID for 4 weeks [Week 2 to 5], 100 mg capsules, original formulation with PEG2b 1.5 µg/kg SC QW for 5 weeks

Treatment C: Boceprevir 600 mg QID for 4 weeks [Week 2 to 5], 100 mg capsules, original formulation with PEG2b 1.5 µg/kg SC QW for 5 weeks

Treatment D: Boceprevir 400 mg TID for 4 weeks [Week 2 to 5], 200 mg capsules, commercial formulation with PEG2b 1.5 µg/kg SC QW for 5 weeks

[a] Median (range).

After administration of 400 mg TID boceprevir original formulation (P04531), the mean C_{min} values of boceprevir were 358, 650, 398, and 247 ng/mL for weeks 4, 8, 14, and 20, respectively.

A high degree of intra-subject variability on boceprevir C_{min} values occurred (56%), but changes in CL/F did not occur with repeated dosing.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients, and what are the major causes of variability?

Boceprevir exhibits high intersubject and intrasubject pharmacokinetic variability in HCV-infected patients. The Phase 2 PPK analysis demonstrated that inter-patient variability in CL/F was 30% and intra-patient variability was higher at 56%. When this analysis was updated to include Phase 3 studies, inter-patient variability in CL/F increased to 42%, and intra-patient variability increased to 60% for dense data and 84% for sparse data, respectively. Estimated central volume variability was even higher at 125%.

The intersubject coefficient of variability (%CV) for boceprevir C_{max}, C_{min}, and AUC values following various doses with boceprevir across trials are listed in Table 17 below. Of note, this PK variability was observed with the proposed commercial formulation of boceprevir.

A population PK analysis using boceprevir PK data from Phases 1 to 3 revealed that age, gender, race, body weight, and health status (healthy vs. HCV-infected)

do not affect the pharmacokinetics of boceprevir. Therefore, the source of intersubject variability in boceprevir PK is currently unknown.

Table 17 Range of % intersubject PK variability of boceprevir across clinical trials in healthy subjects and HCV-infected patients.

	Intersubject		
	C_{max}	AUC	C_{min}
Range inter-subject variability (%CV)	11 – 87	9 – 53	26 - 104

2.3. Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response? What is the effect of any differences in exposure on efficacy or safety responses?

Population PK analysis demonstrated that sex, age, body weight, height, race, HCV infection versus healthy volunteers, previous treatment status, and body mass index did not have a clinically significant impact on boceprevir exposure at 800 mg TID. No difference in boceprevir PK was observed between HCV patients infected with genotype 1 compared to genotype 2/3 in studies P03516, P03527, or P03648.

Multivariate analysis of the Phase 3 trials was performed to determine significant intrinsic factors affecting SVR rates. In trial P05216, the following parameters were significant predictors for achieving SVR:

- Treatment response during the lead-in period (≤1 log10 viral decline; poor interferon response versus >1 log10 viral decline; interferon response).
- HCV genotype (1a versus 1b).
- Baseline HCV-RNA (≤400,000 versus >400,000 IU/mL).
- Age (≤40 versus > 40 years). Note, the mean age of HCV-infected subjects in the Phase 3 trials was 40 years.
- BMI (25-30 versus >30 kg/m^2).
- Fibrosis (0/1/2 versus 3/4).

If week 4 response is removed from the multivariate analysis (related to patient

IL28b genotype, which is related to race) treatment (SOC versus a boceprevir containing arm), viral genotype (1a versus 1b), race (black versus non-black), baseline viral load, and fibrosis score (0/1/2 versus 3/4) were significant predictors for achieving SVR.

A similar multivariate, stepwise logistic regression was performed for trial P05101, and only treatment, week 4 lead-in viral response, and previous treatment response (relapser versus nonresponder) were significant factors for achieving SVR. Removing treatment response during lead-in from the multivariate analysis, treatment, previous treatment response, baseline viral load, and fibrosis were identified as significant predictors of SVR.

In the renal impairment trial, boceprevir exposures were similar in subjects with normal renal function and subjects with end stage renal disease requiring hemodialysis. Subjects with moderate and severe hepatic impairment had higher (32 and 45%) exposures relative to subjects with normal hepatic function. Refer to Sections 2.3.2.5 and 2.3.2.6 for more details.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, what dosage regimen adjustments are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

The clinical trials with boceprevir did not include sufficient numbers of subjects aged 65 and over to determine if there are differences in boceprevir exposure in the geriatric population relative to a younger population. The population PK analysis included age as a covariate using data from subjects ranging from 19 to 65 years of age. Results showed that age did not affect the PK of boceprevir. Thus, the dose of boceprevir does not need adjustment in patients in the age range of 19 to 65 years. Limited information is available for patients >65 years of age.

2.3.2.2 What dosage adjustments are recommended for pediatric patients? In addition, what is the status of pediatric studies and/or any pediatric plan for study?

The safety and efficacy of boceprevir has not been established in pediatric patients less than 18 years of age. The Applicant has requested a deferral for conducting a clinical trial in pediatrics until further safety information on boceprevir is collected from adults during post market surveillance. The pediatric

trial with boceprevir is planned to initiate in 2015.

The Applicant also requested a partial waiver for children less than 3 years of age. Boceprevir will be administered in combination with pegylated interferon-alpha and ribavirin. Currently, both agents are not approved for use in children < 3 years of age.

The proposed clinical trials with boceprevir in pediatrics are:

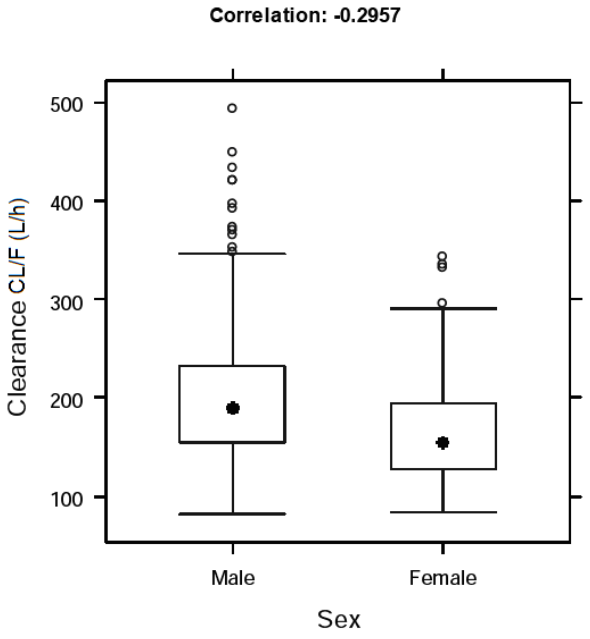
- P07414: Open-label, single dose trial to (1) determine the PK parameters (AUC and C_{max}) of boceprevir, and (2) to determine if weight-based dosing for children results in exposures similar to those observed in adults.

- P08034: Multi-center, open-label, single-arm trial to evaluate efficacy and safety of boceprevir in combination with pegylated interferon-alpha-2b plus ribavirin in treatment-naive (Part A), and treatment-experienced (Part B) pediatric patients for 28 to 48 weeks (response-guided therapy). The trial will also evaluate long-term follow-up (5 years) in pediatric subjects (Part C).

2.3.2.3 Gender

Dose adjustment of boceprevir is not necessary based on gender because men and women have similar boceprevir exposures at the therapeutic dose of 800 mg TID. In the population PK analysis, gender had a minor effect on the clearance of boceprevir. Women on average had 19% (155 L/h) lower clearance values than men (191 L/h). However, the effects of gender on boceprevir clearance were well within the range of estimated intersubject and intrasubject variability (20 – 40%) in boceprevir exposure. The figure below displays the effect of gender on the clearance of boceprevir.

Figure 16 Effect of gender on boceprevir clearance observed in the population PK analysis



2.3.2.4 Race

Dose adjustment of boceprevir is not necessary based on race.

A Phase I clinical trial (P04488) evaluated the steady- state pharmacokinetics of boceprevir in Japanese and Caucasian subjects. Subjects received multiple doses of boceprevir 800 mg TID for 14 days with a low fat meal. The C_{max} and AUC_{tf} of boceprevir were not significantly different between healthy Japanese and Caucasian subjects at 800 mg TID. The table below summarizes the trial results.

Table 18 Comparison of steady-state boceprevir exposures (C_{max} and AUC) following 800 mg TID dosing for 14 days in Japanese and Caucasian subjects.

Analyte	Dose	C_{max} (ng/mL)				AUC_{tf} (ng*hr/mL)			
		LS Means		Japanese vs. Caucasian		LS Means		Japanese vs. Caucasian	
		Japanese (n=6)	Caucasian (n=6)	Ratio	90% CI	Japanese (n=6)	Caucasian (n=6)	Ratio	90% CI
Boceprevir	800 mg TID	1518	1589	95	72 - 126	3965	4588	86	66 - 113

Mean boceprevir exposure was higher in healthy Caucasians relative to African Americans. A Phase I clinical trial (P04133) evaluated the pharmacokinetics of boceprevir after a single 400 mg dose with a low fat meal in African Americans and Caucasians. The mean C_{max} and AUC_{tf} values of boceprevir were 43% and 39% higher in Caucasians relative to African Americans. The following table summarizes the mean PK parameters of boceprevir observed in this trial.

Table 19 Mean (CV%) pharmacokinetic parameters of boceprevir after a single 400 mg dose with a low fat meal in healthy African American and Caucasian subjects.

	Caucasians (n=6)	African Americans (n=6)
T_{max}[a] (hr)	2.5 (2.5 – 4.0)	2.5 (1.5 – 3.0)
C_{max} (ng/mL	1280 (25)	897 (14)
AUC_{tf}(ng*hr/mL)	3590 (22)	2590 (23)
$t_{1/2}$ (hr)	4.7 (12)	4.4 (52)

a: median

The PPK covariate analysis for race included 19 Black, 4 Asian, and 122 Non-Black subjects. The results indicate race did not influence boceprevir PK parameters.

2.3.2.5 Renal impairment

Dose adjustment of boceprevir is not necessary in patients with various degrees of renal impairment.

The Applicant conducted an abbreviated trial with an open-label, single-dose, non-randomized, design in subjects with normal renal function and hemodialysis-dependent subjects with end stage renal disease (ESRD). All subjects received a single 800 mg dose of boceprevir with a high fat meal on day 1. ESRD subjects received a second single dose of boceprevir 4 hours prior to hemodialysis on day 4. Investigators collected plasma samples for PK analysis.

Trial results show that boceprevir exposures (AUC_{tf}) were 10% lower in subjects with end stage renal disease (ESRD) relative to subjects with normal renal function when dosed on a non-hemodialysis day. The following table summarizes the statistical results from this trial.

Table 19 Statistical results for PK parameters of boceprevir on Day 1 following a single oral dose of boceprevir 800 mg to healthy subjects (Group 1) and to patients with ESRD (Group 5).

Parameter	Group	n	LS Mean [a]	Geometric Mean Ratio[b]	90%CI
Cmax	Healthy	6	1472	81	38-174
	ESRD	6	1191		
AUC(tf)	Healthy	6	5079	90	47-173
	ESRD	6	4572		
AUC(I)	Healthy	6	5116	90	47-174
	ESRD	6	4613		

Cmax = maximum observed plasma concentration; CI = confidence interval; LS = least squares; ESRD = end-stage renal disease; ANOVA = analysis of variance; AUC(tf) = area under the concentration-time curve from zero to infinity; AUC(I) = area under the concentration-time curve from time zero to the time of the final quantifiable sample

a: Model-based (least squares) geometric mean; ANOVA extracting the effects due to group and pair

b: Geometric mean ratio of ERSD patients vs. Healthy Subjects

End stage renal disease did not affect the apparent total clearance (CL/F) of boceprevir. Subjects with normal renal function and ESRD had mean CL/F values of 178 L/h and 193 L/h, respectively. The half-life ($t_{1/2}$) values of boceprevir were similar in both groups. Hemodialysis did not affect the PK of boceprevir. Therefore, dose adjustment of boceprevir is not recommended in patients with ESRD undergoing hemodialysis. The following table summarizes the pharmacokinetics of boceprevir obtained from this trial.

Table 20 Mean (CV%) PK parameters of boceprevir in healthy subjects and subjects with ESRD following a single oral dose of boceprevir 800 mg. For ESRD subjects, PK values of boceprevir in the absence of hemodialysis were collected on day 1 and pre-hemodialysis on day 4. ESRD subjects received a single 800 mg dose of boceprevir 4 hours before hemodialysis on day 4.

Parameter	Normal Subjects (n=6)	ESRD Subjects (n=6)	
		Day 1 (no hemodialysis)	Day 4 (dosed 4 hours before hemodialysis)
T_{max}[a] (hr)	2.0 (2.0 – 4.0)	4.0 (1.0 – 6.0)	2.0 (1.3 – 2.0)
C_{max} (ng/mL)	1730 (54)	1340 (52)	1420 (35)
AUC_{tf} (ng*hr/mL)	5710 (50)	5100 (53)	5000 (43)
AUC_{I} (ng*hr/mL)	5760 (50)	5150 (53)	5030 (43)
$t_{1/2}$ (hr)	1.73 (21)	2.2 (60)	1.7 (43)
CL/F (L/hr)	178 (55)	193 (50)	183 (38)

a= median range

2.3.2.6 Hepatic impairment

The exposure of the active diastereomer, SCH534128, increased along with severity of hepatic impairment, but the exposures were not sufficiently increased to warrant dose adjustment of boceprevir in hepatically impaired subjects. Of note, boceprevir will only be approved for patients with compensated hepatic disease. Peg-interferon and ribavirin are contraindicated in patients with hepatic disease with Child-Pugh (CP) class B and C (score >6).

The Applicant conducted a clinical trial in subjects with hepatic impairment (P03747). This trial had an open-label, single-dose, parallel group, design. The trial enrolled 24 subjects with varying degrees of hepatic impairment. Subjects had normal, mild (CP score 5 to 6), moderate (score 7 to 9), or severe hepatic impairment (score 10 to 12). All subjects received a single 400 mg dose of boceprevir in the original capsule formulation under fasting conditions.

Of note, the Applicant did not test the proposed commercial formulation of boceprevir. Instead, they tested the original formulation of boceprevir available when this trial was conducted. The manufacturing processes for both the original and proposed commercial formulations were different, and the formulations contain different excipients. Nevertheless, investigators used the original formulation of boceprevir across all cohorts. Thus, changes in boceprevir exposures should be reflective of differences in absorption, distribution, and hepatic clearance of boceprevir secondary to hepatic dysfunction.

The following table summarizes the statistical results across all cohorts. The table displays only exposures of SCH534128. Boceprevir and SCH534129 exposures were unreliable due to problems during bioanalysis of plasma samples.

Table 21 Ratio estimates and 90% confidence interval for AUC and C_{max} of SCH534128 following a single oral administration of 400 mg boceprevir to healthy subjects and to subjects with various levels of hepatic impairment.

PK Parameter	Group	LS Mean[a]	Treatment Comparison	Ratio	90% CI
AUC_{inf} (ng*hr/mL)	Mild (n=6)	1027	Mild vs. Healthy	107	75 – 152
	Moderate (n=6)	1262	Moderate vs. Healthy	131	93 – 187
	Severe (n=6)	1374	Severe vs. Healthy	143	101 – 203
	Healthy (n=6)	960	-	-	-
AUC_{tf} (ng*hr/mL)	Mild (n=6)	1009	Mild vs. Healthy	107	75 – 152
	Moderate (n=6)	1240	Moderate vs. Healthy	132	93 – 187
	Severe (n=6)	1361	Severe vs. Healthy	145	102 – 205
	Healthy (n=6)	941	-	-	-
C_{max} (ng/mL)	Mild (n=6)	295	Mild vs. Healthy	115	71 – 188
	Moderate (n=6)	327	Moderate vs. Healthy	128	79 – 208
	Severe (n=6)	413	Severe vs. Healthy	162	99 – 263
	Healthy (n=6)	256	-	-	-

a: Model-based (least squares) geometric mean: ANOVA extracting the effects due to treatment

SCH5434128 exposures (AUC_{tf} and C_{max}) were higher in subjects with moderate (32% and 28%) and severe (45% and 62%) hepatic impairment relative to healthy subjects. The mean half-life of SCH534128 was longer in healthy subjects (8.6h) relative to subjects with hepatic impairment (range, 5.2 to 5.7h). However, the half-life in healthy subjects had a large coefficient of variation (86%). The T_{max} values of SCH534128 were similar across all groups. The table below summarizes the PK results of SCH534128 across cohorts.

Table 22 PK of SCH534128 following a single oral dose of boceprevir 400 mg to healthy subjects and to subjects with various levels of hepatic impairment.

Group	C_{max} (ng/mL) (%CV)	T_{max} (hr) (%CV)	AUC_{tf} (ng*hr/mL) (%CV)	AUC_{inf} (ng*hr/mL) (%CV)	$t_{1/2}$ (hr) (%CV)
Mild (n=6)	305 (25)	1.8 (1.0 – 3.0)	1070 (35)	1090 (35)	5.5 (49)
Moderate (n=6)	378 (57)	1.8 (1.0 – 3.5)	1290 (30)	1310 (29)	5.7 (70)
Severe (n=6)	471 (49)	3.0 (1.0 – 6.0)	1410 (29)	1420 (29)	5.2 (65)
Healthy (n=6)	269 (33)	1.5 (1.0 – 8.0)	1030 (39)	1010 (39)	8.6 (86)

As previously mentioned, reliable concentrations of boceprevir were not available in this trial due to problems during plasma sample bioanalysis. SCH534129 has a short frozen stability period (<15 days) in unacidified plasma. Investigators did not analyze the plasma samples for SCH534129 within the frozen stability period. Thus, SCH534129 concentrations were unreliable. Consequently, boceprevir exposures were also unreliable because boceprevir concentrations consist of the

sum of its two stereoisomers, SCH534129 and SCH534128.

SCH534128 is an acceptable surrogate analyte for evaluating the effect of hepatic impairment on the PK of boceprevir. SCH534128 is the active diastereomer of boceprevir. The ratio of active to inactive diastereomer is 2:1. The ratio remained unchanged throughout clinical trials, and diastereomer interconversion is negligible in plasma. Moreover, SCH534128 is stable in unacidified plasma under frozen conditions. In this trial, investigators identified and measured concentrations of SCH534128 for all subjects. For these reasons, it is logical to use SCH534128 exposures to evaluate the effect of hepatic impairment on the PK of boceprevir.

In summary, dose adjustment of boceprevir is not recommended in subjects with any degree of hepatic impairment. Subjects with severe hepatic impairment had mean AUC values of SCH534128 45% higher than healthy subjects. According to results from the exposure-response analysis, higher exposures of boceprevir are associated with increased incidence of anemia. However, subjects with severe hepatic impairment will not receive boceprevir, given that the proposed indication is for use in combination with pegylated interferon and ribavirin and these two drugs are contraindicated for use in subjects with Child-Pugh category B and C (Scores >6).

Two previous clinical trials (P04489 and P04486) with boceprevir established the safety of boceprevir at doses as high as 1200 mg TID for up to 20 days. The C_{max} and AUC at this dose were 15% and 22% higher, respectively, than the corresponding exposures at the therapeutic dose of 800 mg TID. At 1200 mg TID, investigators did not observe severe toxicities that would necessitate dose adjustments of boceprevir.

2.3.2.7 Genetics

IL28B Pharmacogenetics

A genetic polymorphism, rs12979860, near the IL28B gene (encoding interferon-lambda 3; hereafter referred to as “IL28B genotype”) is a strong predictor of SVR in patients receiving therapy with PR. Numerous studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype.

In the two Phase 3 trials (P05216, treatment-naïve; P05101, treatment-failure), DNA samples were collected on a voluntary basis. Treatment responses were evaluated according to IL28B genotype for 62% and 66% of the modified intent-to-treat populations of P05216 and P05101, respectively; some prognostic imbalances were observed, although SVR rates and treatment effects in the substudy were similar to the overall population. For a summary of the prognostic

imbalances, refer to the Genomics review, Table 3, page 350 in this document.

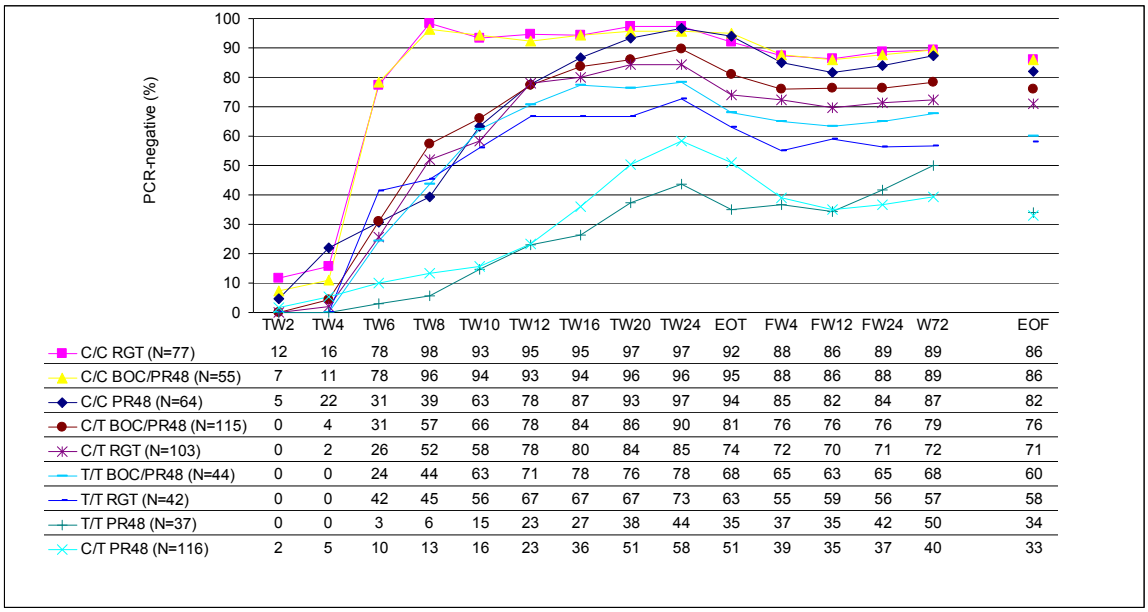
The Applicant's genetic substudy confirms previous reports of IL28B genotype effects on PR responses (Table 23). In treatment-naïve patients with the C/T and T/T genotypes, boceprevir-containing regimens resulted in significantly higher SVR rates than PR alone, whereas SVR rates did not differ significantly between the boceprevir-containing arms and PR alone in the C/C genotype subgroup (genotype x treatment interaction P=0.005). Among C/T and T/T patients, the number-needed to treat (NNT) with boceprevir to achieve one additional SVR was approximately 3 to 4 depending on the boceprevir regimen; among C/C patients the NNT was 27 for boceprevir RGT and 53 for boceprevir/PR48. In treatment-failure patients, IL28B genotype effects were less pronounced and treatment effects did not differ significantly based on IL28B genotype (genotype X treatment interaction P=0.60). However, the results in treatment-failure patients should be considered with caution because of the smaller sample size and selection of previous nonresponders. Pooled analysis of HCV-RNA changes at 4 weeks, reflecting the PR lead-in phase, confirmed that C/C patients have larger responses in both treatment-naïve and treatment-failure patients (not shown).

Table 23 Treatment comparisons by IL28B genotype X treatment interactions

Trial	IL28B Genotype	N	SVR, n/N (%)		
			PR48	RGT-BOC	BOC/PR48
P05216 (naïve)	C/C	196	50/64 (78)	63/77 (82)	44/55 (80)
	C/T	334	33/116 (28)	67/103 (65)	82/115 (71)
	T/T	123	10/37 (27)	23/42 (55)	26/44 (59)
P05101 (failure)	C/C	63	6/13 (46)	22/28 (79)	17/22 (77)
	C/T	157	5/29 (17)	38/62 (61)	48/66 (73)
	T/T	39	5/10 (50)	6/11 (55)	13/18 (72)

While SVR rates were similar for boceprevir-containing regimens and PR48 in treatment-naïve C/C patients, responses to boceprevir occurred more rapidly in patients with the C/C genotype relative to PR48 (Figure 17). The majority of C/C patients treated with boceprevir had undetectable HCV-RNA by TW8, whereas similar response rates were not achieved until TW24 for those treated with PR48.

Figure 17 Virologic response over time by genotype and treatment in treatment-naïve patients (P05216)



	TW2	TW4	TW6	TW8	TW10	TW12	TW16	TW20	TW24	EOT	FW4	FW12	FW24	W72	EOF
C/C RGT (N=77)	12	16	78	98	93	95	95	97	97	92	88	86	89	89	86
C/C BOC/PR48 (N=55)	7	11	78	96	94	93	94	96	96	95	88	86	88	89	86
C/C PR48 (N=64)	5	22	31	39	63	78	87	93	97	94	85	82	84	87	82
C/T BOC/PR48 (N=115)	0	4	31	57	66	78	84	86	90	81	76	76	76	79	76
C/T RGT (N=103)	0	2	26	52	58	78	80	84	85	74	72	70	71	72	71
T/T BOC/PR48 (N=44)	0	0	24	44	63	71	78	76	78	68	65	63	65	68	60
T/T RGT (N=42)	0	0	42	45	56	67	67	67	73	63	55	59	56	57	58
T/T PR48 (N=37)	0	0	3	6	15	23	27	38	44	35	37	35	42	50	34
C/T PR48 (N=116)	2	5	10	13	16	23	36	51	58	51	39	35	37	40	33

Overall, the findings of these retrospective substudies suggest that IL28B genotype is a major contributor to variable treatment responses. Properly controlled trials (e.g., enriched, stratified randomization) will be important to understand the role of IL28B genotyping in patient management.

ITPA polymorphisms have been associated with a lower risk for developing anemia in the course of PR therapy. In addition to IL28B, three ITPA polymorphisms were assayed in the genetic substudies of P05216 and P05101 as follows: rs1127354 (C>A, missense P32T), rs7270101 (A>C, intronic splicing-altering), and rs6051702 (A>C, tagging SNP). The missense and splice-altering polymorphisms are putative ITPA deficiency alleles; subjects were grouped according to the presence or absence of either or both of these alleles. Baseline hemoglobin did not differ according to the composite ITPA genotype. The incidence of anemia-related adverse events (i.e., hemoglobin nadir, absolute and percent change in hemoglobin, erythropoietin use, and DAIDS grade 3/4 anemia) was significantly lower among individuals with ITPA polymorphisms in both PR and the pooled boceprevir/PR arms (P<0.001).

2.3.2.8 What pregnancy and lactation use information is there in the application? Other human factors that are important to understanding the drug's efficacy and safety.

The Applicant did not evaluate the effect of boceprevir in pregnant and lactating women.

2.4. Extrinsic Factors

2.4.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

During clinical development, investigators evaluated various drug-drug interactions, as well as the effect of food on the pharmacokinetics of boceprevir. The drug-drug interaction between boceprevir and efavirenz is concerning because efavirenz decreased the steady-state C_{min} of boceprevir by 44%. More potent CYP3A inducers (e.g. rifampin, phenytoin) are expected to result in further decreases in boceprevir exposure. Lower C_{min} levels of boceprevir may reduce the antiviral efficacy of boceprevir. Phase 2 dose-ranging studies identified a relationship between boceprevir C_{min} and virologic response during monotherapy. However, the exposure-response analysis using Phase 3 data suggested the absence of an exposure-response relationship between boceprevir C_{min} and SVR at the therapeutic dose of boceprevir.

Ketoconazole caused an approximate doubling in boceprevir exposure in the drug-drug interaction trial. This increase in exposure is expected to increase the risk of anemia associated with boceprevir, based on the exposure-response relationship.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes, there is *in vitro* basis to suspect *in vivo* drug-drug interactions. See sections 2.4.2.2 and 2.4.2.3.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, the enzymes CYP3A4 and CYP3A5 metabolize boceprevir to a minor extent *in vivo*. The oxidative metabolites produced by CYP3A accounted for approximately 22.5% of the circulating radioactivity in plasma at 2 and 6 hours post ^{14}C-boceprevir dose.

2.4.2.3 Are there other metabolic/transporter pathways that may be important?

Yes, boceprevir is primarily metabolized by aldo-keto reductase enzymes.

The enzymes AKR1C2 and AKR1C3 metabolize boceprevir to produce M31 and M28, respectively. M31 and M28 are the most abundant metabolites of boceprevir in plasma. Investigators evaluated the *in vitro* metabolic potential of AKR enzymes by monitoring the formation of M28 and M31 in human liver cytosolic fractions in the presence of known AKR inhibitors (Study 03208). Results showed that flufenamic acid, diazepam, ibuprofen, and BNPP decreased the formation of M28 and M31 relative to the experimental control. The figure and table below summarize the results from this *in vitro* experiment.

Figure 18 Effect of inhibitors on the formation of M28 and M31 from 20 µM boceprevir with human liver cytosol (1.6 mg/mL)

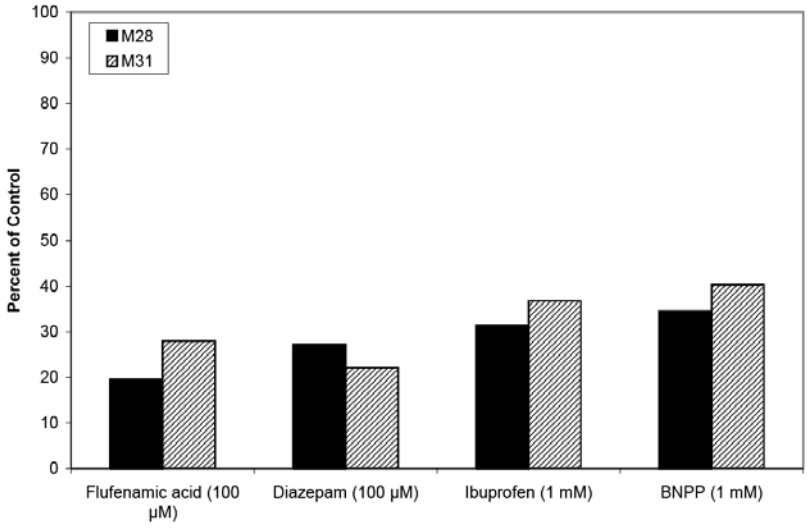


Table 24 Effect of inhibitors on the formation of M28 from boceprevir (20 µM) using pooled human liver cytosol (1.6 mg/mL, 60 minutes incubation)

Inhibitors	Conc (µM)	% of Inhibition
Diazepam	2	15.7
	10	40.3[a]
	100	75.1
Ibuprofen	50	31.3
	100	33.4
	1000	70
Ibuprofen[b]	100	25.9
Diazepam + Ibuprofen[b]	10 + 100	43.7
Midazolam	60	37
Flunitrazepam	60	51
Nitrazepam	50	24
Celecoxib	50	20.5
Naproxen	100	44.7
Ribavirin	10	1.76
	30	0
Ketoconazole	2	0
Ritonavir (coincubation)	2	0
Ritonavir (preincubation)	2	0
Indomethacin	100	19
Gemfibrozil	100	27.4
Phenobarbital	100	0
Testosterone	40	48.2

a: Average of duplicate determinations
b: Experiments done on the same day

Investigators have not evaluated the specificity of boceprevir towards hepatic transporters.

2.4.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Yes, boceprevir is a direct competitive inhibitor of CYP3A4. Boceprevir did not induce CYP450 enzymes *in vitro*.

Boceprevir causes direct inhibition of CYP3A4/5 both *in vitro* and *in vivo*. *In vitro*, boceprevir inhibited the metabolism of midazolam with an IC_{50} of 11 µM and a Ki value of 7.7 µM. *In vivo*, boceprevir increased the exposure of midazolam by 5-fold relative to reference exposures. These results confirm that boceprevir is a strong inhibitor of CYP3A4.

Boceprevir minimally inhibited other CYP450 enzymes *in vitro*. Inhibition of CYP1A2, CYP2A6, and CYP2D6 occurred at boceprevir concentrations >100 µM. Boceprevir is unlikely to inhibit these enzymes *in vivo* because the mean C_{max} of boceprevir is 3.5 µM at the therapeutic dose.

Boceprevir did not induce CYP450 enzymes *in vitro*. Investigators treated

cultured human hepatocytes for three consecutive days with boceprevir (1, 10 and 100 μM), and three known inducers of CYP450 enzymes, including omeprazole, phenobarbital, or rifampin. Results from this *in vitro* experiment (DM27368) showed that boceprevir caused little or no induction (induction defined as >2-fold increase in the metabolism of sensitive CYP450 substrates) of all the CYP450 enzymes examined. In contrast, the control inducers omeprazole, phenobarbital, and rifampin increased the activity of their respective target CYP450 enzymes. Induction was not assessed using mRNA. Because boceprevir is also an inhibitor of CYP450 enzymes, the induction findings from hepatocytes cultures could produce falsely negative results.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Boceprevir was an inhibitor of p-glycoprotein *in vitro*. In a Caco-2 cell bi-directional experiment (DM27866), boceprevir inhibited the efflux ratio of digoxin in a concentration dependent fashion. The IC_{50} for boceprevir was 25 μM versus 0.56 μM for CsA. The $[I]_2/IC_{50}$ ratio for boceprevir is 246. This $[I]_2/IC_{50}$ ratio indicates that boceprevir may interact with sensitive substrates of p-glycoprotein in the gut. However, the Applicant did not evaluate the drug-drug interaction between boceprevir and a sensitive substrate of P-glycoprotein in a clinical trial.

Boceprevir is also a substrate of p-glycoprotein. In the same Caco-2 cell bi-directional experiment, ketoconazole, ritonavir, and cyclosporine almost completely inhibited the efflux of boceprevir (efflux ratio <2). Of note, boceprevir saturated its own efflux ratio in a concentration-dependent manner, with the efflux ratio decreasing to <2 when boceprevir concentrations reached 500 μM.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes, the label indicates that clinicians must administer boceprevir in combination with pegylated interferon alpha and ribavirin.

Pegylated interferon alpha does not affect the pharmacokinetics of boceprevir. In clinical trial P03527, HCV-infected patients received multiple doses of boceprevir 200 mg or 400 mg TID alone or in combination with pegylated interferon alpha-2b (PegIntron®) 1.5 mg/kg once weekly. Boceprevir exposures (C_{max} and AUC) were similar during monotherapy relative to in combination with pegylated interferon. The following table summarizes results from the statistical analysis of the PK of boceprevir 200 mg or 400 mg TID in the presence or absence of pegylated interferon alpha-2b.

Table 25 Relative systemic exposure to boceprevir after dosing with boceprevir 200 mg TID or 400 mg TID monotherapy or in combination with PEG-Intron 1.5 mg/kg subcutaneously once weekly in HCV-infected patients (n=10).

Dose	Parameters	Ratio Estimate[a]	90% CI
200 mg TID	C_{max} (ng/mL)	94.6	76 – 118
	AUC_{tf} (ng*hr/mL)	109	94 – 126
400 mg TID	C_{max} (ng/mL)	88.2	66 – 118
	AUC_{tf} (ng*hr/mL)	100	89 – 113

a: Reference treatments were 200 mg TID and 400 mg TID boceprevir as monotherapy. Ratio expressed as percentage.

Likewise, boceprevir did not affect the pharmacokinetics of pegylated interferon alpha-2b. The following table summarizes the statistical results of pegylated interferon-alpha 2b in the presence of boceprevir. Of note, investigators combined data from two cohorts that evaluated two different doses of boceprevir, 200 mg TID and 400 mg TID.

Table 26 Relative systemic exposure to PEG-Intron after dosing with boceprevir in combination with PEG-Intron versus PEG-Intron monotherapy (combined data of 2 cohorts with different doses of boceprevir: 200 mg TID and 400 mg TID)

Parameters	Ratio Estimate[a] (90% Confidence Interval)
AUC(0 to168)	98.5 (83 to 117)

AUC(0 to168) = area under the plasma concentration-time curve over the 0 to 168 hours dosing interval

Cohort 1 = subjects assigned to the 200 mg TID SCH 503034 dose level. Cohort 2 = subjects assigned to the 400 mg TID SCH 503034 dose level.

a: Reference treatment was PEG-Intron as monotherapy for Cohorts 1 and 2 combined. Ratio expressed as a percentage.

The Applicant did not evaluate the potential drug interaction between boceprevir and ribavirin. We would not expect an interaction with these two drugs because ribavirin is renally eliminated and is not metabolized by CYP450 enzymes. Moreover, ribavirin does not induce or inhibit AKR, CYP450 enzymes, or P-glycoprotein.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Besides standard of care, HCV-infected patients may receive concomitant medications from the following drug classes.

- Anti-depressants (e.g. SSRIs)

- Erythropoietin stimulating factor (e.g. Epogen)
- Human granulocyte colony-stimulating factor (e.g. filgrastim)
- Opiate dependence treatments (e.g. methadone, buprenorphine)
- Anti-anxiolytics (e.g. lorazepam)
- Anti-insomnia agents (e.g. zolpidem)
- Anti-inflammatory and pain modulators (e.g. ibuprofen, acetaminophen)
- Antiemetics (e.g. dronabinol)
- Herbal remedies (e.g. milk thistle)
- Oral contraceptives
- Antibiotics and antifungals (e.g. ketoconazole)
- HIV medications (if approved for HCV/HIV co-infected subjects).

The medication list is not exhaustive. Subjects may take other drugs depending on their medical conditions.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes, the Applicant conducted four multi-part clinical trials to evaluate drug-drug interactions (DDIs) between boceprevir and substrates, inhibitors, and inducers of CYP3A4. The trials also evaluated DDIs between boceprevir and aldo-keto reductase inhibitors. Results from the DDI trials are summarized below. For the magnitude of drug-interaction, please refer to Tables 29 and 30.

1. Boceprevir is a substrate of CYP3A4.

The AUC of boceprevir increased in the presence of ketoconazole, a potent CYP3A4 inhibitor, relative to boceprevir alone. The C_{max}, C_{min}, and AUC of boceprevir decreased in the presence of ritonavir 100 mg BID relative to boceprevir alone. These results are unexpected because ritonavir is a potent inhibitor of CYP3A4; however, it may be an inducer of aldo-keto reductase enzymes.

Moreover, the C_{min} of boceprevir decreased in the presence of efavirenz, a moderate CYP3A4 inducer, relative to boceprevir alone.

2. Boceprevir is a strong inhibitor of CYP3A4.

The C_{max} and AUC of oral midazolam and drospirenone, both substrates of CYP3A4, increased in the presence of boceprevir. The C_{min} of ethinyl estradiol decreased unexpectedly in the presence of boceprevir relative to oral contraceptive alone. Of note, ethinyl estradiol is a substrate of CYP3A4 and UGT1A1. The effects of boceprevir on UGT1A1 are unknown.

3. Boceprevir is a substrate of AKR.
Boceprevir exposures (C_{max}, C_{min}, and AUC) increased (~20%) in the presence of diflunisal relative to boceprevir alone. Ibuprofen did not affect the PK of boceprevir.

4. Boceprevir is not an inhibitor of the renal transporters OAT1 and OAT3.
Boceprevir did not affect the exposure of tenofovir during co-administration.

The following table summarizes the PK parameters of boceprevir in the presence of the probes.

Table 27 Drug interactions: PK parameters of boceprevir in the presence of the co-administered drugs.

					Mean ratio of boceprevir pharmacokinetic parameters 90% CI; No effect = 1.00		
Trial	Probe	Dose	Dose of boceprevir	N	C_{max}	AUC	C_{min}
P03533	Ketoconazole	400 mg BID X 6 days	400 mg single dose	12	1.41 (1.00-1.97)	2.31 (2.00-2.67)	NA
P03533	Ibuprofen	600 mg TID X 6 days	400 mg single dose	12	0.94 (0.67-1.32)	1.04 (0.90-1.20)	NA
P05880	Tenofovir	300 mg QD X 7 days	800 mg TID X 7 days	16	1.05 (0.98-1.12)	1.08 (1.02-1.14)	1.08 (0.97-1.20)
P05880	Efavirenz	600 mg QD X 16 days	800 mg TID X 6 days	12	0.92 (0.78-1.08)	0.81 (0.75-0.89)	0.56 (0.42-0.74)
P04624	Diflunisal	250 mg BID X 8 days	400 mg BID X 7 days	12	1.29 (1.17-1.41)	1.25 (1.06-1.44)	1.20 (0.52-1.88)
P04624	Diflunisal	500 mg BID X 6 days	400 mg BID X 6 days	7	1.23 (0.94-1.61)	1.38 (1.21-1.58)	1.10 (0.79-1.54)
P04624	Diflunisal + Clarithromycin	Clarithromycin: 500 mg TID x 5 days Diflunisal: 500 mg TID x 11 days	Reference (boceprevir alone): 400 mg TID x 5 days Test: 400 mg BID X 10 days	7	1.67 (1.28-2.19)	1.67 (1.46-1.91)	0.94 (0.67-1.31)
P04624	Ritonavir	100 mg QD X 12 days	400 mg TID X 10 days	6	0.73 (0.57-0.93)	0.81 (0.73-0.91)	1.04 (0.62-1.75)
P04624	Ritonavir	100 mg BID X 12 days	400 mg BID X 10 days	6	0.66 (0.56-0.78)	0.82 (0.75-0.88)	0.52 (0.38-0.72)
P03527	PegIFN-α-2b	1.5 mg/kg QWK X 2 weeks	200 mg TID X 7 days	12	0.95 (0.76-1.18)	1.09 (0.94-1.26)	NA
P03527	PegIFN-α-2b	1.5 mg/kg QWK X 2 weeks	400 mg TID X 7 days	10	0.88 (0.66-1.18)	1.00 (0.89-1.13)	NA

NA= not available

The following table summarizes the PK parameters of the probes in the presence of boceprevir.

Table 28 Drug interactions: PK parameters of the probe in the presence of boceprevir.

					Mean ratio of Probe pharmacokinetic parameters 90% CI; No effect = 1.00		
Trial	Probe	Dose	Dose of boceprevir	N	C_{max}	AUC	C_{min}
P05880	Tenofovir	300 mg QD X 7 days	800 mg TID X 7 days	17	1.32 (1.19-1.45)	1.05 (1.01-1.09)	NA
P05880	Efavirenz	600 mg QD X 16 days	800 mg TID X 6 days	12	1.11 (1.02-1.20)	1.20 (1.15-1.26)	NA
P05880	Drospirenone	3 mg QD X 14 days	800 mg TID X 7 days	16	1.57 (1.46-1.70)	1.99 (1.87-2.11)	2.43 (2.25-2.62)
P05880	Ethinyl Estradiol	0.02 mg QD X 14 days	800 mg TID X 7 days	16	1.00 (0.91-1.10)	0.76 (0.73-0.79)	0.69 (0.65-0.73)
P05880	Midazolam	4 mg X 1 dose	800 mg TID X 6 days	12	2.77 (2.36-3.25)	5.30 (4.66-6.03)	NA
P03527	PegIFN-α-2b*	1.5 mg/kg QWK X 2 weeks	200 mg TID X 7 days 400 mg TID X 7 days	22	NA	0.98 (0.83-1.17)	NA

* Data combined from two cohorts with different boceprevir doses 200 mg TID and 400 mg TID. NA= Not available

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No, investigators have not identified potential pharmacodynamic drug-drug interactions with boceprevir.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Yes, the major outstanding clinical pharmacology issue for boceprevir is the lack of a fully characterized drug-drug interaction (DDI) profile. The Applicant assessed the impact of AKR inhibition (ibuprofen and diflunisal) and potent CYP3A4 inhibition (ketoconazole) on boceprevir pharmacokinetics *in vivo*; according to these results there is sufficient information to label boceprevir for safe use with inhibitors of AKR and CYP3A4. However, insufficient information is available to characterize the effect of boceprevir on other likely coadministered agents. Outstanding DDI issues include the following:

- The safety and efficacy of combined oral contraceptive (COC) use during boceprevir co-administration is insufficiently characterized. The completed DDI trial conducted with Yaz® (ethinyl estradiol/drospirenone) showed a 24% decrease in ethinyl estradiol (EE) exposure and a 100% increase in drospirenone (DRSP) exposure during boceprevir administration. The magnitude of increase in DRSP exposure may increase the risk of adverse events, including hyperkalemia and thromboembolism. It is unknown if the doubling of exposure would necessarily occur with other progestational components (e.g. norgestimate or norethindrone). The 25% decrease in EE exposure may result in breakthrough bleeding and may theoretically impact COC efficacy, though there is limited information in which to make a conclusion (please see consult from Dr. Gerald Willett, Division of Reproductive and Urinary Products). The DDI trial design had deficiencies that call into question the reliability of the trial results. As it may be unrealistic for women of childbearing potential to rely on two barrier methods while on concomitant treatment with ribavirin, the safety and efficacy implications of boceprevir coadministration with COCs should be further characterized. The Applicant has acknowledged these concerns and plans to conduct another clinical DDI study with another progestin-containing COC.

- DDI trials were not performed to assess the effect of boceprevir on methadone and buprenorphine PK, two important medications for the intended patient population. Although methadone is metabolized partially by CYP3A4, DDI studies with other potent inhibitors of CYP3A4, including ritonavir-boosted HIV protease inhibitors, have demonstrated unanticipated decreases in methadone exposure. The etiology of these results is unclear, but may involve mixed induction effects on CYP450 enzymes or uncharacterized transporter effects. Thus, the effect of boceprevir on methadone exposure cannot be accurately predicted based on *in vitro* experiments. The Applicant should assess the affect of boceprevir on methadone PK and PD in a drug interaction trial. Buprenorphine is less sensitive to interactions via CYP3A4,

given its alternative glucuronidation pathway, and has a relatively wide therapeutic index; therefore, a drug interaction with buprenorphine is not considered necessary.

- A DDI study was not conducted to assess the effect of boceprevir on antidepressant exposure. Unanticipated decreases in the exposure of selective serotonin reuptake inhibitors (SSRIs), including paroxetine, sertraline and escitalopram, have been observed in DDI studies conducted with other HCV and HIV protease inhibitors. Because the mechanism of these observed decreases have not been characterized, and given the importance of these agents in HCV patient care, an in vivo study is considered important to rule-out a potentially significant interaction.

- A DDI trial was not performed to characterize the effect of boceprevir on a sensitive P-glycoprotein (P-gp) substrate, such as a digoxin. Based on *in vitro* experiments, boceprevir has the potential to inhibit P-gp, particularly in the gut ($[I]_2/IC_{50}$ ratio = 246), which may result in clinically significant increases in the exposure of digoxin and other sensitive substrates.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

The proposed dose of boceprevir (800 mg TID with food) is appropriate; however, the label should state that boceprevir doses are to be administered 7-9 hours apart, consistent with the dosing interval defined in the Phase 3 trials. In addition, the PM reviewer has recommended revisions to the duration of therapy using RGT for treatment naive patients. Refer to section 2.2.4.4.

2.5. General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The Applicant has characterized boceprevir is a BCS class 4 compound with low solubility and low permeability. Boceprevir hydrolyses at low pH and degrades at pH>7.5. The following table summarizes the dissolution method parameters of boceprevir in the final commercial formulation.

Table 29 Dissolution method parameters for boceprevir in the final commercial formulation ((b) (4) SLS).

Parameter	Description
Apparatus	USP II, Paddles Method
Spindle Speed	50 rpm
Medium	900 mL of 0.05 M phosphate with 0.1% SLS, pH 6.8
Sample Analysis	HPLC

HPLC = high performance liquid chromatography; rpm = rotations per minute; SLS = sodium lauryl sulfate; USP = United States Pharmacopeia.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The Phase 3 pivotal trials used the proposed commercial formulation of boceprevir. Therefore, a bioequivalence trial was not necessary.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food increases the exposure (AUC and C_{max}) of boceprevir. The timing of dose relative to food intake (immediately before, during, or immediately after a meal) does not affect exposure. A high-fat meal results in slightly higher absorption relative to a low-fat meal (~10-15% higher AUC), though the difference is unlikely to be clinically significant. In the pivotal Phase 3 trials, P05216 and P05101, subjects were instructed to take all boceprevir doses with food. While the protocols state that dosing of boceprevir with a meal is "ideal," a "small snack, such as a piece of fruit or crackers," was considered adequate. Thus, administration directions in the label that direct patients to take boceprevir "with food," are appropriate.

Three clinical trials evaluated the effect of food type and food timing on the PK of boceprevir. The next section lists the results from each trial.

Effect of low fat meal on the PK of boceprevir using the commercial formulation (Trial P03533):

This food effect trial enrolled nine healthy subjects who ingested a single dose of boceprevir 400 mg with and without a low-fat breakfast. The following table summarizes the components of the meal.

Table 30 Meal components in trial P3533

Standardized Low-Fat Breakfast			
Item	Amount	Calories	Fat (Gm)
Croissant	1.5 oz	175	9
Cheese	1 oz	100	8
Whole Milk	4 oz	80	4
Jam	1/2 oz	39	0
Sugar	1 tsp	16	0
Fruit	2 oz	40	0
Total		450	21

The proposed commercial formulation ((b) (4) SLS) of boceprevir delivered 65% higher exposures (AUC_{tf}) of boceprevir under fed conditions with a low fat meal relative to fasting conditions. The following table displays the statistical results of this trial.

Analyte	Comparison	N	AUC_{tf} (ng*hr/mL)		C_{max} (ng/mL)	
			Ratio (%)	90% CI	Ratio (%)	90% CI
SCH503034	**Boceprevir 400 mg in (b) (4) SLS, low fat vs. fast**	**8**	**165**	**132-207**	**168**	**116-244**

Effect of food timing on the PK of boceprevir using the commercial formulation (Trial P04133):

This trial enrolled twelve healthy subjects who ingested a single 400 mg dose of boceprevir in 4 separate periods. The first three periods evaluated the PK of boceprevir after subjects ingested their dose immediately prior to a low-fat breakfast, during breakfast, or immediately after breakfast. The last period evaluated the PK of boceprevir under fasting conditions. The following table summarizes the components of the meal.

Standardized Low-Fat Breakfast			
Item	Amount	Calories	Fat (gm)
Croissant	1.5 oz	175	9
Cheese	1 oz	100	8
Whole Milk	4 oz	80	4
Jam	½ oz	39	0
Sugar	1 tsp	16	0
Fruit	2 oz	40	0
Total		450	21

Boceprevir exposures (AUC_{inf}) increased similarly when boceprevir was administered 5 minutes prior to (↑ 37%), during (↑ 35%), or immediately after completing (↑ 41%) a low fat meal relative to fasting conditions. The following table displays the statistical results of this trial.

Table 31 Overall comparisons between treatments for boceprevir in all subjects

Analyte	Treatment Group	PK Parameter	n	LS Means	Treatment Comparison	Ratio Estimate	90% Confidence Interval
SCH 503034	A	AUC(I)	11	2915.5	A vs D	137	124-150
	B	AUC(I)	12	2869.2	B vs D	135	123-147
	C	AUC(I)	12	3010.1	C vs D	141	129-155
	D	AUC(I)	12	2132.9	A vs B	102	92-112
	--	AUC(I)	--	--	A vs C	97	88-106
	--	AUC(I)	--	--	B vs C	95	87-104
	A	AUC(tf)	11	2887.9	A vs D	137	125-151
	B	AUC(tf)	12	2847.2	B vs D	135	123-148
	C	AUC(tf)	12	2986.7	C vs D	142	129-156
	D	AUC(tf)	12	2104.6	A vs B	101	92-112
	--	AUC(tf)	--	--	A vs C	97	88-106
	--	AUC(tf)	--	--	B vs C	95	87-105
	A	Cmax	11	899.5	A vs D	122	105-142
	B	Cmax	12	890.6	B vs D	121	104-140
	C	Cmax	12	1051.1	C vs D	142	123-165
	D	Cmax	12	738.6	A vs B	101	87-118
	--	Cmax	--	--	A vs C	86	73-100
	--	Cmax	--	--	B vs C	85	73-98

LS = least-square

Treatment A: Boceprevir capsules administered immediately prior to breakfast
Treatment B: Boceprevir capsules administered during breakfast
Treatment C: Boceprevir capsules administered immediately after breakfast
Treatment D: Boceprevir capsules administered in the fasted state

Effect of high fat vs. low fat meals on the PK of boceprevir using the commercial formulation (Trial P04488):

This trial enrolled thirteen healthy subjects, 6 Caucasians and 7 Japanese. Subjects received three doses of boceprevir at 200 mg, 400 mg, and 800 mg in the fasted state, after a high fat western meal, and after a low fat Japanese meal. The following tables summarize the components of the meals.

Table 32 Contents of the Western high fat meal

Standardized High-Fat Breakfast					
Item	Amount	Calories	Protein (gm)	Fat (gm)	Carbohydrate (gm)
Eggs (Fried)	2	191	14	15	-
Bacon (Strip)	2	96	3.6	8.8	0.4
Toast (Slice)	2	136	4	-	30
Butter (Pat)	2	90	-	10	-
Hash Browned Potatoes	4 oz	158	2	10	15
Whole Milk	8 oz	170	8	10	12
Total		841	31.6	53.8	57.4

Table 33 Contents of the Japanese Meal

Standardized Japanese Breakfast					
Item	Amount	Calories	Protein (gm)	Fat (gm)	Carbohydrate (gm)
Steamed White Rice	1 bowl	205	4g	0.5g	45g
Miso soup	1 bowl	36	2g	1g	5g
Steamed vegetables	½ Cup	20	2g	0g	5g
Fish with some soy sauce	6 oz	250	47g	7g	0
Total		**511**	**55**	**8.5**	**55**

Boceprevir exposures (AUC and C_{max}) were higher when single doses of boceprevir 200 mg, 400 mg, and 800 mg were administered with a high-fat Western meal or a low-fat Japanese meal relative to fasting conditions in Caucasian and Japanese subjects. The food effect was more pronounced with higher doses. The mean ratio estimate for AUC at a single dose of 800 mg ranged from 142% to 196% under low-fat or high-fat fed conditions relative to fasted. Exposure was slightly higher under high-fat conditions relative to low-fat in both Japanese and Caucasians (~10-15%). The mean ratio of diastereomers SCH534128 and SCH534129 were similar regardless of food intake, suggesting the ratio is unaffected by food.

Boceprevir exposures (AUC) were similar in Japanese and Caucasian subjects following single doses of boceprevir 200 mg, 400 mg, and 800 mg under fed conditions with a high or low fat meal.

The following table summarizes the PK of boceprevir when administered in the fasted state, with a high fat meal, or with a low fat meal at the therapeutic dose of 800 mg.

Table 34 Food Effect (high-fat or low-fat vs. fasted) at 800 mg dose in Caucasian and Japanese subjects

.

			LS Means			High-fat vs. Fasted		Low-fat vs. High-fat		Low-fat vs. Fasted	
Food	Dose	n	Fasted	High-fat Meal	Low-fat Meal	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
Caucasian	AUC_{inf}	6	3959	6315	5630	159	130-196	89	73-109	142	116-174
	AUC_{tf}	6	3914	6301	5543	161	131-198	88	71-108	142	115-174
	Cmax	6	1134	1684	1417	148	102-216	84	58-123	125	86-182
Japanese	AUC_{inf}	6	3251	6277	5371	193	162-229	86	72-102	165	139-196
	AUC_{tf}	6	3190	6263	5341	196	165-233	85	72-101	167	141-199
	Cmax	6	1002	2001	1763	200	156-255	88	69-113	176	138-225

2.6. Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the

clinical pharmacology and biopharmaceutics studies?

The Applicant identified and measured boceprevir (SCH503034), SCH534128, and SCH534129 in plasma using validated LC-MS/MS methods.

2.6.2 Which metabolites have been selected for analysis and why?

The Applicant monitored the formation of four metabolites of boceprevir throughout clinical development. The metabolites, SCH783004 (M31), SCH783005, SCH783006 (M30), and SCH783007 (M28), are stereoisomers. Combined, M31, M30, and M28 accounted for approximately 46% to 70% of the circulating radioactivity in plasma within 2-hr and 6-hr post dose of ^{14}C-boceprevir (P03588). Metabolite SCH783005 exists in very low concentrations and it is difficult to measure in plasma. Investigators report the sum of all four metabolites as SCH629144.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision and is it appropriate?

Bioanalytical methods measured the total concentrations of boceprevir, SCH534128, SCH534129, or SCH629144 in plasma. Measuring total plasma concentrations of boceprevir was appropriate because boceprevir is not highly protein bound in plasma (~70% bound). Thus, changes in the extent of plasma binding may not affect the pharmacologically active fraction of boceprevir.

2.6.4 What bioanalytical methods are used to assess concentrations?

The following table summarizes the bioanalytical assay methods, calibration standards, and quality controls used to support the pharmacokinetic parameters for boceprevir and other probes evaluated in clinical trials.

Table 35 Summary of bioanalytical methods used in clinical pharmacology trials with boceprevir

					Calibration Standards			Quality Controls	
Report number	Method	Biological Matrix	Analyte	Calibration Range	Precision (%CV)	Accuracy (% relative error)	R	Precision (%CV)	Accuracy (% relative error)
P03533	SN03330	Plasma	Boceprevir	2.5 – 1250 ng/mL	2.3 – 4.4	≤1.8	≥0.9966	3.9 – 4.9	≤3.6
	SN04921	Plasma	SCH534128	1.3 – 665 ng/mL	2.5 – 6.8	≤4.2	≥0.9929	4.7 – 8.9	≤5.3
P03588	DM27341	Plasma	SCH534128	5.2 – 5240 ng/mL	4.1 – 10.2	≤2.9	≥0.9947	4.1 – 14.9	≤6.4
			SCH534129	4.8 – 4760 ng/mL	1.5 – 8.4	≤4.2	≥0.9959	5.1 – 16.1	≤9.0
			SCH783004	2.5 – 2500 ng/mL	4.8 – 10.5	≤4.0	≥0.9940	3.3 – 30.9	≤19.1
			SCH783005	2.5 – 2500 ng/mL	0.6 – 11.8	≤4.0	≥0.9931	2.8 – 26.1	≤14.4
			SCH783006	2.5 – 2500 ng/mL	3.4 – 10.5	≤3.0	≥0.9938	5.1 – 31.1	≤14.9
			SCH783007	2.5 – 2500 ng/mL	3.4 – 9.0	≤4.0	≥0.9950	4.0 – 28.9	≤11.7
P03747	SN04921	Plasma	SCH534128	1.3 – 665 ng/mL	1.7 - 6.8	≤3.8	≥0.9959	3.7 – 10.8	≤5.7
P04133	DM27268	Plasma	SCH534128	1.3 – 655 ng/mL	1.8 – 4.2	≤2.3	≥0.9975	4.1 – 7.8	≤3.6
			SCH534129	1.2 – 595 ng/mL	1.8 – 3.4	≤2.9	≥0.9976	3.1 – 5.3	≤5.3
P04486	DM27268	Plasma	SCH534128	1.3 – 655 ng/mL	1.6 – 4.7	≤1.5	≥0.9986	1.8 – 5.3	≤7.3
	SN04921	Plasma	SCH534129	1.2 – 595 ng/mL	2.1 – 6.3	≤4.3	≥0.9961	4.1 – 7.1	≤6.4
	DM27268	Plasma	SCH534129	1.2 – 595 ng/mL	1.2 – 6.0	≤3.4	≥0.9963	3.4 – 5.0	≤9.3
	DM27347	Plasma	Diflunisal	1.0 – 100 µg/mL	2.0 – 7.7	≤4.2	≥0.9976	3.2 – 6.1	≤4.8

P04624	DM27341	Plasma	SCH534128	5.2 – 5240 ng/mL	0.7 – 5.2	≤2.9	≥0.9987	2.0 – 7.6	≤8.8
		Plasma	SCH534129	4.8 – 4760 ng/mL	0.7 – 5.9	≤3.7	≥0.9977	2.7 – 8.0	≤9.9
		Plasma	SCH783004	2.5 – 2500 ng/mL	2.8 – 6.6	≤1.5	≥0.9949	4.9 – 7.4	≤9.6
		Plasma	SCH783005	2.5 – 2500 ng/mL	3.2 – 5.5	≤1.2	≥0.9942	4.3 – 5.7	≤2.9
		Plasma	SCH783006	2.5 – 2500 ng/mL	2.7 – 4.9	≤2.7	≥0.9952	2.1 – 6.2	≤10.6
		Plasma	SCH783007	2.5 – 2500 ng/mL	2.9 – 6.0	≤3.6	≥0.9943	4.9 – 7.3	≤4.7
	DM27347	Plasma	Diflunisal	1 – 100 µg/mL	1.9 – 7.7	≤4.2	≥0.9976	3.2 – 6.1	≤4.8
	DM27431	Plasma	Clarithromycin	0.2 – 10 µg/mL	1.8 – 4.9	≤10.8	≥0.9970	1.3 – 9.5	≤7.5
	SN03433	Plasma	Ritonavir	0.1 – 10 µg/mL	1.9 – 4.9	≤10.8	≥0.9970	2.0 – 4.0	≤11.3
P05579	DM27341	Plasma	SCH534128	5.2 – 5240 ng/mL	1.6 – 4.9	≤2.7	≥0.9968	2.5 – 6.5	≤2.3
			SCH534129	4.8 – 4760 ng/mL	2.2 – 5.3	≤3.2	≥0.9968	2.4 – 5.5	≤2.8
			SCH783004	2.5 – 2500 ng/mL	2.9 – 5.7	≤2.4	≥0.9947	2.8 – 6.9	≤3.2
			SCH783005	2.5 – 2500 ng/mL	1.6 – 5.5	≤1.6	≥0.9961	5.6 – 1.3	≤1.6
			SCH783006	2.5 – 2500 ng/mL	2.2 – 4.9	≤1.8	≥0.9968	1.6 – 6.7	≤1.3
			SCH783007	2.5 – 2500 ng/mL	2.0 – 5.8	≤1.4	≥0.9960	0.5 – 6.2	≤2.0
	DM27655	Ultrafiltrate	SCH534128	5.2 – 5240 ng/mL	2.2 – 12.0	≤2.9	≥0.9959	1.8 – 6.7	≤7.6
			SCH534129	4.8 – 4760 ng/mL	0.8 – 11.7	≤5.5	≥0.9963	2.1 – 5.6	≤14.6
			SCH783004	2.5 – 2500 ng/mL	0.0 – 12.2	≤3.2	≥0.9984	1.1 – 13.3	≤8.0
			SCH783005	2.5 – 2500 ng/mL	0.7 – 9.4	≤3.6	≥0.9981	1.4 – 12.9	≤17.6
			SCH783006	2.5 – 2500 ng/mL	0.0 – 5.6	≤3.2	≥0.9991	1.4 – 12.9	≤17.6
			SCH783007	2.5 – 2500 ng/mL	0.0 – 12.2	≤3.2	≥0.9984	1.1 – 13.3	≤8.0
	DM27643	Dialysate	SCH534128	4.8 – 4760 ng/mL	1.6 – 5.4	≤2.4	≥0.9959	3.2 – 9.3	≤6.9
			SCH534129	2.5 – 2500 ng/mL	1.8 – 9.6	≤3.6	≥0.9949	4.2 – 6.2	≤10.1
			SCH783004	2.5 – 2500 ng/mL	1.8 – 6.8	≤2.6	≥0.9953	3.6 – 9.9	≤9.8
			SCH783005	2.5 – 2500 ng/mL	1.7 – 6.2	≤3.5	≥0.9970	3.6 – 10.0	≤7.0
			SCH783006	2.5 – 2500 ng/mL	1.6 – 5.6	≤2.6	≥0.9968	4.3 – 9.2	≤8.3
			SCH783007	2.5 – 2500 ng/mL	1.5 – 4.2	≤2.8	≥0.9982	3.1 – 8.9	≤7.2
	DM27662	Urine	SCH534128	4.8 – 4760 ng/mL	2.3 – 7.3	≤7.3	≥0.9949	6.0 – 17.1	≤12.9
			SCH534129	2.5 – 2500 ng/mL	1.9 – 5.1	≤3.4	≥0.9971	3.7 – 18.8	≤12.4
			SCH783004	2.5 – 2500 ng/mL	1.9 – 6.9	≤2.0	≥0.9970	3.4 – 19.9	≤11.2
			SCH783005	2.5 – 2500 ng/mL	0.8 – 5.9	≤2.4	≥0.9980	2.4 – 16.0	≤13.8
			SCH783006	2.5 – 2500 ng/mL	1.7 – 6.6	≤3.6	≥0.9965	3.6 – 16.3	≤13.8
			SCH783007	2.5 – 2500 ng/mL	2.0 – 5.0	≤2.4	≥0.9974	3.0 – 22.6	≤12.8
P05880	DM27341	Plasma	SCH534128	5.3 – 5250 ng/mL	1.1 - 5.4	≤2.4	≥0.9976	1.0 - 17.6	≤5.3
			SCH534129	4.8 – 4750 ng/mL	1.1 - 4.8	≤2.6	≥0.9978	1.2 - 17.6	≤5.0
			SCH783004	2.5 – 2500 ng/mL	2.0 - 6.1	≤1.0	≥0.9948	2.9 - 7.1	≤6.4
			SCH783005	2.5 – 2500 ng/mL	1.9 - 5.4	≤1.7	≥0.9956	2.9 - 7.1	≤6.4
			SCH783006	2.5 – 2500 ng/mL	2.2 - 4.8	≤1.6	≥0.9965	1.0 - 11.1	≤3.2
			SCH783007	2.5 – 2500 ng/mL	2.6 - 5.1	≤2.8	≥0.9947	0.8 - 11.5	≤3.6
	DM27802	Plasma	Midazolam	0.1 – 50 ng/mL	2.7 - 8.9	≤6.0	≥0.9931	3.6 - 7.5	≤5.0
			1-OH-midazolam	0.1 – 50 ng/mL	2.2 - 7.5	≤3.5	≥0.9945	4.6 - 7.9	≤1.5
	DM27810	Plasma	Efavirenz	10 – 8000 ng/mL	0.6 - 7.2	≤11.8	≥0.9936	3.1 - 7.3	≤9.7
	DM28025	Plasma	Tenofovir	5.0 – 1000 ng/mL	2.1 - 5.7	≤3.8	≥0.9984	2.2 - 6.9	≤4.7
	DM28026	Urine	Tenofovir	50 – 5000 ng/mL	3.5 - 6.6	≤5.0	≥0.9915	5.5 - 7.7	≤3.3
	DM28024	Plasma	Drospirenone	0.5 – 200 ng/mL	1.2 - 6.8	≤3.2	≥0.9972	1.9 - 5.5	≤2.7
	DM28023	Plasma	Ethinyl estradiol	1.0 – 200 ng/mL	2.9 - 6.5	≤3.1	≥0.9937	1.1 - 5.3	≤6.2

Investigators encountered the following issues during sample bioanalysis. Note, we considered these bioanalytical issues during data interpretation.

- Hepatic impairment trial (P03747): The Applicant analyzed all plasma samples within the frozen stability timeframe for SCH534128, but not for SCH534129. Samples for SCH534129 expired before bioanalysis.

  Initially, investigators used a chiral LC-MS/MS method (SN 04921) to measure the individual concentrations of SCH534128 and SCH534129 in non-acidified plasma. During method validation, investigators collected sufficient in process and frozen storage stability for SCH534128, but not for SCH534129. Therefore, concentrations of SCH534129 were unreliable.

Subsequently, investigators used an achiral method (SN 03330) to measure the concentrations of boceprevir in non-acidified plasma. The method determined boceprevir concentrations, but it did not resolve the two diastereomers SCH534128 and SCH534129. Boceprevir concentrations were unusable for the purposes of data interpretation, because method 03330 was only used for Groups 1 and 2 (and one subject from Group 3).

The plasma samples collected from this trial were analyzed as listed below:

Group	Subjects	1st Method	2nd Method
1	6/6	SN 03330	SN 04921
2	6/6	SN 03330	SN 04921
3	1/6	SN 03330	SN 04921
	5/6	SN 04921	-
4	6/6	SN 04921	-

Of note, all plasma samples were assayed with method SN 04921. Method SN 04921 reliably measured the concentrations of SCH534128 in all samples. Thus, data interpretation was based on concentrations of SCH534128 only.

- Boceprevir dose proportionality in trial P04486: Faulty bioanalytical assays rendered the concentrations of boceprevir from Groups 1, 2, and 5 unreliable. After the first sample analysis, investigators observed unexpected concentrations of boceprevir. Suspicious of dilution errors, investigators re-analyzed the plasma samples only to discover that concentrations from the two runs did not meet the acceptable bioanalytical criteria (within ± 20% of the initial concentrations). What is more, some samples exceeded the frozen stability period for bioanalysis. Consequently, the concentrations of boceprevir from groups 1, 2, and 5 were unreliable. We did not report PK or dose proportionality data for boceprevir from this trial.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Refer to Table 35.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Refer to Table 35.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Refer to Table 35.

2.6.4.4 What is the sample stability under the conditions used in the study?

All analytes were stable in acidified plasma at the storage conditions specified by the Applicant. However, SCH534129 had short (<15 days) stability in un-acidified plasma under frozen conditions. This stability issue was corrected in the bioanalytical methods used for the phase 3 pivotal trials. In clinical trials where SCH534129 could not be accurately measured, SCH534128 was reported instead. For example, data interpretation was based on SCH534218 in the hepatic impairment trial (P03747).

2.6.4.5 What is the QC sample plan?

For the analytical methods, QC samples were prepared in the appropriate medium (plasma, urine, ultrafiltrate, and dialysate) to assess the precision and accuracy of the method within each batch and inter-batch, as well as to determine the stability of boceprevir and its diastereomers. The following section summarizes the trials, LC-MS/MS methods, and their respective QC sample plan.

Trial P03533

- Method SN03330
  - QC samples were prepared for analysis of boceprevir (SCH503034) in human plasma at concentrations of 0.5, 1.5, 75, and 750 ng/mL.

- Method SN04921
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 3.93, 79.5, and 477 ng/mL.

  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 3.53, 70.5, and 423 ng/mL.

Trial P03588

- Method DM27341
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 5.24, 15.7, 262, 1310, and 3930 ng/mL.

  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 4.76, 14.3, 238, 1190, and 3570 ng/mL.

Trial P03747

- Method SN04921
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 3.93, 3.98, 78.6, 79.5, 472, and 477 ng/mL.

  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 3.53, 70.5, and 423 ng/mL

Trial P04133

- Method DM27268
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 1.31, 3.93, 78.6, and 472 ng/mL.

- QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 1.19, 3.57, 71.4, and 428 ng/mL.

Trial P04486

- Method SN04921
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 3.93, 3.98, 78.6, 79.5, 472, and 477 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 3.53, 70.5, and 423 ng/mL.
- Method DM27268
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 1.31, 3.93, 78.6, and 472 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 1.19, 3.57, 71.4, and 428 ng/mL.
- Method DM27347
  - QC samples were prepared for analysis of diflunisal in human plasma at concentrations of 0.1, 0.3, 0.8, 3.0, 12.0, and 75.0 μg/mL

Trial P04624

- Method DM27341
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 5.24, 15.7, 262, 1310, and 3930 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 4.76, 14.3, 238, 1190, and 3570 ng/mL.
- Method DM27347
  - QC samples were prepared for analysis of diflunisal in human plasma at concentrations of 0.1, 0.3, 0.8, 3.0, 12.0, and 75.0 μg/mL
- Method DM27431
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 5.24, 15.7, 262, 1310, and 3930 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 4.76, 14.3, 238, 1190, and 3570 ng/mL.
  - QC samples were prepared for analysis of SCH783004, SCH783005, SCH783006, and SCH783007 in acidified human plasma at concentrations of 2.5, 7.5, 125, 625, and 1880 ng/mL.
- Method SN03433
  - QC samples were prepared for analysis of ritonavir in human plasma at concentrations of 10, 25, 5000, 8000, and 10,000 ng/mL.

Trial P05579

- Method DM27341
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 5.24, 15.7, 262, 1310, and 3930 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 4.76, 14.3, 238, 1190, and 3570 ng/mL.
- Method DM27655
  - QC samples were prepared for analysis of SCH534128 in acidified human ultrafiltrate at concentrations of 5.25, 15.8, 263, 1310, and 3490 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified human ultrafiltrate at concentrations of 4.75, 14.3, 238, 1190, and 3560 ng/mL.
  - QC samples were prepared for analysis of SCH783004, SCH783005, SCH783006, and SCH783007 in acidified human ultrafiltrate at concentrations of 2.5, 7.5, 125, 625, and 1880 ng/mL
- Method DM27643
  - QC samples were prepared for analysis of SCH534128 in acidified dialysate at concentrations of 15.8, 263, 1310, and 3940 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified dialysate at concentrations of 14.3, 238, 1190, and 3560 ng/mL.
  - QC samples were prepared for analysis of SCH783004, SCH783005, SCH783006, and SCH783007 in acidified dialysate at concentrations of 7.5, 125, 6.25, and 1880 ng/mL.
- Method DM27662
  - QC samples were prepared for analysis of SCH534128 in acidified human urine at concentrations of 15.8, 263, 1310, and 3940 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified human urine at concentrations of 14.3, 238, 1190, and 3560 ng/mL.

Trial P05880

- Method DM27341
  - QC samples were prepared for analysis of SCH534128 in acidified human plasma at concentrations of 5.24, 15.7, 262, 1310, and 3930 ng/mL.
  - QC samples were prepared for analysis of SCH534129 in acidified human plasma at concentrations of 4.76, 14.3, 238, 1190, and 3570 ng/mL.
- Method DM27802
  - QC samples were prepared for analysis of midazolam and 1-OH-midazolam in human plasma at concentrations of 0.3, 3, and 20 ng/mL.
- Method DM27810
  - QC samples were prepared for analysis of efavirenz in human plasma at

concentrations of 30, 400, and 6000 ng/mL.

- Method DM28023
  - QC samples were prepared for analysis of ethinyl estradiol in human plasma + K_2 EDTA at concentrations of 2.99, 9.98, 69.9, 150, and 2000 pg/mL.

- Method DM28024
  - QC samples were prepared for analysis of drospirenone in human plasma + K_2 EDTA at concentrations of 1500, 20000, 60100, and 140000 pg/mL.

- Method DM28025
  - QC samples were prepared for analysis of tenofovir in human plasma at concentrations of 10, 25, 75, 200, and 750 ng/mL.

- Method DM28026
  - QC samples were prepared for analysis of tenofovir in human urine at concentrations of 150, 1500, 4000, and 18800 ng/mL.

3. Detailed Labeling Recommendations

Refer to section 4.1 below.

4. Appendices

4.1. Proposed Package Insert (Original with annotations)

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Clinical pharmacology and biopharmaceutics individual study review

4.2.1 General pharmacokinetics

Trial P03533

A multi-part trial to evaluate the effect of formulation on the bioavailability of boceprevir

Dates

July 18, 2005 to November 14, 2005.

Trial Site

Parkway Research Center, Inc., 150 N.W. 168th Street, Suite 300, North Miami Beach, Florida 33169, USA

Summary of Reviewer's Findings

- The (b) (4) SLS-containing formulation delivered 35% higher exposures (AUC_{tf}) of boceprevir relative to the original formulation under fasting conditions. Subjects safely tolerated the new formulation. Hence, investigators continued developing boceprevir using the (b) (4) SLS-containing formulation. The (b) (4) SLS-containing formulation is the proposed commercial formulation for boceprevir.

- The (b) (4) SLS-containing formulation delivered 65% higher exposures (AUC_{tf}) of boceprevir under fed conditions (low fat meal) relative to fasting conditions. Boceprevir should be administered with meals.

- Ketoconazole increased the mean AUC_{tf} and C_{max} ratios of boceprevir by 231% and 141%, respectively, during co-administration with boceprevir relative to administration of boceprevir alone.

- Ibuprofen did not affect the exposures of boceprevir during co-administration relative to administration of boceprevir alone. In previous clinical trials with boceprevir, diflunisal did not significantly alter the PK of boceprevir. Thus, boceprevir may be co-administered with strong inhibitors of AKR.

Trial Objectives

Part 1 aimed to determine whether three new formulations of boceprevir

containing sodium lauryl sulfate (SLS) improved the bioavailability of boceprevir versus the original [redacted] capsule formulation.

Part 2 aimed to determine the effect of food on the relative bioavailability of boceprevir administered in two SLS-containing capsule formulations compared to the original formulation.

Part 4 aimed to evaluate the effect of ketoconazole and ibuprofen on the PK of boceprevir.

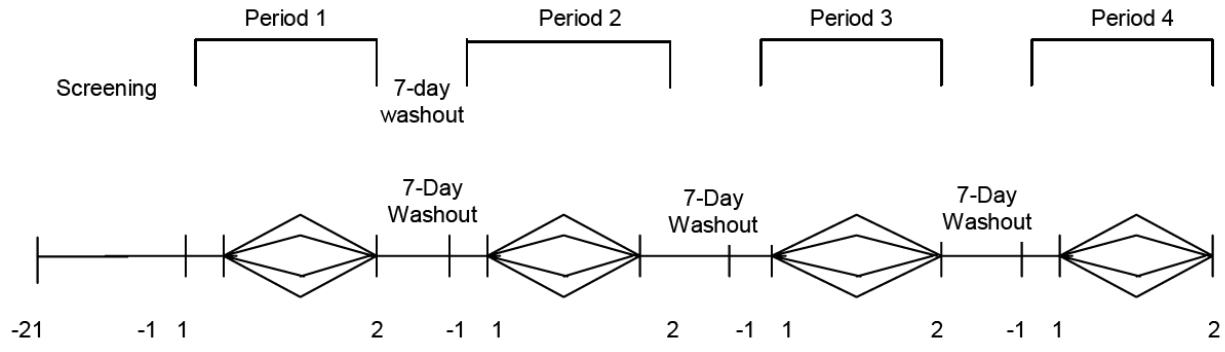
Trial Design

This was a phase 1, single-center, open-label, randomized trial in healthy subjects. The trial consisted of four parts. This review discusses parts 1, 2, and 4, but not part 3. Part 3 evaluated solution formulations of boceprevir that were not developed. Parts 1, 2, and 4 are summarized below.

Part 1 was a 4-treatment, 4-period, crossover sub-trial evaluating the PK of boceprevir in three new SLS-containing formulations compared to the original formulation. Twelve healthy subjects were randomized to receive a single dose of 400 mg boceprevir in the fasted state. All subjects served as their own controls and crossed over to receive the 4 formulations of boceprevir on 4 separate periods. A 7-day washout period was observed before crossing over to a new formulation. All subjects received active treatment (no placebo). The following figure illustrates the design of Part 1.

Treatment A: Oral boceprevir 400 mg [redacted]
Treatment B: Oral boceprevir 400 mg (2 X 200 mg capsules [redacted] SLS).
Treatment C: Oral boceprevir 400 mg (2 X 200 mg capsules, [redacted] SLS).
Treatment D: Oral boceprevir 400 mg (2 X 200 mg capsules [redacted] SLS).

Figure 1 Open-label, randomized, four-treatment, four-period crossover trial (Part 1)



Part 2 was an open-label, 5-treatment, 3-period crossover, and 2-period with

fixed sequence sub-trial. The sub-trial evaluated the effect of food on the relative bioavailability of boceprevir in two SLS-containing formulations compared to the original formulation. Nine subjects received single 400 mg doses of boceprevir in Treatments A (fed), B (fast), and C (fed) in a three-way crossover fashion. A 7-day washout period was observed between Treatments A, B, and C. When Treatment C was completed, subjects received single 400 mg doses of boceprevir in Treatments D (fast) and E (fed) in a fixed sequential fashion. A 48-hour washout period was observed between Treatments D and E. All subjects received active treatment (no placebo). The following figure illustrates the design of Part 2.

Treatment A: Oral boceprevir 400 mg [redacted] (b) (4) original formulation) following a low fat breakfast.

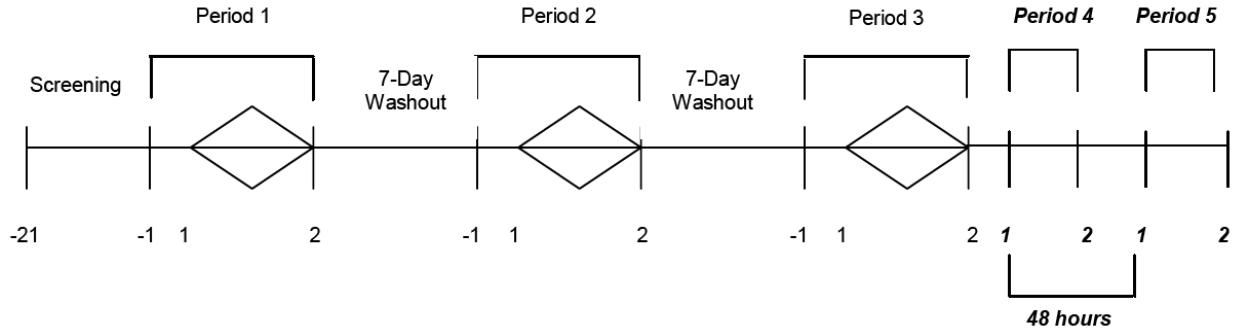
Treatment B: Oral boceprevir 400 mg (2 X 200 mg capsules, [redacted] (b) (4) SLS) following a 10-hour fast.

Treatment C: Oral boceprevir 400 mg (2 X 200 mg capsules, [redacted] (b) (4) SLS) following a low fat breakfast.

Treatment D: Oral boceprevir 400 mg (2 X 200 mg capsules, [redacted] (b) (4) SLS) following a 10-hour fast.

Treatment E: Oral boceprevir 400 mg (2 X 200 mg capsules, [redacted] (b) (4) SLS) following a low fat breakfast.

Figure 2 Open-label, randomized, 3-treatment, 3-period crossover, and 2-treatment, 2-period fixed trial (Part 2).



The content of the low-fat meal is displayed below.

Standardized Low-Fat Breakfast			
Item	Amount	Calories	Fat (Gm)
Croissant	1.5 oz	175	9
Cheese	1 oz	100	8
Whole Milk	4 oz	80	4
Jam	1/2 oz	39	0
Sugar	1 tsp	16	0
Fruit	2 oz	40	0
Total		450	21

Part 4 was an open-label, 3-period, 2-sequence crossover sub-trial to evaluate the effect of ketoconazole and ibuprofen on the PK of boceprevir. Twelve subjects participated in this sub-trial. All subject received active treatment (no placebo).

In period 1, all subjects received a single 400 mg dose of boceprevir in the original formulation (Treatment A) in the fasted state. A 7-day washout period was observed before initiating the next period.

In period 2, all subjects were randomized to receive either ketoconazole 400 mg BID (Treatment B) or ibuprofen 600 mg TID (Treatment C) in the fasted state for 6 consecutive days. Four days after initiating ketoconazole or ibuprofen, subjects received a single 400 mg dose of boceprevir. On day 7, subjects were discharged from the clinic and waited for at least 14 days before initiating period 3.

In period 3, subjects crossed over from their previous treatment (B to C or C to B). Subjects received either ketoconazole 400 mg BID or ibuprofen 600 mg TID for 6 days. Four days after initiating ketoconazole or ibuprofen, subjects received a single 400 mg dose of boceprevir. The trial concluded on day 7. The following figure illustrates the design of Part 4.

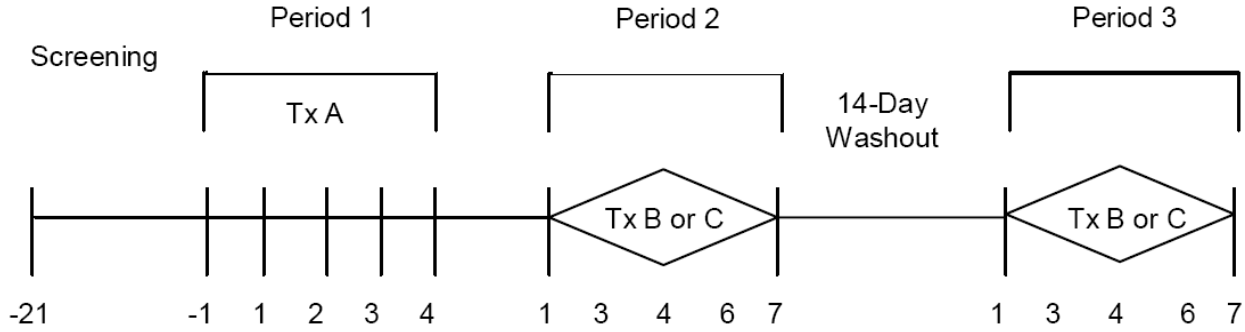
Treatment A: Oral boceprevir 400 mg [redacted] (b) (4), original formulation administered alone on day 1 of period 1.

Treatment B: Ketoconazole 400 mg BID administered from day 1 to day 6; Boceprevir 400 mg [redacted] (b) (4) original formulation) administered on day 4 (2 hours after the morning dose of ketoconazole).

Treatment C: Ibuprofen 600 mg TID administered from day 1 to day 6; Boceprevir 400 mg [redacted] (b) (4) original formulation)

administered on day 4 (2 hours after the morning dose of ibuprofen).

Figure 3 Open-label, randomized, 3-period, 2-sequence, crossover trial (Part 4)



Key Inclusion Criteria

The trial enrolled male or female subjects between 25 to 60 years of age with a body mass index (BMI) between 20 to 30 kg/m^2. Subjects were healthy based on physical examinations, ECGs, and clinical laboratory tests. All subjects used an effective barrier method of contraception, such as condoms with spermicide, during the trial and 30 days after the last dose of boceprevir.

Key Exclusion Criteria

The trial excluded subjects infected with HIV, HBV, or HCV or any clinical signs of systemic infection. Additionally, subjects with medical conditions like asthma, duodenal ulcers, or gastrointestinal bleeding did not participate in the trial.

Investigators prohibited the use of prescription drugs, over-the-counter drugs, herbal remedies, and mineral supplements 14 days before starting and during the trial. Acetaminophen was the only drug allowed for the treatment of adverse events. Moreover, the ingestion of grapefruit, grapefruit juice, alcohol, and caffeinated beverages was strictly prohibited 48 hours prior to starting and during the trial. Light smokers (≤10 cigarettes per day) enrolled in the trial. However, smoking and tobacco use was prohibited during the trial.

Investigational Products

The following table summarizes information about boceprevir formulations used in the trial. The (b) (4) SLS formulation is the proposed commercial formulation for

boceprevir.

	Original Formulation	Commercial Formulation
Drug		(b) (4)
Strength		
Formula No.		
Batch No.		
FMR No.		
Manufacturing Date		
Manufacturing Site		
Recertification Date		
Batch Size		
Description		

Reviewer comment: The report states that investigators were responsible for maintaining documentation (source, batch numbers, etc) for ketoconazole and ibuprofen. However, the trial report did not list this information.

Drug Administration

In Parts 1 and 4, subjects ingested boceprevir capsules with 240 mL of noncarbonated water in the fasted state. Meals or snacks were not allowed within 4 hours following a dose of boceprevir. Lunch was served 4 hours after the morning dose of boceprevir. Water intake was permitted as desired except for 1 hour before and after boceprevir administration. In Part 4, ketoconazole and ibuprofen were also ingested in the fasted state.

Part 2 of the trial required special dietary restrictions. Subjects ingested Treatments A, C, and E within 5 minutes of ingesting a low-fat breakfast, while Treatments B and D were ingested in the fasted state. Meals or snacks were not allowed within 4 hours following a dose of boceprevir. Lunch was served 4 hours after the morning dose of boceprevir. Water intake was permitted as desired except for 1 hour before and after boceprevir administration.

Rationale for Dose Selection

Investigators tested boceprevir 400 mg because the dose was safe and exhibited quantifiable boceprevir concentrations in plasma at the time points selected in this trial. In previous clinical trials with boceprevir, healthy subjects safely tolerated single doses of boceprevir 800 mg under fasted conditions.

Investigators were concerned that food and drug-drug interactions with ketoconazole and ibuprofen could increase boceprevir exposures to unsafe levels. Thus, they selected boceprevir 400 mg because the dose provided a safety cushion relative to 800 mg in case systemic concentrations of boceprevir increased in the presence of food, ketoconazole, or ibuprofen.

Investigators tested ketoconazole 400 mg BID and ibuprofen 600 mg TID. The dose of ibuprofen is close to the maximum daily recommended dose. However, the dose of ketoconazole was twice the maximum daily recommended dose of 400 mg QD. Subjects received ketoconazole and ibuprofen three days before boceprevir administration to ensure maximal enzymatic inhibition at the time of boceprevir administration. The additional three days of ketoconazole and ibuprofen dosing after boceprevir administration were supposed to inhibit 3A4 and AKR throughout the clearance period of boceprevir.

Reviewer comment: The Sponsor used a supratherapeutic dose of ketoconazole 400 mg BID. According to the literature, there is a similar extent of interaction between single dose and multiple dose ketoconazole with substrates that have a short half-life and low bioavailability. Thus, it is reasonable to expect a similar magnitude of interaction between SD and MD ketoconazole and boceprevir[1].

Pharmacokinetic Assessments

Boceprevir, Parts 1 and 2:
Investigators collected blood samples on day 1 of each period immediately prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 24 hours post dose.

Boceprevir, Part 4:
Investigators collected blood samples on Day 1 of Period 1 and day 4 of Periods 2 and 3 immediately prior to drug administration (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 36, 48, and 72 hours post dose.

Ketoconazole and ibuprofen, Part 4:
Investigators collected two blood samples on day 4 of periods 2 and 3 at predose and 24 hours post dose.

Bioanalytical Methods

Plasma samples were analyzed within the frozen stability timeframe for boceprevir and SCH534128, except for SCH534129. Samples for SCH534129 expired before bioanalysis. The frozen stability timeframes for ketoconazole and ibuprofen were not provided.

Initially, investigators used a validated, LC-MS/MS achiral method (SN 03330) to measure the concentrations of boceprevir in non-acidified plasma. The method was accurate and precise for determining boceprevir, but it failed to resolve the two diastereomers SCH534128 and SCH534129.

A chiral LC-MS/MS method (SN 04921) was developed to separate the diastereomers of boceprevir in non-acidified plasma. During method validation, investigators collected sufficient in-process and frozen storage stability for SCH534128, but not for SCH534129. Due to the limited stability of SCH534129, plasma samples were assayed to quantify concentrations of boceprevir using the original achiral method (SN 03330) and for SCH534128 using the chiral method (SN 04921).

Part 1 plasma samples were assayed using the chiral method (SN 04921) to determine concentrations of SCH534128. Plasma samples from Parts 2 and 4 were assayed using both achiral and chiral methods to measure the concentrations of boceprevir and SCH534128, respectively. Concentrations of boceprevir and SCH534128 are reliable, but concentrations of SCH534129 are not. Thus, concentrations of SCH534129 were not reported in this trial.

The following table lists the analytes and their lower and upper limits of quantification during bioanalysis.

Table 36 Analytes, limits of quantification, and LC-MS/MS methods

Analyte	LLOQ (ng/mL)	ULQ (ng/mL)	LC-MS/MS Methods
SCH503034	2.5	1250	SN03330
SCH534128	1.31	665	SN04921
Ketoconazole	Not reported	Not reported	Not reported
Ibuprofen			

The following table summarizes the precision and accuracy of the bioanalytical methods.

Table 2 Precision (% CV) and accuracy (% relative error) of calibration standards and QC samples in human plasma

	Cal Std			QC	
Analyte	**%CV**	**%RE**	**R^2**	**%CV**	**%RE**
SCH503034	2.3 – 4.4	≤1.8	≥0.9966	3.9 – 4.9	≤3.6
SCH534128	2.5 – 6.8	≤4.2	≥0.9929	4.7 – 8.9	≤5.3
Ketoconazole	Not reported	Not reported	Not reported	Not reported	Not reported
Ibuprofen					

All calibration standards and quality controls met the bioanalytical criteria. Investigators defined these criteria as precision (%CV) within ±15%, accuracy (%RE) ≤15%, and coefficient of determination (r^2) ≥0.98.

Pharmacokinetic Analyses

Plasma concentrations of boceprevir and SCH534128 were used to estimate AUC(tf), C_{max}, T_{max}, and t½. These parameters were not available for SCH534129 because the analyte could not be measured in plasma. Investigators did not report plasma concentrations of ketoconazole and ibuprofen.

Statistical Analyses

Investigators used an analysis of variance model (ANOVA) to extract the effects due to treatment, sequence, period, and subject. They calculated point estimates of the mean difference in AUC_{tf} and C_{max} between test and reference treatments, along with corresponding 90% confidence intervals. Treatment comparisons included:

Part 1: Comparison between the new SLS-containing boceprevir formulations (Treatments B, C, and D) versus the original boceprevir formulation (Treatment A).

Part 2: Comparison between the relative bioavailability of Treatment C (low fat, (b) (4) SLS) versus Treatment B (fast, (b) (4) SLS), Treatment C versus Treatment A (low fat, original), Treatment E (low fat, (b) (4) SLS) versus Treatment D (fast, (b) (4) SLS), and Treatment D versus Treatment A.

Part 4: Comparison between Treatment B (boceprevir + ketoconazole) versus Treatment A (boceprevir alone) and Treatment C (boceprevir + ibuprofen) versus Treatment A (boceprevir alone).

Demographic Results:

The subject demographics are listed below.

Table 3 Subject demographics

	Part 1 (n=12)	Part 2 (n=9)	Part 4 (n=12)
Sex (n, %)			
Female	10 (83)	3 (33)	4 (33)
Male	2 (17)	6 (67)	8 (67)
Race (n, %)			
White	12 (100)	7 (78)	12 (100)
Non white (Black or African American)		2 (22)	0
Ethnicity (n, %)			
Hispanic or Latino	11 (92)	8 (89)	10 (83)
Not Hispanic or Latino	1 (8)	1 (11)	2 (17)
Age (years)			
Mean (SD)	43.8 (10.2)	45.2 (9.0)	43.9 (4.8)
Median	45	48.0	43.5
Range	25 - 59	26 - 57	32 - 50
Age (n, %)			
18 to <65	12 (100)	9 (100)	12 (100)
Weight (kg)			
Mean (SD)	67.15 (9.05)	76.0 (11.81)	79.62 (10.43)
Median	65.0	71.0	82.95
Range	51.1 - 84.5	56.8 - 90.7	60.7 - 95.3
Height (cm)			
Mean (SD)	160.04 (7.63)	169.11 (6.43)	168.38 (11.75)
Median	160.25	169.0	170.0
Range	150 - 179	158.0 - 179.0	144.0 - 183.0
BMI			
Mean (SD)	26.18 (2.41)	26.47 (2.94)	28.04 (1.94)
Median	26.45	26.70	28.50
Range	21.3 - 30.3	22.6 - 30.8	25.0 - 30.3

BMI = body mass index; SD = standard deviation.

Part 1, PK results from comparison of boceprevir formulations.

The table below summarizes the geometric mean AUC_{tf} and C_{max} ratios of boceprevir and SCH534128 using 3 new SLS-containing boceprevir formulations versus the original boceprevir formulation.

Table 4 Relative systemic exposure of boceprevir and SCH534128 following a single oral dose of boceprevir in original formulation or in capsules containing (b) (4) SLS to healthy subjects (Part 1).

Analyte	Comparison	N	AUC(tf)		Cmax	
			Ratio Estimate[a] (%)	90% CI	Ratio Estimate[a] (%)	90% CI
SCH 503034	(b) (4) SLS vs Current	12	76	62-94	51	39-68
	SLS vs Current	12	135	109-167	139	106-183
	SLS vs Current	12	140	113-174	147	112-193
SCH 534128	SLS vs Current	12	78	62-96	54	41-72
	SLS vs Current	12	140	113-174	149	112-198
	SLS vs Current	12	145	117-180	155	117-206

a: Ratio expressed as percentage.
90% CI: 90% confidence interval.

Reviewer comment: The original formulation of boceprevir was called "current" formulation.

The (b) (4) SLS-containing formulations delivered 35% and 40% higher exposures (AUC_{tf}) of boceprevir relative to the original formulation. These same SLS-containing formulations also increased the mean C_{max} of boceprevir by 39% and 47% relative to the original formulation. In contrast, the (b) (4) SLS-containing formulation decreased the AUC_{tf} and C_{max} of boceprevir by 24% and 49% relative to the original formulation.

The (b) (4) SLS-containing formulations delivered 40% and 45% higher exposures (AUC_{tf}) of SCH534128 relative to the original formulation. These same formulations also increased the mean C_{max} of SCH534128 by 49% and 55% relative to the original formulation. In contrast, the (b) (4) SLS-containing formulation decreased the AUC_{tf} and C_{max} of SCH534128 by 22% and 46% relative to the original formulation.

The following table summarizes the pharmacokinetics of boceprevir and SCH534128 in 3 SLS-containing formulations versus the original formulation of boceprevir.

Reviewer comment: The table lists the arithmetic mean values, not geometric means. Geometric means were used in the statistical analysis.

Table 5 Mean (CV) PK parameters of boceprevir and SCH534128 following a single oral dose of boceprevir in original formulation or in capsules containing (b) (4) SLS to healthy subjects (Part 1).

Analyte	Treatment	Mean (CV,%)			
		N	AUC(tf) (ng•hr/mL)	Cmax (ng/mL)	Tmax [a] (hr)
SCH 503034	Current	12	1930 (45)	672 (55)	1.50 (1.00-3.00)
	(b) (4) SLS	12	1510 (49)	364 (67)	2.25 (1.00-8.00)
	SLS	12	2540 (40)	865 (35)	1.50 (1.00-4.00)
	SLS	12	2750 (50)	1020 (61)	1.50 (1.00-5.00)
SCH 534128	Current	12	1160 (49)	375 (64)	1.50 (1.00-3.00)
	(b) (4) SLS	12	913 (47)	203 (63)	2.75 (1.50-8.00)
	SLS	12	1570 (36)	502 (35)	1.50 (1.00-4.00)
	SLS	12	1710 (51)	587 (62)	1.50 (1.00-5.00)

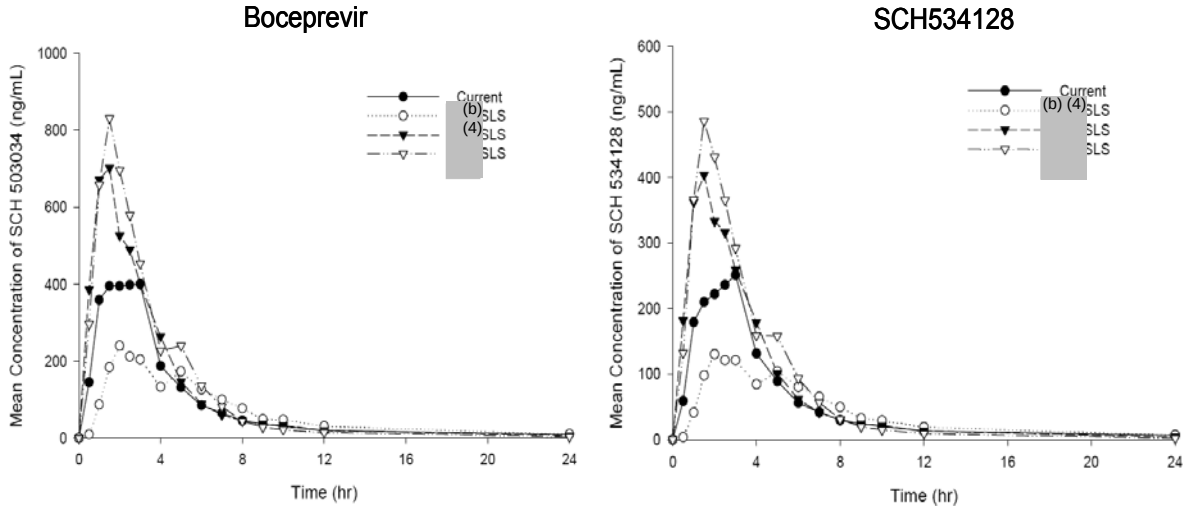
AUC(tf) = area under the plasma-concentration time curve to the final quantifiable sample; Cmax = maximum observed plasma concentration; Tmax = time of observed maximum plasma concentration.

a: Median(range).

The median T_{max} value of boceprevir and SCH534128 was 1.5 hours following administration of boceprevir in the original formulation. Administration of boceprevir in (b) (4) SLS-containing formulations did not change the median T_{max} values of boceprevir and SCH534128 relative to the original formulation. In contrast, administration of boceprevir in (b) (4) SLS-containing formulation delayed the median T_{max} values of both boceprevir and SCH534128 (2.25 and 2.75 hours).

The figure below displays the concentration-time profiles of boceprevir in all four formulations.

Figure 4 Mean (CV) plasma concentration-time data for boceprevir and SCH534128 following a single oral dose of boceprevir in original formulation or in capsules containing (b) (4) SLS to healthy subjects.



Part 2, effect of food on the PK of boceprevir in [(b) (4)] SLS-containing formulations versus original formulation of boceprevir.

The following table summarizes the relative bioavailability of boceprevir and SCH534128 using the [(b) (4)] SLS-containing formulations of boceprevir versus the original formulation under fed (low fat) or fasted conditions.

Table 6 Relative systemic exposures of boceprevir and SCH534128 after a single oral dose of boceprevir in original formulation, [(b) (4)] SLS-containing formulation, and [(b) (4)] SLS-containing formulation administered to healthy subjects under fed (low-fat) and fasted conditions.

Analyte	Comparison	N[a]	AUC(tf)		Cmax	
			Ratio Estimate[b] (%)	90% CI	Ratio Estimate[a] (%)	90% CI
SCH 503034	[(b) (4)] SLS, Low-fat vs Current, Low-fat	8	121	97-152	139	96-203
	[(b) (4)] SLS, Low-fat vs Current, Low-fat	8	75	63-90	83	54-127
	[(b) (4)] SLS, Low-fat vs SLS, Fast	8	165	132-207	168	116-244
	[(b) (4)] SLS, Low-fat vs [(b) (4)] SLS, Fast	8	154	128-184	180	118-276
	[(b) (4)] SLS, Fast vs [(b) (4)] SLS, Fast	8	66	55-79	53	35-82
	[(b) (4)] SLS, Low-fat vs [(b) (4)] SLS, Low-fat	8	62	52-74	59	39-91
SCH 534128	[(b) (4)] SLS, Low-fat vs Current, Low-fat	8	127	100-160	146	100-213
	[(b) (4)] SLS, Low-fat vs Current, Low-fat	8	80	66-96	85	55-131
	[(b) (4)] SLS, Low-fat v [(b) (4)] SLS, Fast	8	159	125-200	168	115-245
	[(b) (4)] SLS, Low-fat vs [(b) (4)] SLS, Fast	8	149	123-180	175	113-272
	[(b) (4)] SLS, Fast vs [(b) (4)] SLS, Fast	8	65	54-79	54	35-84
	[(b) (4)] SLS, Low-fat v [(b) (4)] SLS, Low-fat	8	63	52-76	58	38-91

AUC(tf) = area under the plasma-concentration time curve to the final quantifiable sample; CI = confidence interval; Cmax = maximum observed plasma concentration.

a: Subject 206 discontinued in Period 4 and was excluded from all statistical analysis.

b: Ratio expressed as percentage.

The mean AUC_{tf} and C_{max} of boceprevir increased by 65% and 68%, respectively, when boceprevir was administered in [(b) (4)] SLS-containing formulation under fed conditions relative to fasting conditions. Likewise, the mean AUC_{tf} and C_{max} of SCH534128 increased by 59% and 68% when boceprevir was administered in [(b) (4)] SLS-containing formulation under fed conditions relative to fasting conditions.

Under fed conditions, the mean AUC_{tf} and C_{max} of boceprevir increased by 21% and 39% when boceprevir was administered in [(b) (4)] SLS-containing formulation

relative to the original boceprevir formulation. Similarly, the mean AUC_{tf} and C_{max} of SCH534128 in the (b) (4) SLS formulation increased by 27% and 46% relative to original boceprevir formulation.

In contrast, the mean AUC_{tf} and C_{max} of boceprevir decreased by 25% and 17% when boceprevir was administered in (b) (4) SLS-containing formulation relative to the original boceprevir formulation under fed conditions. Similarly, the mean AUC_{tf} and C_{max} of SCH534128 decreased by 20% and 15% relative to the original boceprevir formulation.

The table below displays the PK of boceprevir and SCH534128 in (b) (4) SLS, (b) (4) SLS, and original boceprevir formulations under fed and fasted conditions.

Reviewer comment: The table lists the arithmetic mean values, not geometric means. Geometric means were used in the statistical analysis.

Table 7 Mean (CV) PK parameters of boceprevir and SCH534128 after a single oral dose of boceprevir in original formulation, (b) (4) SLS-containing formulation, and (b) (4) SLS-containing formulation administered to healthy subjects under fed (low-fat) and fasted conditions.

Analyte	Treatment	Mean (CV,%)			
		N	AUC(tf) (ng•hr/mL)	Cmax (ng/mL)	Tmax [a] (hr)
SCH 503034	Current, Low-fat	9	2940 (50)	767 (48)	5.00 (2.50-5.00)
	(b) (4) SLS, Fast	9	2410 (48)	702 (52)	1.50 (1.00-3.00)
	SLS, Low-fat	9	3310 (30)	972 (34)	2.00 (1.50-3.00)
	SLS, Fast	8[b]	1430 (55)	401(87)	2.25 (1.50-5.00)
	SLS, Low-fat	8[b]	2030 (30)	570 (41)	5.00 (4.00-12.0)
SCH 534128	Current, Low-fat	9	1600 (48)	426 (50)	5.00 (2.50-12.0)
	(b) (4) SLS, Fast	9	1400 (44)	401 (54)	2.00 (1.00-3.00)
	SLS, Low-fat	9	1890 (28)	546 (32)	2.00 (1.00-5.00)
	SLS, Fast	8[b]	856 (54)	227 (84)	2.50 (1.50-5.00)
	SLS, Low-fat	8[b]	1180 (28)	317 (37)	5.00 (4.00-12.0)

AUC(tf) = area under the plasma-concentration time curve to the final quantifiable sample; Cmax = maximum observed plasma concentration; Tmax = time of observed maximum plasma concentration.

a: Median(range).

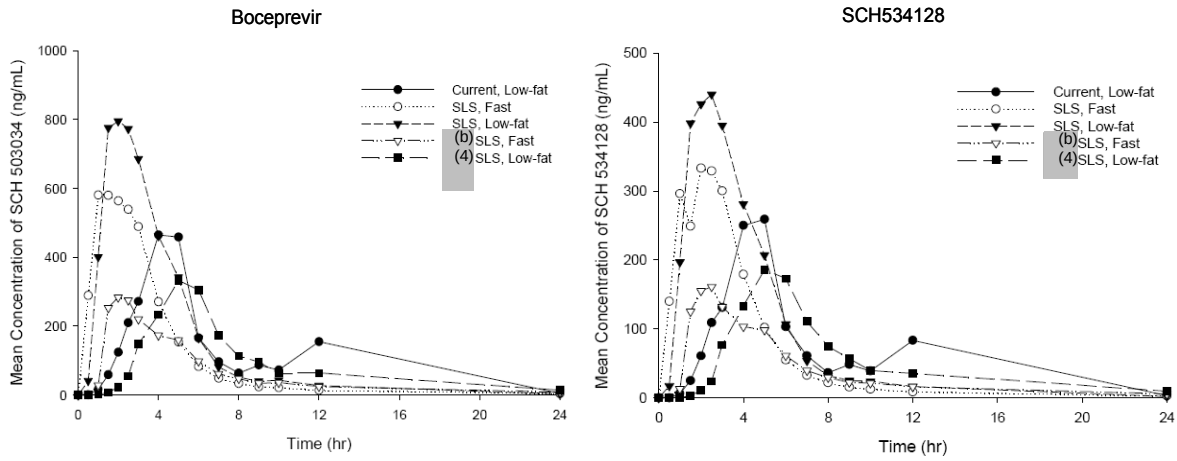
b: Subject 206 discontinued in Period 4. PK parameters for this subject were not available for Periods 4 and 5.

The median T_{max} values of boceprevir and SCH534128 were similar when boceprevir was administered in the (b) (4) SLS-containing formulation under fed conditions relative to fasting conditions. On the other hand, food delayed the median T_{max} of boceprevir and SCH534128 by ~2.5 to 3.5 hours when boceprevir was administered in the (b) (4) SLS-containing and original formulations relative to fasting conditions.

The figure below displays the concentration-time profiles of boceprevir and

SCH534128 in all three formulations in the presence and absence of food.

Figure 5 Mean (CV) plasma concentration-time profiles of boceprevir and SCH534128 after a single oral dose of boceprevir in original formulation, (b) (4) SLS-containing formulation, and (b) (4) SLS-containing formulation administered to healthy subjects under fed (low-fat) and fasted conditions.



Part 4, effect of ketoconazole and ibuprofen on the PK of boceprevir and SCH534128 when boceprevir was administered in the original formulation.

The following table summarizes the PK results from the drug-drug interaction evaluation between ketoconazole and ibuprofen with boceprevir.

Table 8 Relative systemic exposure of boceprevir and SCH534128 following a single oral dose of boceprevir alone, or when co-administered with ketoconazole and ibuprofen in healthy subjects.

Analyte	Comparison	N	AUC(tf)		Cmax	
			Ratio Estimate[a] (%)	90% CI	Ratio Estimate[a] (%)	90% CI
SCH 503034	SCH 503034+KET vs SCH 503034	12	231	200-267	141	100-197
	SCH 503034+IBU vs SCH 503034	12	104	90-120	94	67-132
SCH 534128	SCH 503034+KET vs SCH 503034	12	251	212-296	139	98-198
	SCH 503034+IBU vs SCH 503034	12	104	88-122	95	67-134

AUC(tf) = are under the plasma-concentration time curve to the final quantifiable sample; CI = confidence interval; Cmax = maximum observed plasma concentration; IBU = ibuprofen; KET = ketoconazole; t½ = half-life.

a: Ratio expressed as percentage.

During co-administration, ketoconazole increased the mean AUC_{tf} and C_{max} ratios of boceprevir by 231% and 141% respectively, relative to boceprevir alone. Likewise, ketoconazole also increased the SCH534128 by 251% and 139%

respectively relative to boceprevir alone.

In contrast, the mean AUC_{tf} and C_{max} ratios of boceprevir and SCH534128 were unchanged during co-administration of ibuprofen with boceprevir relative to boceprevir alone.

The table below summarizes the PK of boceprevir and SCH534128 in the presence and absence of ketoconazole and ibuprofen.

Reviewer's comment: Concentrations of ketoconazole and ibuprofen were not reported.

Table 9 Mean (CV) PK parameters of boceprevir and SCH534128 after a single oral dose of boceprevir alone or when co-administered with ketoconazole or ibuprofen to healthy subjects.

Analyte	Treatment	Mean (CV,%)				
		N	AUC(tf) (ng•hr/mL)	Cmax (ng/mL)	Tmax[a] (hr)	t½ (hr)
SCH 503034	SCH 503034	12	2010 (59)	571 (45)	1.75 (1.00-4.00)	9.33 [b] (55)
	SCH 503034 + KET	12	4420 (35)	832 (48)	2.00 (1.00-9.00)	7.78 (39)
	SCH 503034 + IBU	12	2030 (46)	642 (87)	2.00 (1.00-4.00)	8.03 (51)
SCH 534128	SCH 503034	12	1060 (43)	316 (48)	2.00 (1.00-4.00)	9.89 [c] (52)
	SCH 503034 + KET	12	2630 (34)	445 (50)	2.50 (1.50-4.00)	7.45 (32)
	SCH 503034 + IBU	12	1110 (44)	333 (72)	2.25 (1.00-4.00)	7.42 [c] (62)

AUC(tf) = area under the plasma-concentration time curve to the final quantifiable sample; Cmax = maximum observed plasma concentration; IBU = ibuprofen; KET = ketoconazole; t½ = half-life Tmax = time of observed maximum plasma concentration.

a: Median(range).

b: N=11.

c: N=10.

The terminal half-lives of boceprevir and SCH534128 were similar in subjects who received boceprevir alone compared to subjects who received boceprevir with ketoconazole or ibuprofen. Of note, the mean half-lives of boceprevir and SCH534128 reported in this trial are ~2 times longer than historical values (3 to 5 hours) observed in other boceprevir trials.

Moreover, the median T_{max} values of boceprevir and SCH534128 were unaffected during co-administration of ibuprofen with boceprevir or ketoconazole with boceprevir relative to boceprevir alone.

Safety results

Thirty-six subjects participated in the trial. Only one subject discontinued in Part 4 for reasons not related to boceprevir. Nine subjects reported treatments emergent adverse events (TEAEs); five subjects in Part 1 and four subjects in

Part 4. The most common adverse event was mild to moderate headache (4 subjects, 34%).

Discussion and Conclusions

Part 1: Investigators hoped to develop a new formulation that would increase the exposures of boceprevir relative to the original formulation of boceprevir. This trial tested new formulations of boceprevir that contained (b) (4) sodium lauryl sulfate. The results are as follows:

- The (b) (4) SLS-containing formulations delivered ~35% to 45% higher exposures (AUC_{tf}) of boceprevir relative to the original formulation. Both (b) (4) (b) (4) SLS-containing formulations delivered similar boceprevir exposures. Thus, investigators chose the (b) (4) SLS-containing formulation to continue developing boceprevir. Of note, the (b) (4) SLS-containing formulation is the proposed commercial formulation of boceprevir.

- In contrast, the (b) (4) SLS-containing formulation under performed by decreasing the exposures (AUC_{tf}) of boceprevir by 24% relative to the original formulation.

Part 2: Investigators tested the effect of a low-fat meal on the PK of boceprevir when boceprevir was administered in the original formulation, in (b) (4) SLS-containing formulation, and in (b) (4) SLS-containing formulation. The results were as follows:

- A low fat meal increased the exposures (AUC_{tf}) of boceprevir by 65% relative to fasting conditions when boceprevir was administered in (b) (4) SLS-containing formulation. Thus, boceprevir should be administered with meals.

- A low fat meal increased the exposures (AUC_{tf}) of boceprevir by 21% when boceprevir was administered in a (b) (4) SLS-containing formulation relative to the original formulation. Even under fed conditions, the (b) (4) SLS-formulation delivers higher boceprevir exposures compared to the original formulation.

- In contrast, a low fat meal decreased the exposures of boceprevir by 25% when boceprevir was administered in a (b) (4) SLS-containing formulation relative to the original boceprevir formulation. Investigators stopped developing the (b) (4) SLS-containing formulation of boceprevir.

Part 4: Investigators tested the effect of ketoconazole and ibuprofen on the PK of boceprevir when boceprevir was administered in the original formulation. The results were as follows:

- During co-administration, ketoconazole increased the mean AUC_{tf} and C_{max} ratios of boceprevir by 231% and 141% respectively relative to boceprevir alone. These results make sense because ketoconazole is an inhibitor of CYP3A4 and p-glycoprotein. It is currently unknown whether a 2-fold increase in boceprevir exposures poses a substantial safety risk.

- In contrast, the mean AUC_{tf} and C_{max} ratios of boceprevir and SCH534128 were unchanged during co-administration of ibuprofen with boceprevir relative to boceprevir alone. The results are unexpected because ibuprofen inhibits AKR, the primary enzyme responsible for boceprevir metabolism. In previous clinical trials, boceprevir was co-administered with diflunisal, another AKR inhibitor, and no notable increases in boceprevir were observed. Thus, it may be reasonable to conclude that boceprevir may be co-administered with strong inhibitors of AKR.

References

1. Zhao P, I Ragueneau-Majlessi, L Zhang, J Strong, K Reynolds, R Levy, K Thummel, S-M Huang. Quantitative Evaluation of Pharmacokinetic Inhibition of CYP3A Substrates by Ketoconazole — A Simulation Study. J Clin Pharmacol. 49 (3):351-359 (2009).

P04133

A single dose crossover study to characterize the dose proportionality of SCH 503034 oral capsules and the timing of food administration in healthy volunteers

Trial Periods

Trial Initiation Date: December 16, 2005
Trial Early Termination Date: January 17, 2006. The trial was terminated after the completion of part 1 and prior to the initiation of part 2 because a concurrent trial assessed the dose proportionality of SCH 503034 at a more clinically relevant higher dose.

Reviewer's comment: The results of a single dose trial (P03533) which compared the bioavailability of the (b) (4) *capsule formulation ("current" formulation at the time of the conduct of trial P03533) with the new 200 mg SLS-containing capsule formulation (formulations with various SLS content were evaluated in the trial) indicated that at the 400 mg dose, the systemic exposure of SCH 503034 was higher with the 200 mg SLS containing capsule formulation as compared with the* (b) (4) *capsule formulation. Therefore, the purpose of trial P04133 was to further characterize the PK profile of the new SCH 503034 SLS containing formulation and evaluate dose proportionality to help transition from the original capsule formulation to the new SLS containing capsule formulation.*

Objectives

- Characterize the pharmacokinetic (PK) profile and dose proportionality of the new SCH 503034 capsule formulation in healthy volunteers.

- Establish the optimal dosing time relative to food intake.

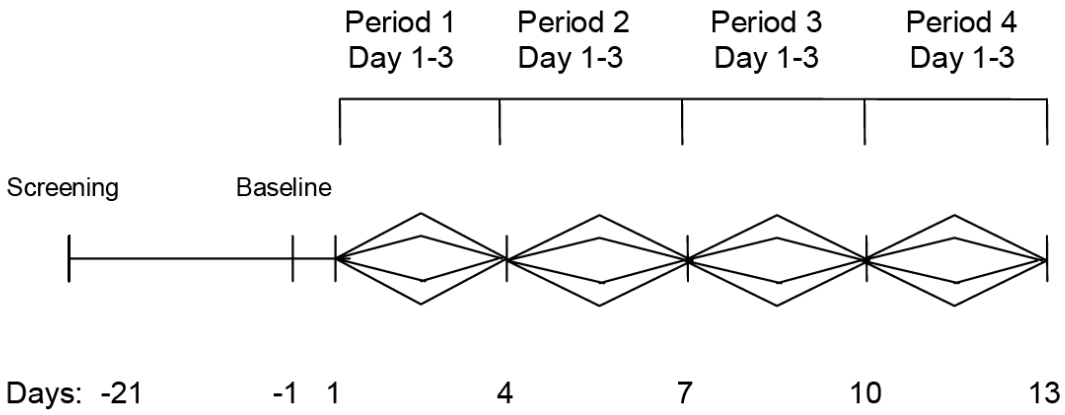
Trial Design

Open-label, single-dose balanced crossover trial in healthy adult volunteers at a single study center. The trial was to be conducted in two parts, part 1 (enrolling 12 subjects) and part 2 (enrolling 24 subjects). Part 2 of the trial was to be conducted after the optimal dosing time relative to food intake was determined based on preliminary PK data from part 1 of the trial.

Part 1:

Randomized, 4-way crossover design. Schematic 1 shows the trial design.

Schematic 1: Trial Design for Part 1 of the trial



Treatment A: SCH 503034 capsules, 400 mg, new formulation, administered immediately prior to breakfast.

Treatment B: SCH 503034 capsules, 400 mg, new formulation, administered during breakfast.

Treatment C: SCH 503034 capsules, 400 mg, new formulation, administered immediately after breakfast.

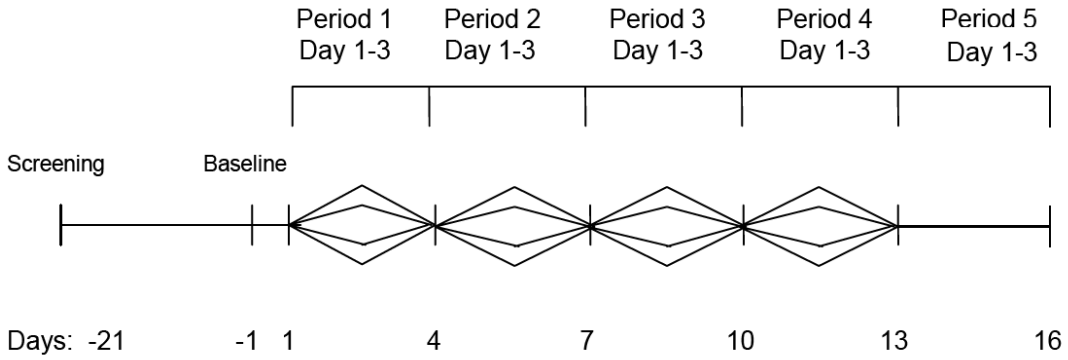
Treatment D: SCH 503034 capsules, 400 mg, new formulation, administered under fasting conditions.

The formulation used in part 1 of the trial (200 mg capsule formulation; "new formulation") is the commercial formulation. Subjects were to be randomized to their treatment sequence on day 1 of period 1 after fulfilling the entry criteria and were to be sequentially allocated subjects numbers. Subjects were to receive a single dose of SCH 503034 on Day 1 of each period at approximately 8 AM following an overnight fast. Subjects randomized to Treatment A were to receive their treatment immediately before a low-fat breakfast (450 calories; 21 gm fat); subjects randomized to Treatment B were to receive their treatment during a low-fat breakfast (dosing to take place when approximately 50 % of the breakfast had been consumed); subjects randomized to Treatment C were to receive treatment immediately after a low-fat breakfast (breakfast was to start 30 minutes prior to dosing and was to be completed within 20 to 25 minutes); subjects randomized to Treatment D were to receive their treatment under fasting conditions.

<u>Part 2:</u>

Schematic 2 shows the trial design of part 2 of the trial. However, part 2 was not completed.

Schematic 2: Trial design of part 2 of the trial (not completed)



Treatment E: SCH 503034 capsules, 200 mg, [redacted](1 X 200 mg capsules), administered under an optimal food regimen (Periods 1, 2, 3, 4).

Treatment F: SCH 503034 capsules, 400 mg, [redacted]l (2 X 200 mg capsules), administered under an optimal food regimen (Periods 1, 2, 3, 4).

Treatment G: SCH 503034 capsules, 800 mg, [redacted] (4 X 200 mg capsules), administered under an optimal food regimen (Periods 1, 2, 3, 4).

Treatment H: SCH 503034 capsules, 400 mg, original formulation [redacted], administered under an optimal food regimen.

Treatment I: SCH 503034 capsules, 400 mg, new formulation by batch process (2 X 200 mg capsules), administered under an optimal food regimen.

Reviewer's comment: During the process of formulation optimization, the applicant developed a manufacturing process ([redacted]) and the active pharmaceutical ingredient produced from the new process [redacted] may possess different physiochemical characteristics and thus impact the bioavailability of SCH 503034. Therefore, to evaluate the new [redacted], also formulated with [redacted] SLS, part 2 of the trial was to evaluate the dose proportionality of the [redacted] with three doses (200 mg, 400 mg, and 800 mg). The "optimal" food regimen was to be determined from part 1 of the trial. However, part 2 of the trial was never completed.

Subjects were to receive a single dose of SCH 503034 with 240 mL of noncarbonated water under the optimal dosing condition determined from Part 1.

No food was served until 4 hours following drug administration, at which time lunch was to be served. Subjects randomized to treatments B and C were to fast for 4 hours following completion of breakfast. Water was to be permitted as desired except for 1 hour before and after SCH 503034 administration. There was to be a washout period of at least 72 hours between dose administrations.

Drugs Used in the Trial

Table 1 provides the description of the investigational products used in the trial.

Table 1: Description of the investigational products used in the trial

Drug	SCH 503034	SCH 503034	SCH 503034
Strength	(b) (4)		
Formula No.			
Batch No.			
Manufacturing Date			
Manufacturing Site			
Expiry Date			
Recertification Date			
Batch Size			
Description			

The 200 mg capsule formulation ("new formulation") is the commercial formulation. The drug was to be stored in a refrigerator between 2-8^{0}C and was to be compliant until the recertification date (date after the date of the last dose administered).

Permitted Medications Before- and During the Trial

No medication (over-the-counter or prescription) was to be taken by the subject, except acetaminophen (paracetamol), within 14 days of treatment or during the course of the trial without prior approval from the principal investigator and Sponsor, unless it was a medical emergency. All medications taken by the subject within 14 days of study start (Day 1) and were to be recorded on the eCRF.

Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Blood samples were to be collected on Day 1 of each period immediately prior to dosing (0 hour) and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48, and 72

hours post-dose. Since the pre-dose sample for periods 2, 3, and 4 in part 1 and for periods 2, 3, 4, and 5 in part 2 are the same as the 72-hour sample from the previous period, additional pre-dose sample for periods 2, 3, and 4 in part 1 and for periods 2, 3, 4, and 5 in part 2 were not collected.

A 5 mL whole blood sample was to be collected for pharmacogenetic assessments. DNA was to be extracted and stored for a period of up to 10 years for possible genetic analysis.

SCH 503034 consists of two inter-convertible stereoisomers: SCH 534128 and SCH 534129. All plasma samples were to be assayed for these two compounds using a validated chiral liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method. All assays were to be conducted by the (b) (4)

Pharmacokinetic Assessments

Plasma SCH 503034 (SCH 534128 and SCH 534129) concentration data were to be used to estimate the following pharmacokinetic parameters: C_{max}, T_{max}, $AUCUC_{tf}$. The secondary parameters were to include comparison of pharmacokinetic parameters between African- American and other races.

Results (from Part 1 of the trial)

Bioanalytical Assessments

The applicant used method DM 27268 for the bioanalytical assessments. The samples were assayed within the stability period (267 days at -20^{o}C). The calibration range for SCH 534128 and SCH 534129 was from1.31 ng/mL to 655 ng/mL and 1.19 ng/mL to 595 ng/mL respectively. The following quality control samples were analyzed for SCH 534128: low QC (3.93 ng/mL), medium QC (78.6 ng/mL) and high QC (472 ng/mL). The inter-run precision was 7.8 %, 4.4 %, and 4.1 % and the inter-run accuracy was 3.6 %, 2.5 %, and 2.8 % at the low-, medium-, and high QC respectively. For SCH 534129, following quality control samples were analyzed: low QC (3.57 ng/mL), medium QC (71.4 ng/mL) and high QC (428 ng/mL). The inter-run precision was 5.5 %, 4.4 %, and 4.3 % and the inter-run accuracy was 5.3 %, 3.1 %, and 4.4 % at the low-, medium-, and high QC respectively.

Demographics

Table 2 shows the summary of the demographic data from the trial.

Table 2: Summary of the demographic data from the trial

	Treatment A/B/C/D (n=3)	Treatment B/D/A/C (n=3)	Treatment C/A/D/B (n=3)	Treatment D/C/B/A (n=3)
Sex (n,%)				
Female	1 (33)	1 (33)	2 (67)	1 (33)
Male	2 (67)	2 (67)	1 (33)	2 (67)
Race (n,%)				
White	1 (33)	2 (67)	2 (67)	1 (33)
Non-White	2 (67)	1 (33)	1 (33)	2 (67)
Black or African-American	2 (67)	1 (33)	1 (33)	2 (67)
Ethnicity (n,%)				
Hispanic or Latino	1 (33)	2 (67)	2 (67)	1 (33)
Not Hispanic or Latino	2 (67)	1 (33)	1 (33)	2 (67)
Age (yrs)				
Mean (SD)	39.3 (10.0)	41.0 (13.0)	33.3 (7.6)	36.0 (7.2)
Median	43.0	41.0	35.0	34.0
Range	28-47	28-54	25-40	30-44
Age (n,%)				
18 - <65	3 (100)	3 (100)	3 (100)	3 (100)
Weight (kg)				
Mean (SD)	88.23 (20.09)	72.93 (11.03)	76.57 (10.55)	83.43 (3.98)
Median	82.00	71.00	76.80	84.00
Range	72.0-110.7	63.0-84.8	65.9-87.0	79.2-87.1
Height (cm)				
Mean (SD)	170.33 (18.23)	171.00 (7.21)	165.33 (10.21)	175.17 (7.15)
Median	167.00	169.00	161.00	173.50
Range	154.0-190.0	165.0-179.0	158.0-177.0	169.0-183.0
BMI				
Mean (SD)	30.17 (0.68)	24.90 (2.43)	27.93 (1.60)	27.20 (1.04)
Median	30.40	26.10	27.80	27.70
Range	29.4-30.7	22.1-26.5	26.4-29.6	26.0-27.9

BMI = body mass index; SD = standard deviation

Pharmacokinetics

SCH 503034

Table 3 shows the mean pharmacokinetic parameters of SCH 503034 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy subjects.

Table 3: Mean pharmacokinetic parameters of SCH 503034 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy subjects

Parameters	Treatment A (n=11)	Treatment B (n=12)	Treatment C (n=12)	Treatment D (n=12)
Tmax [a] (hr)	2.50 (1.00-5.00)	3.00 (1.50-4.00)	2.50 (1.50-4.00)	1.50 (1.00-2.50)
Cmax (ng/mL)	1020 (58)	953 (39)	1090 (28)	765 (27)
AUC(tf) (ng·hr/mL)	3050 (31)	2950 (29)	3090 (28)	2200 (32)
AUC(I) (ng·hr/mL)	3080 (31)	2970 (29)	3110 (28)	2230 (32)
$t_{½}$ (hr)	4.55 (28)	3.69 (46)	4.54 (35)	4.71 (32)

Data presented as mean (CV%).

CV = coefficient of variation

a: Median (range)

Treatment A: SCH 503034 capsules administered immediately prior to breakfast.

Treatment B: SCH 503034 capsules administered during breakfast.

Treatment C: SCH 503034 capsules administered immediately after breakfast.

Treatment D: SCH 503034 capsules administered in a fasted state.

Table 4 shows the overall comparisons between treatments for SCH 503034 in all subjects

Table 4: Overall comparisons between treatments for SCH 503034 in all subjects

Analyte	Treatment Group	PK Parameter	n	LS Means	Treatment Comparison	Ratio Estimate	90% Confidence Interval
SCH 503034	A	AUC(I)	11	2915.5	A vs D	137	124-150
	B	AUC(I)	12	2869.2	B vs D	135	123-147
	C	AUC(I)	12	3010.1	C vs D	141	129-155
	D	AUC(I)	12	2132.9	A vs B	102	92-112
	--	AUC(I)	--	--	A vs C	97	88-106
	--	AUC(I)	--	--	B vs C	95	87-104
	A	AUC(tf)	11	2887.9	A vs D	137	125-151
	B	AUC(tf)	12	2847.2	B vs D	135	123-148
	C	AUC(tf)	12	2986.7	C vs D	142	129-156
	D	AUC(tf)	12	2104.6	A vs B	101	92-112
	--	AUC(tf)	--	--	A vs C	97	88-106
	--	AUC(tf)	--	--	B vs C	95	87-105
	A	Cmax	11	899.5	A vs D	122	105-142
	B	Cmax	12	890.6	B vs D	121	104-140
	C	Cmax	12	1051.1	C vs D	142	123-165
	D	Cmax	12	738.6	A vs B	101	87-118
	--	Cmax	--	--	A vs C	86	73-100
	--	Cmax	--	--	B vs C	85	73-98

LS = least-square

The median SCH 503034 t_{max} value was 1.50 hours following administration of SCH 503034 in fasted state. Administration of SCH 503034 with food (immediately prior, during, and immediately after dosing) delayed the median t_{max} values (2.50 to 3.00 hours). The least-square mean (LS_{mean}) ratio of SCH 503034 C_{max} value increased by 22 %, 21 %, 42 %, when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the C_{max} observed under fasting conditions. Similarly the LS_{mean} ratio of SCH 503034 AUC value increased by 37 %, 35 %, and 41%, when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the AUC observed under fasting conditions.

SCH 534128

Table 5 shows the mean pharmacokinetic parameters of SCH 534128 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy subjects.

Table 5: Mean pharmacokinetic parameters of SCH 534128 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy subjects

Parameters	Treatment A (n=11)	Treatment B (n=12)	Treatment C (n=12)	Treatment D (n=12)
Tmax [a] (hr)	3.00 (1.00-5.00)	3.00 (2.00-5.00)	3.00 (1.50-4.00)	1.50 (1.00-2.50)
Cmax (ng/mL)	606 (54)	548 (39)	636 (28)	450 (27)
AUC(tf) (ng·hr/mL)	1950 (32)	1860 (30)	1940 (28)	1430 (33)
AUC(I) (ng·hr/mL)	1960 (32)	1880 (30)	1960 (28)	1450 (33)
$t_{½}$ (hr)	4.50 (33)	3.74 (49)	4.84 (36)	4.95 (36)

Data presented as mean (CV%).

CV = coefficient of variation

a: Median (range)

Treatment A: SCH 503034 capsules administered immediately prior to breakfast.

Treatment B: SCH 503034 capsules administered during breakfast.

Treatment C: SCH 503034 capsules administered immediately after breakfast.

Treatment D: SCH 503034 capsules administered in a fasted state.

Table 6 shows the overall comparisons between treatments for SCH 534128 in all subjects

Table 6: Overall comparisons between treatments for SCH 534128 in all subjects

Analyte	Treatment Group	PK Parameter	n	LS Means	Treatment Comparison	Ratio Estimate	90% Confidence Interval
SCH 534128	A	AUC(I)	11	1847.4	A vs D	133	121-145
	B	AUC(I)	12	1800.1	B vs D	129	119-141
	C	AUC(I)	12	1893.5	C vs D	136	125-149
	D	AUC(I)	12	1391.0	A vs B	103	94-112
	--	AUC(I)	--	--	A vs C	98	89-107
	--	AUC(I)	--	--	B vs C	95	87-104
	A	AUC(tf)	11	1829.2	A vs D	133	122-146
	B	AUC(tf)	12	1783.5	B vs D	130	119-142
	C	AUC(tf)	12	1875.1	C vs D	137	125-150
	D	AUC(tf)	12	1370.5	A vs B	103	94-112
	--	AUC(tf)	--	--	A vs C	98	89-107
	--	AUC(tf)	--	--	B vs C	95	87-104
	A	Cmax	11	541.9	A vs D	124	108-144
	B	Cmax	12	512.4	B vs D	118	102-135
	C	Cmax	12	614.6	C vs D	141	123-162
	D	Cmax	12	435.6	A vs B	106	91-122
	--	Cmax	--	--	A vs C	88	76-102
	--	Cmax	--	--	B vs C	83	72-96

LS = least-square

The median SCH 534128 t_{max} value was 1.50 hours following administration of SCH 503034 in fasted state. Administration of SCH 503034 with food (immediately prior, during, and immediately after dosing) delayed the median t_{max} values of SCH 534128 to 3 hours. The least-square mean (LS_{mean}) ratio of SCH 534128 C_{max} value increased by 24 %, 18 %, and 41 %, when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the C_{max} observed under fasting conditions. Similarly the LS_{mean} ratio of SCH 534128 AUC value increased by 33 %, 29 %, and 36 %, when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the AUC observed under fasting conditions. The mean $t_{1/2}$ of SCH 534128 ranged from approximately 3.75 hours to 5 hours and was not affected by food administration.

SCH 534129

Table 7 shows the mean pharmacokinetic parameters of SCH 534129 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy subjects.

Table 7: Mean pharmacokinetic parameters of SCH 534129 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy subjects

Parameters	Treatment A (n=11)	Treatment B (n=12)	Treatment C (n=12)	Treatment D (n=12)
Tmax [a] (hr)	2.50 (1.00-4.00)	2.75 (1.50-4.00)	2.50 (1.50-4.00)	1.50 (1.00-2.50)
Cmax (ng/mL)	429 (62)	411 (40)	460 (28)	316 (28)
AUC(tf) (ng·hr/mL)	1120 (29)	1090 (27)	1140 (27)	756 (31)
AUC(I) (ng·hr/mL)	1130 (29)	1090 (27)	1150 (27)	771 (31)
$t_{½}$ (hr)	4.25 (44)	3.01 (68)	3.58 (61)	4.70 (45)

Data presented as mean (CV%).

CV = coefficient of variation

a: Median (range)

Treatment A: SCH 503034 capsules administered immediately prior to breakfast.

Treatment B: SCH 503034 capsules administered during breakfast.

Treatment C: SCH 503034 capsules administered immediately after breakfast.

Treatment D: SCH 503034 capsules administered in a fasted state.

Table 8 shows the overall comparisons between treatments for SCH 534129 in all subjects

Table 8: Overall comparisons between treatments for SCH 534129 in all subjects

Analyte	Treatment Group	PK Parameter	n	LS Means	Treatment Comparison	Ratio Estimate	90% Confidence Interval
SCH 534129	A	AUC(I)	11	1077.5	A vs D	146	132-161
	B	AUC(I)	12	1060.9	B vs D	144	131-158
	C	AUC(I)	12	1110.7	C vs D	150	137-166
	D	AUC(I)	12	738.1	A vs B	102	92-112
	--	AUC(I)	--	--	A vs C	97	88-107
	--	AUC(I)	--	--	B vs C	96	87-105
	A	AUC(tf)	11	1066.6	A vs D	147	133-163
	B	AUC(tf)	12	1053.1	B vs D	145	132-160
	C	AUC(tf)	12	1101.2	C vs D	152	138-168
	D	AUC(tf)	12	724.1	A vs B	101	92-112
	--	AUC(tf)	--	--	A vs C	97	88-107
	--	AUC(tf)	--	--	B vs C	96	87-105
	A	Cmax	11	376.8	A vs D	124	106-144
	B	Cmax	12	384.4	B vs D	127	109-147
	C	Cmax	12	444.5	C vs D	146	126-170
	D	Cmax	12	303.9	A vs B	98	84-114
	--	Cmax	--	--	A vs C	85	73-99
	--	Cmax	--	--	B vs C	86	75-100

LS = least-square

The median SCH 534129 t_{max} value was 1.50 hours following administration of SCH 503034 in fasted state. Administration of SCH 503034 with food (immediately prior, during, and immediately after dosing) delayed the median t_{max} values of SCH 534129 (2.5 hours to 2.75 hours). The least-square mean (LS_{mean}) ratio of SCH 532149 C_{max} value increased by 24 %, 27 %, and 46 % when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the C_{max} observed under fasting conditions. Similarly the LS_{mean} ratio of SCH 534129 AUC value increased by 46 %, 44 %, and 50 %, when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the AUC observed under fasting conditions. The mean $t_{1/2}$ of SCH 534129 ranged from approximately 3 hours to 5 hours and was not affected by food administration.

Comparison of the Pharmacokinetic Parameters between Healthy African American Subjects and Caucasian Subjects

SCH 503034

Table 9 shows the mean pharmacokinetic parameters of SCH 503034 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy African-American subjects and Caucasian subjects

Table 9: Mean pharmacokinetic parameters of SCH 503034 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy African American subjects and Caucasian subjects

Parameters	Treatment A		Treatment B		Treatment C		Treatment D	
	African-American (n=5)	White (n=6)	African-American (n=6)	White (n=6)	African-American (n=6)	White (n=6)	African-American (n=6)	White (n=6)
Tmax[a] (hr)	2.50 (2.50-4.00)	2.75 (1.00-5.00)	2.25 (1.50-3.00)	3.00 (2.00-4.00)	2.50 (1.50-3.00)	2.50 (2.50-4.00)	1.25 (1.00-1.50)	1.50 (1.00-2.50)
Cmax (ng/mL)	747 (22)	1240 (60)	748 (23)	1160 (36)	897 (14)	1280 (25)	670 (22)	860 (27)
AUC(tf) (ng·hr/mL)	2700 (20)	3340 (34)	2430 (17)	3470 (25)	2590 (23)	3590 (22)	1750 (15)	2640 (28)
AUC(I) (ng·hr/mL)	2730 (20)	3370 (34)	2450 (18)	3500 (25)	2620 (23)	3610 (23)	1770 (14)	2680 (28)
$t_{½}$ (hr)	3.88 (36)	5.11 (19)	3.08 (55)	4.30 (37)	4.39 (52)	4.68 (12)	3.80 (39)	5.61 (17)

Data presented as mean (CV%).

CV = coefficient of variation

a: Median (range)

Treatment A: SCH 503034 capsules administered immediately prior to breakfast.

Treatment B: SCH 503034 capsules administered during breakfast.

Treatment C: SCH 503034 capsules administered immediately after breakfast.

Treatment D: SCH 503034 capsules administered in a fasted state.

SCH 534128

Table 10 shows the mean pharmacokinetic parameters of SCH 534128 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy African-American subjects and Caucasian subjects

Table 10: Mean pharmacokinetic parameters of SCH 534128 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy African-American subjects and Caucasian subjects

Parameters	Treatment A		Treatment B		Treatment C		Treatment D	
	African-American (n=5)	White (n=6)	African-American (n=6)	White (n=6)	African-American (n=6)	White (n=6)	African-American (n=6)	White (n=6)
Tmax[a] (hr)	3.00 (2.50-4.00)	2.75 (1.00-5.00)	2.50 (2.00-3.00)	3.00 (2.00-5.00)	2.50 (1.50-3.00)	3.00 (2.50-4.00)	1.50 (1.00-1.50)	1.50 (1.00-2.50)
Cmax (ng/mL)	456 (25)	732 (55)	430 (26)	667 (35)	514 (14)	759 (23)	397 (22)	504 (26)
AUC(tf) (ng·hr/mL)	1690 (21)	2160 (35)	1500 (18)	2220 (25)	1600 (23)	2290 (22)	1130 (11)	1740 (29)
AUC(I) (ng·hr/mL)	1710 (21)	2180 (35)	1520 (18)	2240 (25)	1620 (24)	2310 (22)	1140 (11)	1770 (28)
$t_{½}$ (hr)	3.66 (48)	5.21 (15)	3.40 (61)	4.08 (42)	4.60 (51)	5.08 (20)	4.20 (42)	5.70 (27)

Data presented as mean (CV%).

CV = coefficient of variation

a: Median (range)

Treatment A: SCH 503034 capsules administered immediately prior to breakfast.

Treatment B: SCH 503034 capsules administered during breakfast.

Treatment C: SCH 503034 capsules administered immediately after breakfast.

Treatment D: SCH 503034 capsules administered in a fasted state.

SCH 534129

Table 11 shows the mean pharmacokinetic parameters of SCH 534129 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy African-American subjects and Caucasian subjects.

Table 11: Mean pharmacokinetic parameters of SCH 534129 after dosing with SCH 503034 capsules (400 mg, new formulation) in healthy African-American subjects and Caucasian subjects

Parameters	Treatment A		Treatment B		Treatment C		Treatment D	
	African-American (n=5)	White (n=6)	African-American (n=6)	White (n=6)	African-American (n=6)	White (n=6)	African-American (n=6)	White (n=6)
Tmax[a] (hr)	2.50 (1.00-4.00)	2.75 (1.00-4.00)	2.25 (1.50-3.00)	3.00 (1.50-4.00)	2.50 (1.50-3.00)	2.50 (2.50-4.00)	1.25 (1.00-1.50)	1.50 (1.00-2.50)
Cmax (ng/mL)	297 (18)	540 (60)	329 (20)	493 (39)	389 (12)	530 (28)	276 (23)	356 (28)
AUC(tf) (ng·hr/mL)	1010 (20)	1200 (33)	928 (18)	1240 (26)	987 (23)	1290 (25)	620 (22)	893 (27)
AUC(I) (ng·hr/mL)	1020 (20)	1220 (33)	934 (19)	1260 (26)	997 (23)	1300 (25)	628 (22)	914 (26)
$t_{½}$ (hr)	4.22 (32)	4.27 (55)	2.06 (57)	3.96 (60)	3.87 (73)	3.29 (49)	3.11 (52)	6.30 (18)

Data presented as mean (CV%).

CV = coefficient of variation

a: Median (range)

Treatment A: SCH 503034 capsules administered immediately prior to breakfast.

Treatment B: SCH 503034 capsules administered during breakfast.

Treatment C: SCH 503034 capsules administered immediately after breakfast.

Treatment D: SCH 503034 capsules administered in a fasted state.

Overall, the plasma concentration of all three analytes (SCH 503034, SCH 534128, and 534129) were higher in Caucasian subjects as compared with African-American subjects. For SCH503034, the mean AUC was 23-43% higher under fed conditions in Caucasian subjects as compared to the AUC under fed conditions in African-American subjects. Due to the small sample size, further evaluation of the PK of all three analytes is required to determine if the higher concentrations of all three analytes in Caucasian subjects are clinically and statistically significant.

Summary of Results (from Part 1 of the trial)

- LS_{mean} ratio of SCH 503034 AUC value increased by 37 %, 35 %, and 41%, when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the AUC observed under fasting conditions.

- LS_{mean} ratio of SCH 534128 AUC value increased by 33 %, 29 %, and 36 %, when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the AUC observed under fasting conditions.

- LS_{mean} ratio of SCH 534129 AUC value increased by 46 %, 44 %, and 50 %, when SCH 503034 was administered immediately prior to breakfast, during breakfast, or immediately after breakfast, respectively as compared to the AUC observed under fasting conditions.

- Due to the small sample size, further evaluation of the PK of all three analytes is required to determine if the higher concentrations of all three analytes in Caucasian subjects are clinically and statistically significant.

Conclusion

The systemic exposure of the three analytes (SCH 503034, SCH 534128 and SCH 534129) increased in the presence of a low-fat meal as compared to fasting conditions. The timing of the meal does not have an impact on the systemic exposure of SCH 503034. Plasma concentrations of all three analytes (SCH 503034, SCH 534128, and 534129) were higher in Caucasian subjects (n=6) as compared with African-American subjects (n=6). However, given the small sample size, results should be interpreted with caution.

Since part 2 of the trial was not conducted, no conclusions can be made regarding the dose proportionality of SCH 503034.

Labeling Recommendation

The systemic exposure of boceprevir was similar when boceprevir was administered 5 minutes prior to the meal, during the meal, or immediately following completion of the meal. Therefore, boceprevir can be taken regardless of the timing of the meal.

P03588

The single dose absorption, metabolism and excretion of ^{14}C-SCH 503034 administered as an oral suspension in healthy male subjects.

Objectives

The primary objective of this trial was to characterize the absorption, metabolism, and excretion of SCH 503034, administered as a single dose in an oral suspension containing approximately 125 µCi of total radioactivity, in healthy male subjects.

Study Design

Open label, single-dose trial. Cohort 1 received formulation A ([^{14}C]-SCH 503034, 800 mg (~125 µCi) with methylcellulose) as an oral suspension, and Cohort 2 received formulation B ([^{14}C]-SCH 503034, 800 mg (~125 µCi) with Orasweet®) as an oral suspension. The second cohort was enrolled in the trial due to tolerability issues (associated with the palatability of formulation A) in Cohort 1. The planned sample size of the trial was 12 subjects (six healthy adult male subjects for each of the two cohorts).

In Cohort 1, after an overnight fast, subjects were to be administered a single dose of ^{14}C-SCH 503034 800 mg (~125 µCi) using a suspension after a standard breakfast on Day 1. In Cohort 2, after an overnight fast, subjects were to be administered a single dose of ^{14}C-SCH 503034 800 mg (~125 µCi) on Day 1. The dosing procedures were followed by consumption of a bran muffin. The modifications made to the dose administration in Cohort 2 two were designed to increase the tolerability of the formulation.

In both cohorts, no additional food intake was to be permitted until collection of the 4-hour post-dose blood sample.

Reviewer's comment: The second cohort was added to the trial because the subjects in the first cohort were unable to tolerate the formulation used in the first cohort. The subjects enrolled in the second cohort were to undergo the same procedures as the first cohort, except for the following: the suspension was to contain a sweetener, the suspension was to be less concentrated (per amendment, the concentration was changed from 40 mg/mL to 20 mg/mL), and the subjects were to be dosed in a fasted state.

Drugs Used in the Trial

Table 1 shows the drugs used in the trial

Table 1: Drugs used in the trial

Drug	SCH 503034
Strength	800 mg (125 µCi/bottle)
Batch No.	084195-017-16
Recertification Date	16 FEB 2007
Description	white powder with a specific activity of 0.156 µCi/mg and a radiochemical purity of not less than 95%

Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Blood

Whole blood samples were collected to determine the concentrations of SCH 503034, its stereoisomers (SCH 534128 and SCH 534129), its metabolite (SCH 629144), and the stereoisomers of the metabolite (SCH 783007, SCH 783005, SCH 783006, and SCH 783004) and total radioactivity in blood. The blood samples were collected at the following time points: pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours post-dose. Blood was collected for metabolic profiling at 2, 6, and 24 hours post-dose.

Urine Collection

Urine samples were collected pre-dose and then in block collections at 0-12 hours, 12-24 hours, 24-36 hours, 36-48 hours, and then every 24 hours up to day 8.

Fecal Collection

Fecal samples were collected pre-dose and then in block collections at 0-12 hours, 12-24 hours, 24-36 hours, 36-48 hours, and then every 24 hours up to day 8.

Pharmacokinetic Assessments

Plasma concentrations of two SCH 503034 diastereomers, SCH 534128 and SCH 534129, were analyzed using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Also, plasma concentrations of four isomers of SCH 629144, a ketone-reduced metabolite of SCH 503034, were analyzed. Plasma concentrations of SCH 503034 and SCH 629144 were determined from the sum of SCH 534128 and SCH 534129 (SCH 503034) and the four isomers of SCH 629144, respectively.

Blood, plasma, urine, and fecal samples were analyzed for drug-derived radioactivity by using liquid scintillation spectrometry (LSS); radioactivity was expressed as disintegrations per min (dpm). The sample concentrations of radioactivity were expressed as ng equivalents (equiv)/g and the recovery of administered radioactivity was expressed as a percent (%) of the administered dose.

The plasma concentrations (SCH 503034, SCH 534128, SCH 534129, and SCH 629144) and the total radioactivity in blood and plasma were used to determine the standard pharmacokinetic parameters.

Results

Bioanalytical Assessments

The applicant used method DM 27341 for the bioanalytical assessments. The following analytes were assayed: SCH 534128, SCH 534129, SCH 783007, SCH 783005, SCH 783006, and SCH 783004. All the samples were assayed within the stability period (153 days for SCH 534128 and SCH 534129, 134 days for SCH 783007, 153 days for SCH 783005, and 182 days for SCH 783006 and SCH 783004 at -20^{o}C). The calibration range was the following: 5.24-5240 ng/mL (SCH 534128), 4.76-4760 ng/mL (SCH 534129), 2.5-2500 ng/mL (SCH 783007, SCH 783005, and SCH 783004).

The following quality control samples were analyzed for SCH 534128: low QC (15.7 ng/mL), medium QC (262 ng/mL), medium-high (1310 ng/mL) and high QC (3930 ng/mL). The inter-run precision (% CV) was 5.1 %, 6.1 %, 4.6 %, and 4.1 % and the inter-run accuracy (% difference) was 5.7 %, 4.6 %, 2.3 %, and 2.8 % at the low-, medium-, medium-high, and high QC respectively. For SCH 534129, the following quality control samples were analyzed: low QC (14.3 ng/mL), medium QC (238 ng/mL), medium-high (1190 ng/mL) and high QC (3570 ng/mL). The inter-run precision was 6.4 %, 7.2 %, 5.6 %, and 5.1 % and the inter-run accuracy was 2.1 %, 5 %, 2.5 %, and 1.4 % at the low-, medium-, medium-high, and high QC respectively. For all other analytes, inter-run precision (% CV) and inter-run accuracy (% difference) was < 10 %.

Subject Disposition

A total of 7 subjects completed the trial (all 6 subjects from Cohort 2 and 1 subject from Cohort 1). Out of the 5 subjects who discontinued from Cohort 1, 3 subjects discontinued due to vomiting; 2 subjects were randomized into the study, but did not receive a dose because the investigator and sponsor concluded that the formulation used in Cohort 1 was not tolerable. Therefore, the last two subjects were discontinued for administrative reasons.

The samples generated from Cohort 2 (formulation B) were used in the plasma and whole blood PK analysis.

Demographics

Table 2 shows the summary of the demographic data.

Table 2: Summary of the demographic data

	[^{14}C]SCH 503034 800 mg With Methycellulose Cohort 1 Formulation A (n=6)	[^{14}C]SCH 503034 800 mg With Ora-Sweet Cohort 2 Formulation B (n=6)	Total (n=12)
SEX (n,%)			
Male	6 (100)	6 (100)	12 (100)
RACE (n,%)			
White	4 (67)	3 (50)	7 (58)
Non-White	2 (33)	3 (50)	5 (42)
Asian	0	1 (17)	1 (8)
Black or African-American	0	2 (33)	2 (17)
Multiracial	1 (17)	0	1 (8)
Native Hawaiian or Other Pacific Islander	1 (17)	0	1 (8)
ETHNICITY (n,%)			
Not Hispanic or Latino	6 (100)	6 (100)	12 (100)
AGE (yrs)			
Mean (SD)	22.7 (5.6)	35.7 (9.5)	29.2 (10.1)
Median	20.5	33.5	27.5
Range	19-34	27-52	19-52
AGE (n,%)			
18 - <65	6 (100)	6 (100)	12 (100)
WEIGHT (kg)			
Mean (SD)	74.22 (6.05)	73.37 (11.36)	73.79 (8.69)
Median	73.50	73.15	73.50
Range	67.6-83.1	61.0-88.9	61.0-88.9
HEIGHT (cm)			
Mean (SD)	177.42 (6.65)	175.70 (10.41)	176.56 (8.38)
Median	179.00	176.65	179.00
Range	168.1-186.4	161.4-188.6	161.4-188.6
BMI (kg/m^2)			
Mean (SD)	23.58 (1.68)	23.63 (1.24)	23.61 (1.41)
Median	22.90	23.50	23.10
Range	21.6-25.8	21.8-25.0	21.6-25.8

Height and weight recorded at Visit 1.
BMI = body mass index; SD = standard deviation

Pharmacokinetics

Fig 1 shows the mean plasma concentrations of SCH 503034, SCH 629144,

SCH 534128, and SCH 534129 following a single oral dose of ^{14}C-SCH 503034 (formulation B).

Fig 1: Mean plasma concentrations of SCH 503034, SCH 629144, SCH 534128, and SCH 534129 following a single oral dose of ^{14}C-SCH 503034 (formulation B)

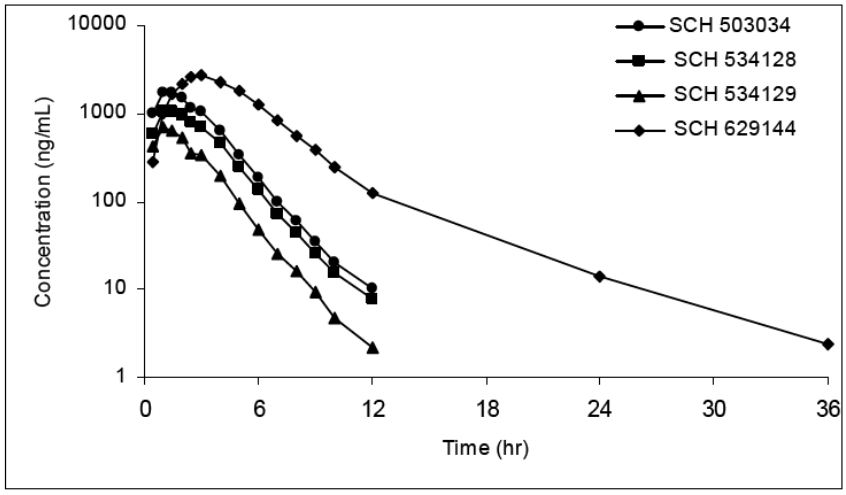


Table 3 shows the mean pharmacokinetic parameters following a single 800 mg oral dose of ^{14}C-SCH 503034 (formulation B)

Table 3: Mean pharmacokinetic parameters following a single 800 mg oral dose of ^{14}C-SCH 503034 (formulation B)

	Plasma SCH 503034		Plasma SCH 534128		Plasma SCH 534129		Plasma SCH 629144	
	Mean (n=6)	(CV)	Mean (n=6)	(CV)	Mean (n=6)	(CV)	Mean (n=6)	(CV)
Cmax (ng/mL)	1860	(22)	1140	(21)	726	(25)	2790	(34)
Tmax (hr)[a]	1.25	(1.0-2.0)	1.25	(1.0-2.0)	1.0	(1.0-2.0)	3.0	(2.5-4.0)
t½ (hr)	1.60	(30)	1.68	(18)	1.97	(44)	-	-
AUC(tf) (ng·hr/mL)	5680	(27)	3730	(28)	1940	(28)	14200	(43)
tf (hr)	11.7	(7)	11.7	(7)	10.3	(13)	28.0	(22)
Cmax/Dose (ng/mL/mg/kg])	168	(18)	103	(21)	64.9	(17)	257	(40)
AUC(tf)/Dose (ng·hr/mL/[mg/kg])	513	(29)	338	(32)	174	(26)	1310	(50)
Cmax Ratio[b]	-	-	-	-	-	-	1.52	(28)
AUC(tf) Ratio[c]	-	-	-	-	-	-	2.47	(21)

Mean (CV) subject weight = 73.4 (15) kg; Mean (CV) weight-adjusted dose = 11.1 (15) mg/kg

CV = coefficient of variation; SLS = sodium laurel sulfate

a: Tmax is reported as median (range).

b: Cmax ratio of SCH 629144:SCH 503034

c: AUC(tf) ratio of SCH 629144:SCH 503034

After oral administration of ^{14}C-SCH 503034 suspension, the plasma concentrations of SCH 503034 in plasma were quantifiable at the earliest sampling time point (0.5 hour). The mean systemic exposure of SCH 534128 was approximately 2-fold greater than the mean systemic exposure of SCH 534129.

^{14}C-SCH 503034 was extensively metabolized to the ketone-reduced metabolite, SCH 629144. The plasma concentrations of SCH 503034 were quantifiable up to 12 hours post-dose whereas the plasma concentrations of SCH629144 were quantifiable up to 36 hours post dose. Fig 2 shows the mean plasma and blood radioactivity and plasma concentration of SCH 503034 following a single oral dose of ^{14}C-SCH 503034 (formulation B).

Fig 2: Mean plasma and blood radioactivity and plasma concentration of SCH 503034 following a single oral dose of ^{14}C-SCH 503034 (formulation B)

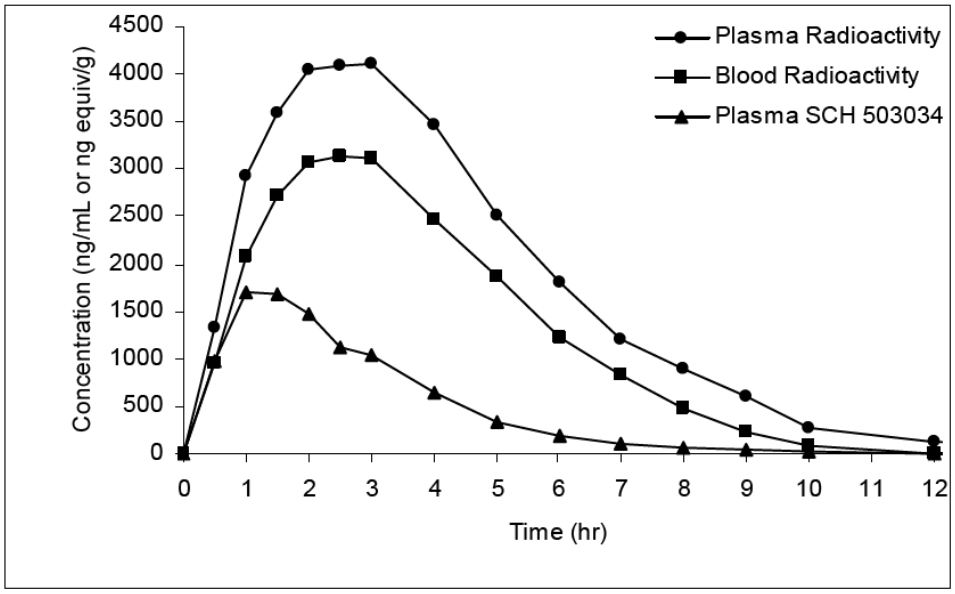


Table 4 shows the mean plasma and blood radioactivity concentrations and pharmacokinetic parameters following a single oral dose of 800 mg ^{14}C-SCH 503034 (formulation B).

Table 4: Mean plasma and blood radioactivity concentrations and pharmacokinetic parameters following a single oral dose of 800 mg 14C-SCH 503034 (formulation B)

	Plasma [^{14}C]SCH 503034 Derived Radioactivity		Whole Blood [^{14}C]SCH 503034 Derived Radioactivity	
Time (hr)	Mean (n=6)	(CV)	Mean (n=6)	(CV)
Cmax (ng equiv/g)	4280	(24)	3320	(21)
Tmax (hr)[a]	2.5	(1.5-3.0)	2.50	(1.5-4.0)
AUC(tf) (ng equiv·hr/g)	21800	(32)	15200	(28)
tf (hr)	10.3	(13)	8.50	(12)
Cmax Ratio (SCH 503034:Radiocarbon)	0.441	(16)	-	-
AUC(tf) Ratio (SCH 503034:Radiocarbon)	0.262	(11)	-	-

CV = coefficient of variation; SLS = sodium laurel sulfate

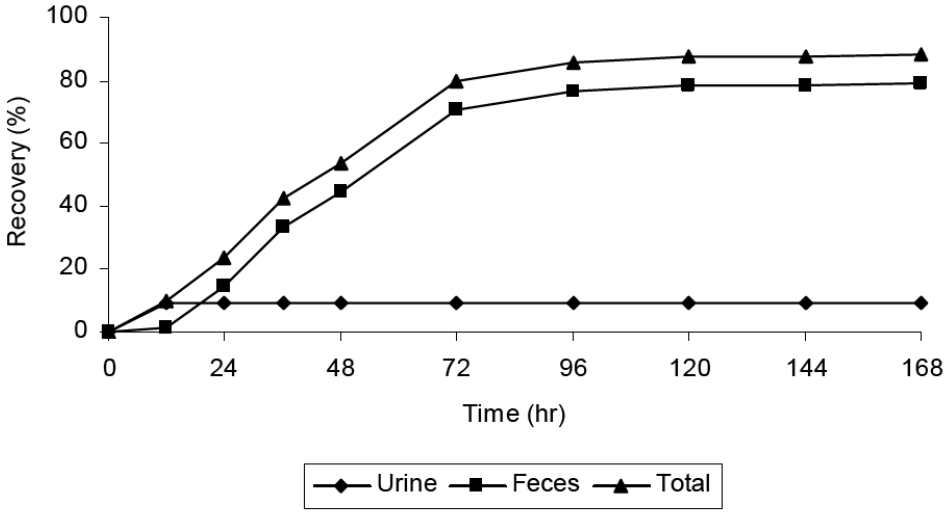
a: Tmax is reported as median (range).

The concentrations of radioactivity in the plasma were greater than the radioactivity in whole blood, suggesting limited partitioning into the red blood cells. The mean SCH 503034 plasma concentration/plasma radioactivity declined from 0.745 to 0.0536 over 12 hours, suggesting extensive metabolism. Based on the ratio of AUC_{tf} values for unchanged drug and total radioactivity, unchanged SCH 503034 accounted for 26 % of the total radioactivity in plasma, thereby suggesting extensive metabolism of SCH 503034.

Total Radioactivity in Urine and Feces

Fig 3 shows the mean cumulative excretion of radioactivity in the urine and feces following a single 800 mg oral dose of ^{14}C-SCH 503034 administered as formulation B.

Fig 3: Mean cumulative excretion of radioactivity in the urine and feces following a single 800 mg oral dose of 14C-SCH 503034 administered as formulation B



The radioactivity in the urine and feces accounted for 9.28 % (range: 7.26-11.8 %) and 78.9 % (75.8 % to 83.5 %) of the dose, respectively. The excretion of radioactivity into the urine was fast with ~95 % of the radioactivity collected in the 0-12 hour sample collection period. With the exception of one subject, the excretion of radioactivity in feces was quantifiable in all subjects at the final collection interval (144-168 hours). Table 5 shows the urinary and fecal recovery of radioactivity following a single 800 mg dose of ^{14}C-SCH 503034 (formulation B).

Table 5: Urinary and fecal recovery of radioactivity following a single 800 mg dose of 14C-SCH 503034 (formulation B)

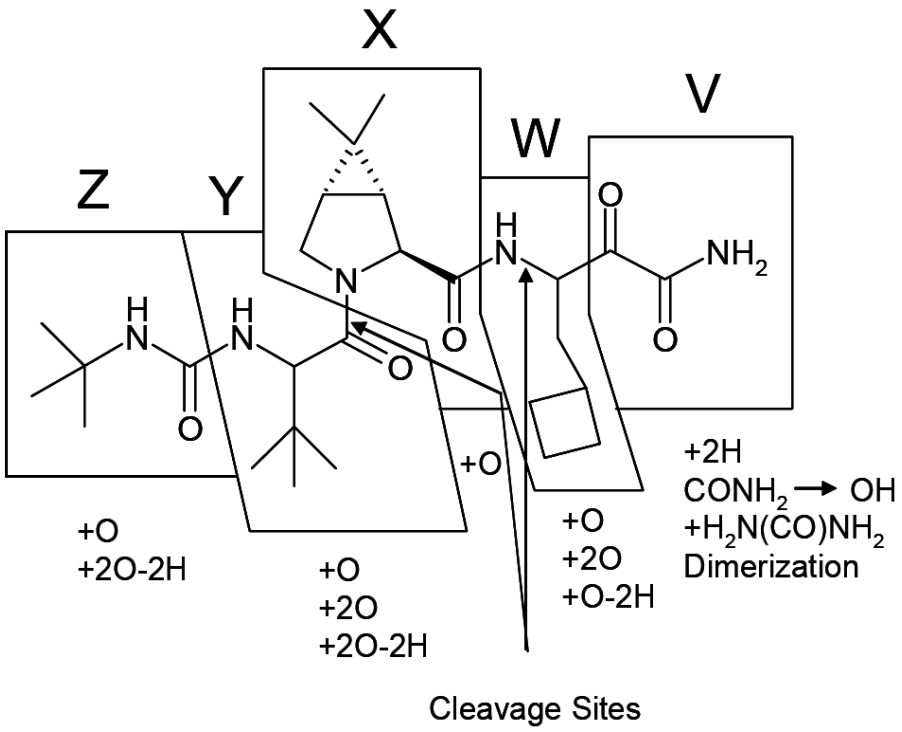
Matrix	Time (hr)	Percent of Dose							
		Subject Number							
		1/000201	1/000202	1/000203	1/000204	1/000205	1/000206	Mean	CV (%)
Urine	0-12	(b) (4)						8.85	(22)
	12-24							0.294	(24)
	24-36							0.0883	(52)
	36-48							0.0275	(114)
	48-72							0.0213	(172)
	72-96							0.00512	(245)
	96-120							0	NC
	120-144							0	NC
	144-168							0	NC
Feces	0-12							0.986	(168)
	12-24							16.6	(137)
	24-36							31.8	(49)
	36-48							23.0	(96)
	48-72							25.9	(76)
	72-96							6.75	(122)
	96-120							2.18	(135)
	120-144							0.319	(164)
	144-168							0.463	(205)
Urine (total)		9.79	11.2	8.11	7.26	7.53	11.8	9.28	(21)
Feces (total)		77.9	77.0	83.5	81.9	77.5	75.8	78.9	(4)
Total		87.7	88.2	91.6	89.2	85.0	87.6	88.2	(2)

CV = coefficient of variation; NC = not calculated; NS = no sample; SLS = sodium laurel sulfate

Metabolite Profiling

The metabolite profiling was performed on pooled plasma, urine, and feces samples. Fig 4 shows the major metabolic regions of ^{14}C-SCH 503034.

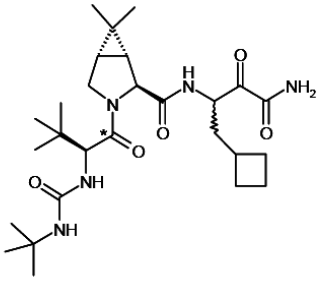
Fig 4: Major metabolic regions of ^{14}C-SCH 503034



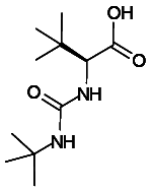
SCH 503034 accounted for approximately 38 % and 10 % of the circulating radioactivity in 2-hour and 6-hour plasma, respectively. The ketone reduced metabolite M+2 metabolites (M28, M30, M31) were the most abundant circulating metabolites; combined, they accounted for approximately 46 % and 70 % of the circulating radioactivity in the 2-hour and 6-hour plasma, respectively. The only other major circulating metabolite that exceeded 3 % of the dose was MOBA (SCH 503034-K; hydrolytic cleavage product), which accounted for 13 % and 19 % of the circulating radioactivity in the 2-hour and 6-hour plasma, respectively. Of note, MOBA was also detected in another clinical trial (P04983) in which the boceprevir formulation contained (b) (4) SLS, thereby suggesting that MOBA may be formed by the SLS catalyzed hydrolysis in the stomach and the circulating levels of MOBA could be due to the SLS in the suspension.

Fig 5 shows the chemical structures of ^{14}C-SCH 503034 and some of its major metabolites.

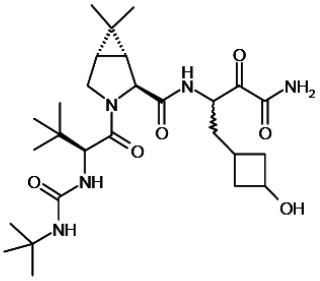
Fig 5: Chemical structures of ^{14}C-SCH 503034 and some of its major metabolites



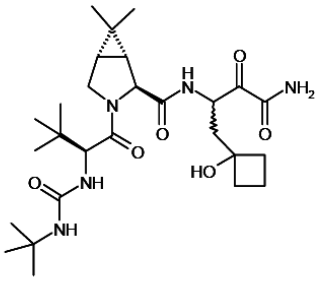
^{14}C-SCH 503034
(SCH 534128 and SCH 534129)



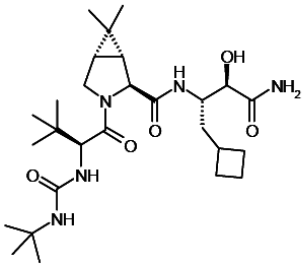
M0BA (SCH 503034-K)



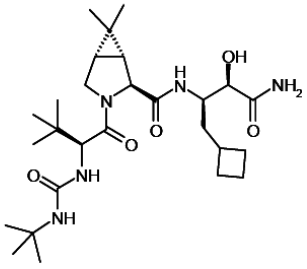
M11, M16 (SCH 641574)



M23, M24 (SCH 564649)



M28 (SCH 783007)
Peak #2 of SCH 629144 in
Metabolite Profiling Method



M31 (SCH 783004)
Peak #4 of SCH 629144 in
Metabolite Profiling Method

Note: * denotes the site of the ^{14}C label

Metabolite Profiling in Urine

Table 6 shows the metabolites contained within radioactive peaks representing ≥ 3 % of the radiochromatographic profiles in pooled urine obtained from healthy male subjects following a single oral administration of 800 mg ^{14}C-SCH 503034.

Table 6: Metabolites contained within radioactive peaks representing ≥ 3 % of the radiochromatographic profiles in pooled urine obtained from healthy male subjects following a single oral administration of 800 mg ^{14}C-SCH 503034.

Designation	Rt (min)[a]	m/z (Th)	Δ[b]	% of Profiled Radioactivity	% of Dose[c]
M0BA	12.0	231	-289	4.02	0.356
M1AC	14.5	554	+34	3.61	0.319
M1AB		383	-137		
M1CB/M1CBB		568	+48		
M15	22.2	367	-153	7.80	0.690
M16 (SCH 641574) (minor)		536	+16		
M17 (minor)		538	+18		
M28 (SCH 783007)[d]	40.1	522	+2	15.2	1.34
M29	41.4	580	+60	5.25	0.465
M30 (SCH 783006)[e]		522	+2		
SCH 534128	43.3	520	0	21.8[f]	1.93
M31 (SCH 783004)[g]		522	+2	23.8[f]	2.11
SCH 534129	44.8	520	0	12.5	1.10

a: Retention time taken from the radiochromatogram of C7042703.

b: Difference between the m/z of the metabolite and SCH 503034 molecular ion.

c: Metabolite % of Dose = fraction of dose excreted in the pooled urine (0.0885) x % of profiled radioactivity.

d: M28 (SCH 783007) is Peak #2 in the four diastereomers of SCH 629144.

e: M30 (SCH 783006) is Peak #3 in the four diastereomers of SCH 629144.

f: SCH 534128 overlapped with M31, relative contribution of each component was calculated based on the relative MS response factor between SCH 503034 and SCH 629144 (P02727).

g: M31 (SCH 783004) is Peak #4 in the four diastereomers of SCH 629144.

M28, M31, SCH 534128, and SCH 534129 were the major (> 10 % of the profiled radioactivity) drug-related compounds excreted in the urine. Approximately 3 % of the radioactivity was recovered in the urine as boceprevir (SCH 534128 and SCH 534129 combined). M28 and M31 represented 3.45 % of the radioactivity.

Metabolite Profiling in Feces

Table 7 shows the metabolites contained within radioactive peaks representing ≥ 3 % of the radiochromatographic profiles in pooled feces obtained from healthy male subjects following a single oral administration of 800 mg ^{14}C-SCH 503034.

Table 7: Metabolites contained within radioactive peaks representing ≥ 3 % of the radiochromatographic profiles in pooled feces obtained from healthy male subjects following a single oral administration of 800 mg ^{14}C-SCH 503034.

Designation	Rt (min)[a]	m/z (Th)	Δ[b]	% of Profiled Radioactivity	% of Dose[c]
M0B	12.3	566	+46	3.20	2.36
M0DC		568	+48		
M0BA		231	-289		
M1AA	14.0	568	+48	3.00	2.22
M1AC		554	+34		
M1AD		552	+32		
M1E	15.9	554	+34	6.82	5.04
M2/M2AA		552	+32		
M2A/M2AB		550	+30		
M3		554	+34		
M4		368	-152		
M4A	17.4	383	-137	4.34	3.21
M4B		534	+14		
M5A		552	+32		
M6		554	+34		
M7	19.1	538	+18	5.11	3.78
M8		538	+18		
M8A		550	+30		
M9/M9A		552	+32		
M10B	20.1	554	+34	3.15	2.33
M11 (SCH 641574)		536	+16		
M12		536	+16		
M12A		552	+32		
M13	21.5	538	+18	3.46	2.56
M13A		534	+14		
M14		552	+32		
M15	22.2	367	-153	3.58	2.65
M15A		534	+14		
M16 (SCH 641574)		536	+16		
M17		538	+18		
M18	23.8	552	+32	5.52	4.08
M18A/M18AA		538	+18		
M18C		536	+16		
M18D		534	+14		
M19/M19A		538	+18		
M20	28.1	552	+32	13.3	9.83
M21/M21A		536	+16		
M22		538	+18		
M22AA		538	+18		
M22B		493	-27		
M28 (SCH 783007)[d]	40.3	522	+2	15.2	11.2
M30 (SCH 783006)[e]		522	+2		
SCH 534128	43.3	520	0	6.44[f]	4.76
M31 (SCH 783004)[g]		522	+2	9.47[f]	7.00
SCH 534129	44.8	520	0	4.08	3.02
M32B	49.9	1072	+552	3.99	2.95
M33		1056	+536		
M34		1040	+520		

a: Retention time taken from the radiochromatogram of C7072503.

b: Difference between the m/z of the metabolite and SCH 503034 molecular ion.

c: Metabolite % of Dose = fraction of dose excreted in the pooled feces (0.739) x % of profiled radioactivity.

d: M28 (SCH 783007) is Peak #2 in the four diastereomers of SCH 629144.

e: M30 (SCH 783006) is Peak #3 in the four diastereomers of SCH 629144.

f: SCH 534128 overlapped with M31, relative contribution of each component was calculated based on the average relative MS response factor between SCH 503034 and SCH 629144 in plasma and urine (P02727).

g: M31 (SCH 783004) is Peak #4 in the four diastereomers of SCH 629144.

The M+2 metabolites, M28, M30, and M31 were the major drug-related compounds excreted in the feces and collectively represent 18 % of the dose. Approximately 8 % of the dose was excreted as boceprevir (SCH 534128 and 534129 combined). The fecal excretion of MOBA accounted for less than 2 % of the dose.

Results

- After oral administration of ^{14}C-SCH 503034, the mean $t_{½}$ values were 1.60 hours, 1.68 hours, and 1.97 hours for SCH 503034, SCH 534128, and SCH 534129, respectively.

- After oral administration of ^{14}C-SCH 503034, SCH 503034 was extensively metabolized to the ketone-reduced metabolite, SCH 629144.

- The mean systemic exposure of SCH 534128 was approximately 2-fold greater than the mean exposure of SCH 534129.

- After 168 hours of oral drug administration of ^{14}C-SCH 503034, a total of 88.2 % (range, 85.0 %-91.6 %) of the radioactive dose was recovered in the urine (9.28 %) and feces (78.9 %), respectively.

    - Approximately, 3 % and 8 % of the radioactivity was recovered in the urine and feces as boceprevir (SCH 534128 and SCH 534129 combined), respectively.

Conclusion

- The results of the trial suggest that the major pathway of elimination of SCH 503034 is via metabolism. The metabolites are primarily excreted in the feces.

- Renal elimination seems to play a minor role in the elimination of SCH 503034 and its metabolites.

P04488

Influence of Race/Ethnic Origin on the Pharmacokinetics of SCH 503034

Trial Periods

Study Initiation Date: June 5, 2006
Study Completion Date: March 20, 2007

Objectives

- Determine if steady state pharmacokinetics (PK) of SCH 503034 differ between Japanese and Caucasian subjects while subjects were maintained on a Japanese meal.

- To evaluate the PK of SCH 503034 after a single dose administration under fasted and fed conditions in Japanese and Caucasian subjects.

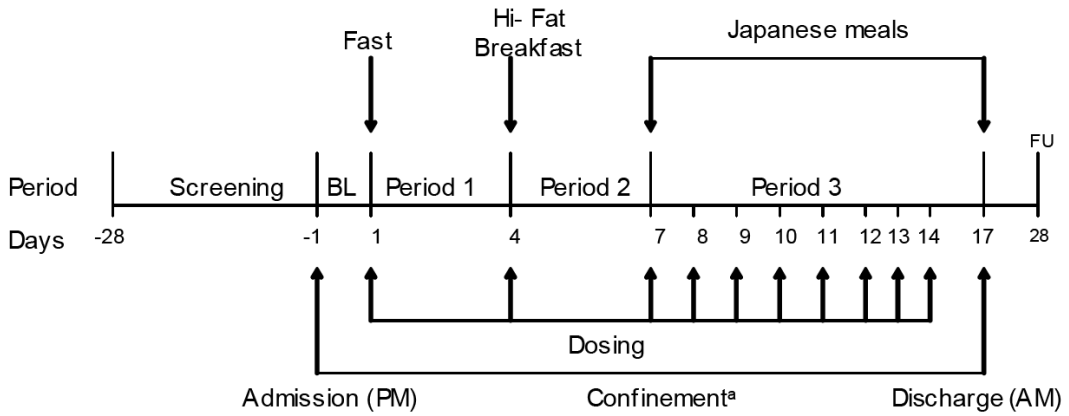
- To evaluate the dose proportionality in Japanese and Caucasian subjects

Trial Design

Phase 1, open label, single- and multiple-dose (three-dose levels), randomized trial of SCH 503034 conducted in a fixed sequence fashion in healthy Japanese and Caucasian volunteers.

Schematic 1 shows the outline of the study design.

Schematic 1: Outline of the Study Design



a: Subjects that were discharged between periods after completion of all the procedures scheduled on Day 3 and Day 6, were to return to the study center within 7 days. If a subject was to leave the study center between the periods, he/she was to return to the study center the night before the next dosing and a urine drug test was to be performed to ensure eligibility.

Subjects were randomized to one of the three treatments (Treatment A: SCH 5030304 200 mg; treatment B: SCH 503034 400 mg, and treatment C: SCH 503034 800 mg) and received the study medication in the following three periods:

Period 1 (Day 1-3): Subjects were administered SCH 503034 as a single dose following an overnight fast.

Period 2 (Day 4-6): Subjects were administered SCH 503034 as a single dose with a high fat breakfast (western diet; standardized high-fat breakfast).

Period 3 (Day 7-17): Subjects were administered SCH 503034 TID (8 AM, 4 PM, and 12 PM) for 6 days (Days 8-13) with a Japanese meal or a snack plus a single dose in the morning of days 7 and 14 with a Japanese breakfast.

The comparison of the pharmacokinetic parameters from Period 1 and Period 2 were to allow the examination of the food effect in Japanese and Caucasian subjects. The plasma concentration data collected after the first dose in Period 3 were to allow the comparison of the effect of the Western Diet and Japanese diet on the pharmacokinetics of SCH 503034 in Japanese and Caucasian subjects.

Table 1 shows the sample standardized high fat breakfast.

Table 1: Sample High Fat Breakfast menu

Standardized High-Fat Breakfast					
Item	Amount	Calories	Protein (gm)	Fat (gm)	Carbohydrate (gm)
Eggs (Fried)	2	191	14	15	-
Bacon (Strip)	2	96	3.6	8.8	0.4
Toast (Slice)	2	136	4	-	30
Butter (Pat)	2	90	-	10	-
Hash Browned Potatoes	4 oz	158	2	10	15
Whole Milk	8 oz	170	8	10	12
Total		841	31.6	53.8	57.4

Table 2 shows the sample standardized Japanese meal menu

Table 2: Sample Standardized Japanese Meal Menu

Standardized Japanese Breakfast					
Item	Amount	Calories	Protein (gm)	Fat (gm)	Carbohydrate (gm)
Steamed White Rice	1 bowl	205	4g	0.5g	45g
Miso soup	1 bowl	36	2g	1g	5g
Steamed vegetables	½ Cup	20	2g	0g	5g
Fish with some soy sauce	6 oz	250	47g	7g	0
Total		**511**	**55**	**8.5**	**55**

Reviewer's comment: The timing of dosing, relative to the meal or snack was to be determined from the results of trial P04133 which indicated that the exposure SCH 503034 did not differ significantly when the compound was administered before, during, or after the meal, therefore, to be consistent, it was decided (by the applicant) that dosing of SCH 503034 should occur after the meal.

Drugs Used in the Trial

Table 3 provides the description of the investigational products used in the trial. The 200 mg capsule formulation used in this trial was the commercial formulation.

Table 3: Description of the investigational products used in the trial

Drug	SCH 503034	SCH 503034
Strength	200 mg	200 mg
Batch No.	K-H07164	K-H06953
FMR No.	(b) (4)	
Manufacturing Date		
Manufacturing Site		
Recertification Date		
Batch Size		
Description		

The drug was to be stored in a refrigerator between 2-8^{0}C and was to be compliant until the recertification date (date after the date of the last dose administered)

Prior and Concomitant Therapy

All prior medication taken by the subject within 14 days of initiation of the trial (Day 1) and all concomitant therapy taken by the subject during the trial were to be recorded on the eCRF. The identity of the therapy, the dose, route, and regimen, the dates started and stopped (or notation of “continuing” if that was the case), and the reason for use were to be recorded.

No medications (other than the study medication) were to be taken by the subject within 14 days of treatment or during the course of the trial without prior approval from the principal investigator and Sponsor, unless it was a medical emergency.

Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Blood samples were to be collected on Days 1, 4, 7, and 14 prior to 8 AM (0-hours dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 hours post-dose. On days 2 and 5, a sample was to be collected 24 hours post dose. On days 3 and 6, a 48-hour post-dose sample was also collected. On days 8, 9, 10, 11, 12, and 13, a sample was to be collected immediately prior to the morning dose. Additional samples were to be collected on days 15, 16, and 17 at approximately 24, 48, and 72 hours after the last dose.

SCH 503034 consists of two inter-convertible stereoisomers: SCH 534128 and SCH 534129. All plasma samples were to be assayed for SCH 534128 and 534129 using a validated chiral liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method. All assays were to be conducted

by the [redacted] (b) (4)

Pharmacokinetic Assessments

Plasma concentration data for SCH 534128 and SCH 534129 were added to derive the plasma concentration of SCH 503034. The plasma concentration-time data of SCH 503034, SCH 534128 and SCH 534129 was used to estimate the standard pharmacokinetic parameters.

Results

Bioanalytical Assessments

The applicant used method DM 27268 for the bioanalytical assessments. A total of 2327 samples were assayed within the stability period (277 days at -20^{o}C). The samples were assayed between August 10, 2006 to April 23, 2007. The calibration range for SCH 534128 and SCH 534129 was from 1.31 ng/mL to 655 ng/mL and 1.19 ng/mL to 595 ng/mL respectively. The following quality control samples were analyzed for SCH 534128: low QC (3.93 ng/mL), medium QC (78.6 ng/mL) and high QC (472 ng/mL). The inter-run precision was 6.9 %, 4.7 %, and 3.6 % and the inter-run accuracy was 0.3 %, 0.5 %, and 3 % at the low-, medium-, and high QC respectively. For SCH 534129, the following quality control samples were analyzed: low QC (3.57 ng/mL), medium QC (71.4 ng/mL) and high QC (428 ng/mL). The inter-run precision was 6.5 %, 4.9 %, and 4 % and the inter-run accuracy was 0.6 %, 1.5 %, and 3.3 % at the low-, medium-, and high QC respectively.

Subject Disposition

A total of 38 subjects (18 Caucasian and 20 Japanese) were randomized to receive SCH 503034: 12 in the 200 mg group, 13 in the 40 mg group, and 13 in the 800 mg group. 36 subjects were matched (age, weight, and height were to be within ± 8 years, ± 7 kg, and ± 15 centimeters, respectively) into 18 Japanese/Caucasian pairs, and two Japanese subjects were unmatched.

Protocol Deviations

During the course of the study there were instances of deviations from the protocol. The differences between the matched pairs of subjects for those continuous variables used to establish a match (age, weight, height) were to be within ±8 years, ±7 kilograms, ±15 centimeters, respectively. All matched pairs met these criteria except the match between Subject 213 and Subject 113. For these subjects, there was a site-specific protocol deviation in the weight

differences. The protocol deviations and the deviations in pharmacokinetic sampling times were not considered to have a significant effect on the study assumptions, results or conclusions derived from the experimental data.

In Period 3 (multiple-dose, Japanese diet), subjects were to receive SCH 503034 three times daily for 6 days (Days 8 to 13) and a single dose of SCH 503034 on Days 7 and 14. However, study drug suppies were consumed after Day 10 due to shortage. Therefore, end-of-study procedures on Day 14 were completed on Day 11. PK data reported as “Day 14” results below are actually from Day 11.

Summary of Demographic Data

Table 4 shows the summary of the demographic data.

Table 4: Summary of the demographic data

	SCH 503034 200 mg		SCH 503034 400 mg		SCH 503034 800 mg	
	Caucasian (n=6)	Japanese (n=6)	Caucasian (n=6)	Japanese (n=7)	Caucasian (n=6)	Japanese (n=7)
SEX (n,%)						
Male	6 (100)	6 (100)	6 (100)	7 (100)	6 (100)	7 (100)
AGE (yrs)						
Mean (SD)	31.3 (9.2)	31.8 (12.3)	40.0 (11.5)	33.3 (11.4)	27.0 (5.4)	25.3 (3.8)
Median	27.0	27.0	40.5	33.0	27.5	25.0
Range	22-43	21-48	26-52	21-45	21-35	20-31
AGE (n,%)						
18 - <65	6 (100)	6 (100)	6 (100)	7 (100)	6 (100)	7 (100)
WEIGHT (kg)						
Mean (SD)	76.98 (4.74)	75.88 (8.35)	72.03 (6.67)	72.13 (11.00)	65.37 (7.44)	64.41 (6.76)
Median	75.15	74.85	69.40	67.60	63.90	66.10
Range	72.5-84.2	67.7-87.9	66.0-83.2	59.0-88.6	58.4-78.7	53.0-72.9
HEIGHT (cm)						
Mean (SD)	180.33 (4.32)	177.58 (3.51)	177.17 (4.78)	172.06 (7.47)	175.65 (4.51)	171.34 (4.17)
Median	182.20	176.95	178.20	169.70	176.10	170.70
Range	174.0-184.3	173.2-182.8	169.1-183.2	163.7-181.5	168.3-180.8	166.3-179.2
BMI (kg/m^2)						
Mean (SD)	23.68 (1.81)	24.10 (2.97)	22.93 (1.77)	24.27 (2.27)	21.15 (1.93)	21.94 (2.01)
Median	23.55	23.60	23.05	24.80	20.80	21.90
Range	21.6-26.3	20.8-28.6	20.5-24.8	21.2-27.9	19.2-24.6	19.2-25.7

Height, weight, and BMI recorded at Visit 1.
BMI = body mass index; SD = standard deviation

Pharmacokinetics

Out of the 38 subjects were randomized in the trial; 36 subjects were matched into 18 Japanese/Caucasian pairs, and two Japanese subjects were unmatched. Mean PK parameters were estimated for a total of 33 subjects (17 Japanese and 16 Caucasian): 12 subjects who received SCH 503034 200 mg, 9 subjects who received SCH 503034 400 mg, and 12 subjects who received SCH 503034 800 mg. Day 14 analysis was conducted in 15 Japanese and 15 Caucasian subjects and included 12 subjects in the 200 mg group, 6 subjects in the 400 mg group, and 12 subjects in the 800 mg group.

Single Dose Pharmacokinetics (under fasted conditions on day 1, fed conditions {

high fat breakfast} on day 4, and fed conditions (Japanese breakfast) on day 7

SCH 503034

After single dose administration of 200 mg SCH 503034 to Caucasian and Japanese subjects, the mean PK parameters of SCH 503034 were estimated from 6 subjects on day 1, 6 subjects on day 4, and 6 subjects on day 7.

After single dose administration of 400 mg SCH 503034 to Caucasian subjects, the mean PK parameters of SCH 503034 were estimated from 6 subjects on day 1, 6 subjects on day 4, and 5 subjects on day 7 (subject 210 was included in estimation of day 1 and day 4 PK parameters but discontinued before day 7). After single dose administration of 400 mg SCH 503034 to Japanese subjects, mean PK parameters of SCH 503034 were estimated from 5 subjects on day 1, 5 subjects on day 4, and 5 subjects on day 7

After single dose administration of 800 mg SCH 503034 to Caucasian and Japanese subjects, the mean PK parameters of SCH 503034 were estimated from 6 subjects on day 1, 6 subjects on day 4, and 6 subjects on day 7.

Table 5 shows the mean pharmacokinetic parameters of SCH 503034 after a single oral dose of SCH 503434 in Caucasian subjects

Table 5: Mean pharmacokinetic parameters of SCH 503034 after a single oral dose of SCH 503434 in Caucasian subjects

	SCH 503034 200 mg			SCH 503034 400 mg			SCH 503034 800 mg		
	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)
Tmax [a] (hr)	1.00 (1.00-2.50)	3.00 (1.50-6.00)	2.75 (2.00-4.00)	1.50 (1.00-3.00)	3.00 (2.00-3.00)	2.50 (2.50-5.00)	1.50 (0.500-3.00)	3.50 (2.50-4.00)	4.00 (2.00-5.00)
Cmax (ng/mL)	346 (36)	339 (36)	345 (33)	435 (14)	698 (24)	664 (19)	1370 (74)	1710 (18)	1450 (25)
AUC(tf) (ng·hr/mL)	861 (29)	994 (25)	1020 (31)	1280 (15)	2100 (20)	1930 (15)	4210 (42)	6350 (14)	5560 (9)
AUC(I) (ng·hr/mL)	869 (29)	1000 (26)	1030 (30)	1300 (15)	2120 (20)	1960 (15)	4240 (42)	6370 (14)	5650 (9)
AUC(0-8) (ng·hr/mL)	-	-	969 (33)	-	-	1850 (16)	-	-	5150 (10)
t½ (hr)	2.25 (48)	2.05 (29)	1.90 (24)	3.43 (57)	1.95 (37)	2.05 (38)	3.58 (37)	3.00 (31)	1.61 (10)
tf (hr)	13.7 (38)	14.0 (35)	12.0 (0)	18.0 (37)	14.0 (35)	12.0 (0)	22.0 (22)	22.0 (22)	12.0 (0)
CL/F (L/hr)	244 (25)	209 (21)	210 (31)	314 (16)	196 (21)	208 (16)	216 (40)	128 (14)	143 (9)
Vd/F (L)	727 (22)	625 (36)	595 (49)	1550 (55)	576 (62)	611 (38)	1170 (71)	541 (28)	331 (14)
Cmax_D [b] (ng/mL)	346 (36)	339 (36)	345 (33)	217 (14)	349 (24)	332 (19)	342 (74)	427 (18)	363 (25)
AUC(tf)_D [b] (ng·hr/mL)	861 (29)	994 (25)	1020 (31)	639 (15)	1050 (20)	966 (15)	1050 (42)	1590 (14)	1390 (9)
AUC(I)_D [b] (ng·hr/mL)	869 (29)	1000 (26)	1030 (30)	649 (15)	1060 (20)	981 (15)	1060 (42)	1590 (14)	1410 (9)
AUC(0-8)_D [b] (ng·hr/mL)	-	-	969 (33)	-	-	926 (16)	-	-	1290 (10)

Data presented as mean (CV)

a: Median (range)

b: Dose-normalized to 200 mg SCH 503034

CV = coefficient of variation

Day 1: A single dose under fasted conditions, plasma data collected until 48 hours postdose

Day 4: A single dose with high-fat breakfast, plasma data collected until 48 hours postdose

Day 7: A single dose with Japanese meal, plasma data collected until 12 hours postdose

<u>Reviewer's comment:</u> The mean pharmacokinetic parameters determined on day 7 after administration of a single dose of SCH 503034 to Caucasian subjects

is based on pharmacokinetic data collected in 5 subjects (instead of the 6 subjects as shown in table 5.)

Table 6 shows the mean pharmacokinetic parameters of SCH 503034 after a single oral dose of SCH 503434 in Japanese subjects

Table 6: Mean pharmacokinetic parameters of SCH 503034 after a single oral dose of SCH 503434 in Japanese subjects

	SCH 503034 200 mg			SCH 503034 400 mg			SCH 503034 800 mg		
	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)	Day 1 (n=5)	Day 4 (n=5)	Day 7 (n=5)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)
Tmax [a] (hr)	1.00 (0.500-1.50)	2.75 (2.50-5.00)	2.75 (2.00-5.00)	2.50 (1.50-4.00)	3.00 (3.00-5.00)	2.50 (2.50-5.00)	1.50 (1.00-2.50)	2.75 (2.50-5.00)	3.00 (1.50-4.00)
Cmax (ng/mL)	394 (22)	460 (11)	545 (56)	453 (32)	753 (19)	763 (26)	1100 (44)	2040 (24)	1830 (29)
AUC(tf) (ng·hr/mL)	884 (23)	1090 (18)	1100 (37)	1350 (25)	2280 (17)	2260 (15)	3380 (37)	6360 (20)	5410 (17)
AUC(I) (ng·hr/mL)	898 (23)	1100 (18)	1120 (37)	1370 (25)	2290 (17)	2280 (15)	3440 (37)	6370 (20)	5440 (17)
AUC(0-8) (ng·hr/mL)	-	-	1060 (38)	-	-	2180 (16)	-	-	5250 (17)
t½ (hr)	2.77 (54)	1.58 (17)	1.85 (25)	4.71 (53)	1.36 (25)	1.44 (17)	4.84 (33)	2.40 (37)	1.62 (18)
tf (hr)	13.7 (38)	12.0 (0)	12.0 (0)	21.6 (25)	12.0 (0)	12.0 (0)	24.0 (0)	18.0 (37)	12.0 (0)
CL/F (L/hr)	233 (24)	188 (19)	196 (28)	313 (34)	179 (16)	179 (15)	260 (36)	129 (18)	151 (19)
Vd/F (L)	920 (63)	421 (16)	508 (28)	2340 (81)	341 (14)	368 (12)	1790 (43)	432 (34)	351 (23)
Cmax_D [b] (ng/mL)	394 (22)	460 (11)	545 (56)	226 (32)	377 (19)	382 (26)	276 (44)	511 (24)	458 (29)
AUC(tf)_D [b] (ng·hr/mL)	884 (23)	1090 (18)	1100 (37)	674 (25)	1140 (17)	1130 (15)	844 (37)	1590 (20)	1350 (17)
AUC(I)_D [b] (ng·hr/mL)	898 (23)	1100 (18)	1120 (37)	684 (25)	1140 (17)	1140 (15)	861 (37)	1590 (20)	1360 (17)
AUC(0-8)_D [b] (ng·hr/mL)	-	-	1060 (39)	-	-	1090 (16)	-	-	1310 (17)

Data presented as mean (CV)

a: Median (range)

b: Dose-normalized to 200 mg SCH 503034

CV = coefficient of variation

Day 1: A single dose under fasted conditions, plasma data collected until 48 hours postdose

Day 4: A single dose with high-fat breakfast, plasma data collected until 48 hours postdose

Day 7: A single dose with Japanese meal, plasma data collected until 12 hours postdose

SCH 534128

Table 7 shows the mean pharmacokinetic parameters of SCH 534128 after a single oral dose of SCH 503434 in Caucasian subjects

Table 7: Mean pharmacokinetic parameters of SCH 534128 after a single oral dose of SCH 503434 in Caucasian subjects

	SCH 503034 200 mg			SCH 503034 400 mg			SCH 503034 800 mg		
	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=5)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)
Tmax [a] (hr)	1.00 (1.00-2.50)	3.00 (1.50-6.00)	3.00 (2.50-4.00)	1.75 (1.00-3.00)	3.00 (2.50-4.00)	2.50 (2.50-5.00)	1.75 (1.00-3.00)	3.50 (2.50-4.00)	4.00 (2.50-6.00)
Cmax (ng/mL)	203 (31)	192 (37)	198 (28)	266 (17)	418 (23)	420 (22)	807 (72)	1080 (21)	918 (25)
AUC(tf) (ng·hr/mL)	541 (21)	593 (19)	616 (27)	851 (17)	1320 (18)	1270 (14)	2720 (42)	4170 (16)	3610 (6)
AUC(I) (ng·hr/mL)	548 (21)	601 (20)	628 (26)	868 (18)	1330 (19)	1290 (14)	2750 (41)	4180 (16)	3680 (5)
AUC(0-8) (ng·hr/mL)	-	-	583 (29)	-	-	1210 (15)	-	-	3310 (9)
$t_{½}$ (hr)	2.52 (57)	2.37 (35)	2.09 (20)	3.69 (60)	1.96 (55)	1.66 (10)	3.79 (39)	3.36 (39)	1.60 (8)
tf (hr)	13.7 (38)	14.0 (35)	12.0 (0)	18.0 (37)	14.0 (35)	12.0 (0)	22.0 (22)	22.0 (22)	12.0 (0)

Data presented as mean (CV)

a: Median (range)

CV = coefficient of variation

Day 1: A single dose under fasted conditions, plasma data collected until 48 hours postdose

Day 4: A single dose with high-fat breakfast, plasma data collected until 48 hours postdose

Day 7: A single dose with Japanese meal, plasma data collected until 12 hours postdose

Table 8 shows the mean pharmacokinetic parameters of SCH 534128 after a single oral dose of SCH 503434 in Japanese subjects

Table 8: Mean pharmacokinetic parameters of SCH 534128 after a single oral dose of SCH 503434 in Japanese subjects

	SCH 503034 200 mg			SCH 503034 400 mg			SCH 503034 800 mg		
	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)	Day 1 (n=5)	Day 4 (n=5)	Day 7 (n=5)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)
Tmax [a] (hr)	1.00 (1.00-1.50)	2.75 (2.50-5.00)	2.75 (2.00-5.00)	2.50 (1.50-4.00)	4.00 (3.00-5.00)	2.50 (2.50-5.00)	1.75 (1.00-2.50)	2.75 (2.50-5.00)	3.00 (1.50-5.00)
Cmax (ng/mL)	226 (24)	272 (9)	305 (48)	291 (34)	470 (22)	472 (30)	698 (46)	1270 (24)	1140 (25)
AUC(tf) (ng·hr/mL)	566 (18)	671 (16)	684 (30)	912 (27)	1460 (19)	1500 (17)	2270 (39)	4170 (23)	3560 (17)
AUC(I) (ng·hr/mL)	577 (18)	679 (16)	695 (30)	929 (26)	1470 (19)	1510 (17)	2320 (39)	4180 (22)	3580 (17)
AUC(0-8) (ng·hr/mL)	-	-	651 (32)	-	-	1440 (18)	-	-	3440 (18)
$t_{½}$ (hr)	3.00 (59)	2.35 (47)	2.00 (26)	5.30 (56)	1.46 (22)	1.59 (19)	5.22 (29)	2.55 (48)	1.49 (19)
tf (hr)	13.7 (38)	12.0 (0)	12.0 (0)	21.6 (25)	12.0 (0)	12.0 (0)	24.0 (0)	18.0 (37)	12.0 (0)

Data presented as mean (CV)

a: Median (range)

CV = coefficient of variation

Day 1: A single dose under fasted conditions, plasma data collected until 48 hours postdose

Day 4: A single dose with high-fat breakfast, plasma data collected until 48 hours postdose

Day 7: A single dose with Japanese meal, plasma data collected until 12 hours postdose

SCH 534129

Table 9 shows the mean pharmacokinetic parameters of SCH 534129 after a single oral dose of SCH 503434 in Caucasian subjects.

Table 9: Mean pharmacokinetic parameters of SCH 534129 after a single oral dose of SCH 503434 in Caucasian subjects

	SCH 503034 200 mg			SCH 503034 400 mg			SCH 503034 800 mg		
	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=5)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)
Tmax [a] (hr)	1.00 (0.500-2.50)	2.75 (1.50-4.00)	2.50 (2.00-4.00)	1.50 (1.00-3.00)	2.75 (2.00-3.00)	2.50 (2.50-5.00)	1.50 (0.500-3.00)	3.25 (1.00-4.00)	4.00 (1.50-5.00)
Cmax (ng/mL)	147 (42)	153 (35)	150 (40)	169 (18)	287 (31)	244 (15)	568 (77)	658 (26)	565 (34)
AUC(tf) (ng·hr/mL)	316 (42)	399 (37)	398 (40)	420 (15)	773 (29)	660 (17)	1480 (46)	2160 (18)	1950 (21)
AUC(I) (ng·hr/mL)	321 (42)	402 (38)	404 (40)	428 (16)	779 (28)	668 (17)	1490 (45)	2170 (18)	1970 (20)
AUC(0-8) (ng·hr/mL)	-	-	387 (42)	-	-	640 (18)	-	-	1840 (19)
t½ (hr)	1.96 (27)	1.09 (16)	1.82 (33)	2.60 (75)	1.64 (26)	2.10 (25)	3.17 (44)	1.76 (30)	1.73 (25)
tf (hr)	10.7 (15)	10.2 (22)	10.7 (15)	14.0 (35)	11.7 (7)	12.0 (0)	20.0 (31)	14.0 (35)	12.0 (0)

Data presented as mean (CV)

a: Median (range)

CV = coefficient of variation

Day 1: A single dose under fasted conditions, plasma data collected until 48 hours postdose

Day 4: A single dose with high-fat breakfast, plasma data collected until 48 hours postdose

Day 7: A single dose with Japanese meal, plasma data collected until 12 hours postdose

Table 10 shows the mean pharmacokinetic parameters of SCH 534129 after a single oral dose of SCH 503434 in Japanese subjects.

Table 10: Mean pharmacokinetic parameters of SCH 534129 after a single oral dose of SCH 503434 in Japanese subjects

	SCH 503034 200 mg			SCH 503034 400 mg			SCH 503034 800 mg		
	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)	Day 1 (n=5)	Day 4 (n=5)	Day 7 (n=5)	Day 1 (n=6)	Day 4 (n=6)	Day 7 (n=6)
Tmax [a] (hr)	1.00 (0.500-1.50)	2.75 (2.50-5.00)	2.75 (1.50-5.00)	2.00 (1.50-4.00)	3.00 (2.50-5.00)	2.50 (2.50-5.00)	1.25 (0.500-2.00)	3.25 (1.00-5.00)	2.75 (1.50-4.00)
Cmax (ng/mL)	169 (19)	188 (16)	241 (65)	165 (33)	304 (19)	291 (20)	415 (39)	792 (22)	740 (27)
AUC(tf) (ng·hr/mL)	314 (33)	417 (24)	418 (49)	430 (25)	822 (15)	765 (14)	1100 (35)	2180 (15)	1850 (21)
AUC(I) (ng·hr/mL)	321 (32)	420 (23)	422 (48)	436 (25)	825 (15)	769 (14)	1120 (35)	2190 (15)	1860 (22)
AUC(0-8) (ng·hr/mL)	-	-	408 (49)	-	-	746 (15)	-	-	1810 (21)
t½ (hr)	2.37 (61)	1.37 (41)	1.65 (29)	2.89 (73)	1.47 (39)	1.50 (14)	3.35 (66)	1.94 (25)	1.85 (28)
tf (hr)	9.83 (24)	10.0 (13)	11.0 (15)	16.4 (43)	12.0 (0)	11.6 (8)	18.0 (37)	12.0 (0)	12.0 (0)

Data presented as mean (CV)

a: Median (range)

CV = coefficient of variation

Day 1: A single dose under fasted conditions, plasma data collected until 48 hours postdose

Day 4: A single dose with high-fat breakfast, plasma data collected until 48 hours postdose

Day 7: A single dose with Japanese meal, plasma data collected until 12 hours postdose

Statistical Assessments Based on Single Dose Pharmacokinetic Parameters

Table 11 shows the single dose comparison between Japanese and Caucasian subjects (day 1-fasted).

Table 11: Single dose comparison between Japanese and Caucasian subjects (day 1-fasted)

			Cmax				AUC(tf)			
			LS Means		Japanese vs Caucasian		LS Means		Japanese vs Caucasian	
Analyte	Dose	n	Japanese	Caucasian	Ratio[a]	90% CI	Japanese	Caucasian	Ratio[a]	90% CI
SCH 503034	200 mg	6	386	330	117	81-169	865	834	104	79-136
	400 mg	4[c]	409	453	90	54-150	1219	1345	91	58-142
	800 mg	6	1002	1134	88	50-156	3190	3914	82	57-117
SCH 534128	200 mg	6	221	195	113	79-161	558	531	105	85-130
	400 mg	4[b]	255	286	89	53-149	812	909	89	59-136
	800 mg	6	629	676	93	55-158	2135	2544	84	61-115
SCH 534129	200 mg	6	167	137	122	80-186	300	296	101	69-148
	400 mg	4[b]	157	167	94	55-160	399	431	93	56-155
	800 mg	6	385	464	83	45-153	1042	1353	77	48-124
SCH 503034	pooled[c]	16	-	-	99	78-125	-	-	92	78-108
SCH 534128	pooled[c]	16	-	-	99	80-123	-	-	93	80-107
SCH 534129	pooled[c]	16	-	-	99	76-128	-	-	89	72-111

a: Ratio (Japanese/Caucasian) and 90% CI are based on paired analysis.

b: Subjects 201 and 110 were excluded due to lack of matched subject.

c: The three doses were pooled for this analysis.

CI = confidence interval; LS = least-square.

Table 12 shows the single dose comparison between Japanese and Caucasian subjects (day 4-fed).

Table 12: Single dose comparison between Japanese and Caucasian subjects (day 4-fed)

			Cmax				AUC(tf)			
			LS Means		Japanese vs Caucasian		LS Means		Japanese vs Caucasian	
Analyte	Dose	n	Japanese	Caucasian	Ratio[a]	90% CI	Japanese	Caucasian	Ratio[a]	90% CI
SCH 503034	200 mg	6	457	324	141	106-188	1074	971	111	90-136
	400 mg	4[c]	750	647	116	71-189	2272	1977	115	74-178
	800 mg	6	2001	1684	119	104-135	6263	6301	99	84-118
SCH 534128	200 mg	6	271	183	148	111-197	664	583	114	97-133
	400 mg	4[c]	458	401	114	65-202	1428	1276	112	68-184
	800 mg	6	1245	1056	118	99-140	4092	4127	99	82-120
SCH 534129	200 mg	6	186	146	127	95-171	407	381	107	79-145
	400 mg	4[c]	304	255	119	82-174	843	688	123	86-176
	800 mg	6	778	641	121	108-136	2161	2126	102	83-124
SCH 503034	pooled[c]	16	-	-	126	110-144	-	-	107	96-120
SCH 534128	pooled[c]	16	-	-	127	110-148	-	-	108	96-121
SCH 534129	pooled[c]	16	-	-	123	109-138	-	-	108	95-124

a: Ratio (Japanese/Caucasian) and 90% CI are based on paired analysis.

b: Subjects 201 and 110 were excluded due to lack of matched subject.

c The three doses were pooled for this analysis.

CI = confidence interval; LS = least-square.

Table 13 shows the single dose comparison between Japanese and Caucasian subjects (day 7-fed with Japanese meal).

Table 13: Single dose comparison between Japanese and Caucasian subjects (day 7-fed with Japanese Meal)

			Cmax				AUC(tf)			
			LS Means		Japanese vs Caucasian		LS Means		Japanese vs Caucasian	
Analyte	Dose	n	Japanese	Caucasian	Ratio[a]	90% CI	Japanese	Caucasian	Ratio[a]	90% CI
SCH 503034	200 mg	6	477	329	145	76-276	1051	974	108	76-154
	400 mg	4[c]	682	649	105	67-165	2180	1830	119	103-138
	800 mg	6	1763	1417	124	85-181	5341	5543	96	78-119
SCH 534128	200 mg	6	275	191	144	80-260	662	596	111	82-150
	400 mg	4[c]	412	411	100	60-166	1419	1213	117	98-139
	800 mg	6	1107	896	123	94-161	3513	3607	97	82-115
SCH 534129	200 mg	6	203	142	144	71-289	386	374	103	66-161
	400 mg	4[c]	269	237	113	78-164	760	617	123	111-138
	800 mg	6	716	537	133	83-215	1818	1916	95	68-132
SCH 503034	pooled[c]	16	-	-	126	99-162	-	-	106	93-121
SCH 534128	pooled[c]	16	-	-	124	99-156	-	-	107	95-120
SCH 534129	pooled[c]	16	-	-	132	100-173	-	-	105	88-125

a: Ratio (Japanese/Caucasian) and 90% CI are based on paired analysis.

b: Subjects 201 and 110 were excluded due to lack of matched subject.

c: The three doses were pooled for this analysis.

CI = confidence interval; LS = least-square.

Analysis of Dose Proportionality

Caucasian Subjects

Table 14 shows the dose proportionality on day 1 and day 4 for Caucasian subjects.

Table 14: Dose proportionality on day 1 and day 4 for Caucasian subjects

Day	Analyte	Label	Cmax[a]		AUC(tf)[a]		AUC(I)[a]		AUC(τ)[a]	
			Ratio	90% CI	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
1	SCH 503034	400 mg vs 200 mg	65	42-101	76	56-103	76	57-103	-	-
		800 mg vs 200 mg	86	56-133	117	87-159	118	87-158	-	-
		800 mg vs 400 mg	131	85-203	155	114-209	154	114-207	-	-
	SCH 534128	400 mg vs 200 mg	67	44-102	79	60-105	79	60-105	-	-
		800 mg vs 200 mg	86	57-131	120	90-159	120	91-158	-	-
		800 mg vs 400 mg	129	85-195	151	114-201	151	114-199	-	-
	SCH 534129	400 mg vs 200 mg	61	38-98	70	49-102	70	49-101	-	-
		800 mg vs 200 mg	85	53-136	114	79-165	114	79-163	-	-
		800 mg vs 400 mg	139	87-224	163	112-235	162	112-232	-	-
4	SCH 503034	400 mg vs 200 mg	105	80-137	107	87-130	106	87-130	-	-
		800 mg vs 200 mg	130	99-170	162	133-198	161	132-197	-	-
		800 mg vs 400 mg	124	95-162	152	125-186	152	124-185	-	-
	SCH 534128	400 mg vs 200 mg	111	85-146	112	93-134	111	92-133	-	-
		800 mg vs 200 mg	144	110-189	177	147-212	175	146-210	-	-
		800 mg vs 400 mg	130	99-170	158	132-190	157	131-189	-	-
	SCH 534129	400 mg vs 200 mg	94	70-127	98	75-129	99	75-129	-	-
		800 mg vs 200 mg	109	81-147	139	106-182	139	106-182	-	-
		800 mg vs 400 mg	116	86-156	142	108-186	141	108-185	-	-

Day 1=Single dose fasted; Day 4=Single dose fed.
n=6/6/6 for 200mg/400mg/800mg; Total n=18.
a: Ratio and 90% CI are based on log-transformed and dose-normalized data.
CI = confidence interval.

Table 15 shows the dose proportionality on day 7 and day 14 for Caucasian subjects.

Table 15: Dose proportionality on day 7 and day 14 for Caucasian subjects

Day	Analyte	Label	Cmax[a]		AUC(tf)[a]		AUC(I)[a]		AUC(τ)[a]	
			Ratio	90% CI	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
7	SCH 503034	400 mg vs 200 mg	99	74-133	98	78-124	98	79-123	-	-
		800 mg vs 200 mg	108	81-142	142	114-177	142	115-176	-	-
		800 mg vs 400 mg	108	81-145	145	115-182	145	116-181	-	-
	SCH 534128	400 mg vs 200 mg	108	82-143	106	86-130	105	86-127	-	-
		800 mg vs 200 mg	117	90-153	151	124-184	151	125-181	-	-
		800 mg vs 400 mg	109	82-144	143	117-175	144	118-175	-	-
	SCH 534129	400 mg vs 200 mg	85	61-120	87	65-118	87	65-116	-	-
		800 mg vs 200 mg	95	69-131	128	96-170	128	97-169	-	-
		800 mg vs 400 mg	111	79-156	147	109-198	147	110-197	-	-
14	SCH 503034	400 mg vs 200 mg	88	62-124	-	-	-	-	101	73-139
		800 mg vs 200 mg	81	59-110	-	-	-	-	89	66-118
		800 mg vs 400 mg	92	65-129	-	-	-	-	88	64-122
	SCH 534128	400 mg vs 200 mg	94	70-127	-	-	-	-	106	80-140
		800 mg vs 200 mg	89	68-116	-	-	-	-	95	74-121
		800 mg vs 400 mg	94	70-128	-	-	-	-	89	68-118
	SCH 534129	400 mg vs 200 mg	83	52-132	-	-	-	-	90	58-139
		800 mg vs 200 mg	71	47-107	-	-	-	-	76	51-112
		800 mg vs 400 mg	85	54-135	-	-	-	-	85	55-131

Day 7=Single dose Japanese meal; Day 14=Multiple dose Japanese meal
n=6/5/6 for 200mg/400mg/800mg on Day 7 and n=6/4/6 for 200mg/400mg/800mg on Day 14
a: Ratio and 90% CI are based on log-transformed and dose-normalized data
CI = confidence interval

Japanese Subjects

Table16 shows the dose proportionality on day 1 and day 4 for Japanese

subjects.

Table 16: Dose proportionality on day 1 and day 4 for Japanese subjects

Day	Analyte	Label	Cmax[a]		AUC(tf)[a]		AUC(I)[a]		AUC(τ)[a]	
			Ratio	90% CI	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
1	SCH 503034	400 mg vs 200 mg	56	37-84	76	55-104	76	55-105	-	-
		800 mg vs 200 mg	65	44-96	92	68-125	93	68-126	-	-
		800 mg vs 400 mg	116	77-174	122	88-169	123	88-170	-	-
	SCH 534128	400 mg vs 200 mg	63	41-96	79	58-108	79	58-108	-	-
		800 mg vs 200 mg	71	48-107	96	71-129	96	71-129	-	-
		800 mg vs 400 mg	114	74-174	121	88-166	121	88-166	-	-
	SCH 534129	400 mg vs 200 mg	47	32-69	69	48-100	69	48-99	-	-
		800 mg vs 200 mg	58	40-83	87	62-122	86	61-122	-	-
		800 mg vs 400 mg	122	84-178	125	87-179	125	87-180	-	-
4	SCH 503034	400 mg vs 200 mg	81	67-99	105	86-127	105	86-127	-	-
		800 mg vs 200 mg	109	91-132	146	121-175	145	121-175	-	-
		800 mg vs 400 mg	135	111-164	139	114-169	139	114-168	-	-
	SCH 534128	400 mg vs 200 mg	85	69-104	108	89-132	108	88-131	-	-
		800 mg vs 200 mg	115	95-140	154	127-187	153	126-185	-	-
		800 mg vs 400 mg	135	111-166	142	116-174	142	116-173	-	-
	SCH 534129	400 mg vs 200 mg	80	66-98	100	82-122	100	82-122	-	-
		800 mg vs 200 mg	105	86-127	133	109-161	132	109-160	-	-
		800 mg vs 400 mg	130	106-159	133	108-162	133	109-162	-	-

Day 1=Single dose fasted; Day 4=Single dose fed
n=6/5/6 for 200mg/400mg/800mg; Total n=17
a: Ratio and 90% CI are based on log-transformed and dose-normalized data
CI = confidence interval

Table 17 shows the dose proportionality on day 7 and day 14 for Japanese subjects.

Table 17: Dose proportionality on day 7 and day 14 for Japanese subjects

Day	Analyte	Label	Cmax[a]		AUC(tf)[a]		AUC(I)[a]		AUC(τ)[a]	
			Ratio	90% CI	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
7	SCH 503034	400 mg vs 200 mg	78	50-121	107	83-137	106	82-136	-	-
		800 mg vs 200 mg	92	61-141	127	100-162	126	99-161	-	-
		800 mg vs 400 mg	119	76-185	119	93-153	119	92-153	-	-
	SCH 534128	400 mg vs 200 mg	82	55-124	112	89-141	111	88-139	-	-
		800 mg vs 200 mg	100	68-148	133	107-165	131	106-163	-	-
		800 mg vs 400 mg	122	81-183	119	94-149	118	94-149	-	-
	SCH 534129	400 mg vs 200 mg	70	44-112	98	72-134	98	72-133	-	-
		800 mg vs 200 mg	88	57-137	118	88-158	117	87-157	-	-
		800 mg vs 400 mg	125	79-198	120	88-163	120	88-163	-	-
14	SCH 503034	400 mg vs 200 mg	50	34-72	-	-	-	-	70	52-94
		800 mg vs 200 mg	57	40-81	-	-	-	-	71	53-93
		800 mg vs 400 mg	114	79-166	-	-	-	-	101	75-135
	SCH 534128	400 mg vs 200 mg	54	37-78	-	-	-	-	72	54-97
		800 mg vs 200 mg	60	42-86	-	-	-	-	74	56-98
		800 mg vs 400 mg	112	76-163	-	-	-	-	102	77-137
	SCH 534129	400 mg vs 200 mg	45	30-67	-	-	-	-	65	48-89
		800 mg vs 200 mg	50	34-74	-	-	-	-	63	47-85
		800 mg vs 400 mg	112	75-169	-	-	-	-	97	71-132

Day 7=Single dose Japanese meal; Day 14=Multiple dose Japanese meal
n=6/5/6 for 200mg/400mg/800mg; Total n=17
a: Ratio and 90% CI are based on log-transformed and dose-normalized data
CI = confidence interval

Multiple Dose Pharmacokinetics at Various Dose Levels in Japanese and Caucasian Subjects.

After multiple dose administration of SCH 503034 to Caucasian subjects, the mean PK parameters of SCH 503034 were estimated from 6 subjects (200 mg TID), 4 subjects (400 mg TID) and 6 subjects (800 mg TID).

After multiple dose administration of SCH 503034 to Japanese subjects, the mean PK parameters of SCH 503034 were estimated from 6 subjects (200 mg TID), 5 subjects (400 mg TID) and 6 subjects (800 mg TID).

SCH 503134

Table 18 shows the mean pharmacokinetic parameters of SCH 503034 on day 14 after TID administration of SCH 503034 in Caucasian and Japanese subjects.

Table 18: Mean pharmacokinetic parameters of SCH 503034 on day 14 after TID administration of SCH 503034 in Caucasian and Japanese subjects.

	Caucasian Subjects			Japanese Subjects		
	SCH 503034 200 mg (n=6)	SCH 503034 400 mg (n=4)	SCH 503034 800 mg (n=6)	SCH 503034 200 mg (n=6)	SCH 503034 400 mg (n=5)	SCH 503034 800 mg (n=6)
Tmax [a] (hr)	2.25 (1.00-3.00)	3.00 (1.50-4.00)	2.00 (1.50-3.00)	2.00 (1.00-3.00)	2.00 (1.50-4.00)	1.50 (0.500-4.00)
Cmax (ng/mL)	505 (26)	881 (22)	1680 (35)	684 (23)	735 (40)	1550 (21)
AUC(τ) (ng·hr/mL)	1330 (30)	2620 (12)	4830 (32)	1430 (24)	2100 (35)	3980 (11)
$t_{½}$ (hr)	3.49 (29)	5.10 (32)	10.2 (98)	2.44 (64)	3.28 (43)	4.48 (53)
tf (hr)	18.0 (37)	24.0 (0)	40.0 (49)	14.0 (35)	19.2 (34)	28.0 (35)
CL/F (L/hr)	158 (22)	155 (13)	185 (40)	145 (17)	223 (54)	203 (10)
Vd/F (L)	762 (19)	1130 (29)	2450 (89)	512 (67)	1140 (80)	1320 (57)
R	1.44 (26)	1.45 (26)	0.936 (33)	1.41 (16)	0.961 (35)	0.773 (17)
Cmax_D [b] (ng/mL)	505 (26)	440 (22)	420 (35)	684 (23)	368 (40)	386 (21)
AUC(τ)_D [b] (ng·hr/mL)	1330 (30)	1310 (12)	1210 (32)	1430 (24)	1050 (35)	996 (11)

Data presented as mean (CV). Subjects 201, 110, and 306 were included despite the lack of a matched subject.

a: Median (range)

b: Dose-normalized to 200 mg SCH 503034

CV = coefficient of variation; TID = three times daily

Day 14: Multiple doses with Japanese meal, plasma data collected until 72 hours postdose

SCH 534128

Table 19 shows the mean pharmacokinetic parameters of SCH 534128 on day 14 after TID administration of SCH 503034 in Caucasian and Japanese subjects.

Table 19: Mean pharmacokinetic parameters of SCH 534128 on day 14 after TID administration of SCH 503034 in Caucasian and Japanese subjects.

	Caucasian			Japanese		
	SCH 503034 200 mg (n=6)	SCH 503034 400 mg (n=4)	SCH 503034 800 mg (n=6)	SCH 503034 200 mg (n=6)	SCH 503034 400 mg (n=5)	SCH 503034 800 mg (n=6)
Tmax [a] (hr)	2.25 (1.00-3.00)	3.00 (1.50-4.00)	2.25 (1.50-3.00)	2.25 (1.50-3.00)	3.00 (1.50-5.00)	1.75 (1.00-4.00)
Cmax (ng/mL)	315 (20)	590 (19)	1150 (32)	425 (20)	497 (41)	1020 (22)
AUC(τ) (ng·hr/mL)	883 (22)	1850 (10)	3430 (30)	959 (19)	1470 (36)	2820 (11)
$t_{½}$ (hr)	3.71 (39)	5.46 (22)	10.7 (91)	2.71 (69)	3.74 (50)	5.07 (24)
tf (hr)	18.0 (37)	24.0 (0)	40.0 (49)	14.0 (35)	19.2 (34)	28.0 (35)
R	1.59 (25)	1.56 (25)	1.04 (32)	1.52 (14)	1.02 (37)	0.837 (17)

Data presented as mean (CV). Subjects 201, 110, and 306 were included despite the lack of a matched subject.

a: Median (range)

CV = coefficient of variation; TID = three times daily

Day 14: Multiple doses with Japanese meal, plasma data collected until 72 hours postdose

SCH 534129

Table 20 shows the mean pharmacokinetic parameters of SCH 534129 on day 14 after TID administration of SCH 503034 in Caucasian and Japanese subjects.

Table 20: Mean pharmacokinetic parameters of SCH 534129 on day 14 after TID administration of SCH 503034 in Caucasian and Japanese subjects.

	Caucasian			Japanese		
	SCH 503034 200 mg (n=6)	SCH 503034 400 mg (n=4)	SCH 503034 800 mg (n=6)	SCH 503034 200 mg (n=6)	SCH 503034 400 mg (n=5)	SCH 503034 800 mg (n=6)
Tmax [a] (hr)	2.25 (1.00-4.00)	2.50 (1.50-3.00)	2.00 (1.50-2.50)	2.00 (1.00-3.00)	2.00 (1.50-4.00)	1.50 (0.500-4.00)
Cmax (ng/mL)	190 (42)	300 (24)	539 (42)	278 (34)	266 (40)	549 (22)
AUC(τ) (ng·hr/mL)	452 (44)	771 (17)	1400 (39)	473 (32)	635 (34)	1160 (15)
$t_{½}$ (hr)	2.41 (34)	4.02 (76)	10.2 (135)	2.25 (46)	2.08 (18)	2.69 (33)
tf (hr)	14.0 (35)	15.0 (40)	26.0 (68)	11.3 (9)	12.0 (0)	16.0 (39)
R	1.21 (28)	1.24 (30)	0.750 (37)	1.23 (17)	0.841 (31)	0.653 (17)

Data presented as mean (CV). Subjects 201, 110, and 306 were included despite the lack of a matched subject.

a: Median (range)

CV = coefficient of variation; TID = three times daily

Day 14: Multiple doses with Japanese meal, plasma data collected until 72 hours postdose

Summary of Results

Single Dose Pharmacokinetics (Caucasian Vs. Japanese Subjects)

Day 1 (Fasted Conditions)

- After administration of a single dose of SCH 503034 at three different dose levels (200 mg, 400 mg, and 800 mg) under fasted conditions, the LS_{means} ratios of the AUCs of SCH503034, SCH 534128, and SCH 534129 were not significantly different between Japanese subjects and Caucasian subjects.

Day 4 (Fed Conditions-Western Diet)

- After administration of a single dose of SCH 503034 at three different dose levels (200 mg, 400 mg, and 800 mg) under fed conditions (western diet, high-fat), the LS_{means} ratios of the AUCs of SCH503034, SCH 534128, and SCH 534129 were not significantly different between Japanese subjects and Caucasian subjects across the three dose levels.

Day 7 (Fed Conditions-Japanese Diet)

- After administration of a single dose of SCH 503034 at three different dose levels (200 mg, 400 mg, and 800 mg) under fed conditions (Japanese diet), the LS_{means} ratios of the AUCs of SCH503034, SCH 534128, and SCH 534129 were not significantly different between Japanese subjects and Caucasian subjects across the three dose levels.

Multiple Dose Pharmacokinetics (Caucasian Vs. Japanese Subjects)

- The pharmacokinetics of SCH 503034, SCH 534128, and 534129 administered as multiple dose (200 mg, 400 mg, 800 mg TID) with a Japanese diet were comparable between Japanese and Caucasian subjects.

Dose proportionality

- In Caucasians, based on a comparison of mean AUC_I, SCH503034 was approximately dose proportional from 200 mg to 400 mg and greater than dose proportional from 400 mg to 800 mg when given as a single dose under fed conditions (Day 4 and Day 7). At steady-state, following administration with a Japanese meal (Day 14), SCH503034 was roughly dose proportional from 200 mg to 800 mg in Japanese and Caucasian subjects.

Food effect

- Caucasian Subjects

    - 200 mg: After single dose administration of 200 mg SCH 503034, the mean AUC on day 4 (fed conditions-western diet) and day 7 (fed conditions-Japanese diet) was 15 % and 18.5 % higher, as compared with the mean AUC on day 1 (fasted conditions).

    - 400 mg: After single dose administration of 400 mg SCH 503034, the mean AUC on day 4 (fed conditions-western diet) and day 7 (fed conditions-Japanese diet) was 63 % and 51 % higher, as compared with the mean AUC on day 1 (fasted conditions).

    - 800 mg: After single dose administration of 800 mg SCH 503034, the mean AUC on day 4 (fed conditions-western diet) and day 7 (fed

conditions-Japanese diet) was 50% and 33.2 % higher, as compared with the mean AUC on day 1 (fasted conditions).

- Japanese Subjects

  - 200 mg: After single dose administration of 200 mg SCH 503034, the mean AUC on day 4 (fed conditions-western diet) and day 7 (fed conditions-Japanese diet) was 22 % and 25 % higher, as compared with the mean AUC on day 1 (fasted conditions).

  - 400 mg: After single dose administration of 400 mg SCH 503034, the mean AUC on day 4 (fed conditions-western diet) and day 7 (fed conditions-Japanese diet) was 67 % and 66 % higher, as compared with the mean AUC on day 1 (fasted conditions).

  - 800 mg: After single dose administration of 800 mg SCH 503034, the mean AUC on day 4 (fed conditions-western diet) and day 7 (fed conditions-Japanese diet) was 85 % and 58 % higher, as compared with the mean AUC on day 1 (fasted conditions).

Conclusion

- After single dose administration of SCH 503034 200 mg, 400 mg, and 800 mg, the systemic exposure of SCH 503034, 534128, and 534129 were higher under fed conditions as compared to the systemic exposures under fasted conditions in both Japanese and Caucasian subjects. Therefore, SCH 503034 should be administered under fed conditions.

- After single dose administration of SCH 503034 200 mg, 400 mg, and 800 mg with either a Western diet or a Japanese diet, the systemic exposure of SCH 503034, 534128, and 534129 were similar between Japanese subjects and Caucasian subjects. Therefore, the dose of SCH503034 does not need to be adjusted in subjects of Japanese descent.

Labeling Recommendation

- The mean systemic exposure of boceprevir was increased by 50 % when a single 800 mg dose of TRADENAME was administered with a high fat meal (841 calories, 53.8 gms fat) as compared with when a single 800 mg dose of TRADENAME was administered under fasting conditions. Therefore, TRADENAME should always be taken with food. Within the range of meals evaluated (511 calories (8.5 gms fat) to 841 calories (53.8 gms fat)), the systemic exposure of boceprevir was similar.

4.2.2 Intrinsic Factors

Trial P03747

A single-dose, open-label, single-center, parallel-group trial of boceprevir in subjects with various degrees of hepatic impairment

Dates

July 06, 2005 to March 31, 2006

Trial Site

1500 NW 12th Avenue, 15th Floor West, University of Miami School of Medicine, Miami, FL, 33136, USA

Summary of Reviewer Findings

SCH534128 exposures (AUC_{tf}) were higher in subjects with moderate (32%) and severe (45%) hepatic impairment relative to healthy subjects. The higher SCH534128 exposures are likely clinically irrelevant and may not warrant dose adjustment in patients with any degree of hepatic impairment. A similar magnitude of effect is anticipated for boceprevir.

Trial Objectives

This trial aimed to compare the safety, tolerability, and PK of boceprevir (SCH53418 + SCH534129) in subjects with various degrees of stable chronic liver disease.

Trial Design

This was an open-label, single-dose, single-center, parallel-group trial.

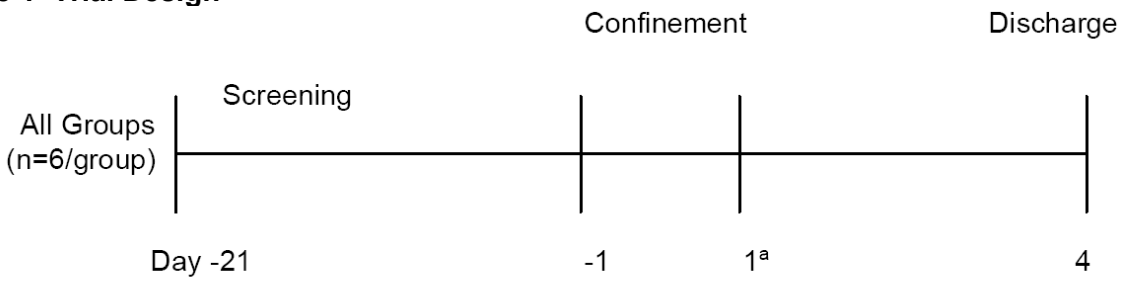
Twenty-four adult male and female subjects with healthy liver function (n=6) or with chronic liver disease (n=18) enrolled in the trial. Subjects divided evenly into four groups according to their Child-Pugh scores for liver disease. Groups 1, 2, 3, and 4 enrolled subjects with mild, moderate, severe, and normal hepatic function, respectively.

Subjects in group 4 served as controls for subjects in groups 1, 2, and 3. Investigators maintained a homogenous population by matching the

demographics of subjects in group 4 as closely as possible to subjects in groups 1, 2, and 3. Mean values of age, height, weight, and sex were ±10% across all groups.

On day -1, subjects arrived to the trial site and remained there for four days. On day 1, subjects received a single dose of boceprevir 400 mg (b) (4)) under fasted conditions. All subjects received active treatment (no placebo). Investigators collected intense PK sampling from days 1 to 4. On day 4, subjects went home after the 72-hr blood sample was collected. In order to begin dosing subjects in group 3, the safety of boceprevir was proven in at least three subjects from groups 1 and 2. The following figure illustrates the trial design.

Figure 1 Trial Design



a Treatment: SCH 503034 administered as a single 400 mg oral dose.

Group 1:	Child-Pugh score 5 to 6 (mild impairment).
Group 2:	Child-Pugh score 7 to 9 (moderate impairment).
Group 3:	Child-Pugh score 10 to 12 (severe impairment).
Group 4:	Healthy volunteers with no evidence of hepatic impairment.

Key Inclusion Criteria

For groups 1 through 3, the trial enrolled male or female subjects of any race with chronic liver disease, between 18 and 65 years of age, and a body mass index (BMI) between 19 to 31 kg/m^2. Subjects were healthy based on physical examinations, ECGs, and clinical laboratory tests, except for liver dysfunction. Liver function was classified based on Child-Pugh criteria as mild (score 5 to 6), moderate (score 7 to 9), and severe (score 10 to 12) impairment.

For group 4, the trial enrolled male or female subjects of any race having a BMI between 19 to 29 kg/m^2. Subjects in group 4 matched the sex, age, height, and weight by ±10% of the mean values of these parameters to subjects in groups 1,

2, and 3.

In all groups, male and female subjects used an effective method of barrier contraception, such as condoms with spermicide, during the trial and 30 days post last dose of trial medication.

Key Exclusion Criteria

The trial excluded subjects infected with HIV, HBV, or HCV, or who tested positive for illicit drug use. The trial also excluded subjects with medical conditions that may have affected the absorption, distribution, metabolism, or excretion of boceprevir. For instance, subjects with portacaval shunts, primary biliary cirrhosis, cholestasis, or a Child-Pugh score of 13 to 15 did not participate in the trial.

Investigators prohibited the intake of new prescription or over-the-counter medications during the trial. Inhibitors or inducers of aldoketo reductase (AKR) or cytochrome P450 3A4/5 were strictly prohibited. The only allowable medication was acetaminophen at doses ≤500 mg per day to treat potential adverse events. Subjects in groups 1, 2, and 3 maintained their established medication regimens except for the day of dosing with boceprevir. On day 1, subjects halted their medications from the morning dose of boceprevir until 12 hours post dose. Subjects continued their regular medications after 12 hours post boceprevir dose. On the other hand, subjects in group 4 stopped all medication intake at least 14 days prior to and during the trial.

The ingestion of grapefruit, grapefruit juice, alcohol, and caffeinated beverages was strictly prohibited 48 hours prior to and during the trial.

Reviewer's comment: Acetaminophen is mainly metabolized by Phase II conjugation and sulfation reactions. In vitro data suggests that boceprevir does not undergo glucuronidation; therefore, boceprevir is unlikely to interact with acetaminophen.

Investigational Products

The (b) (4) capsules of boceprevir were manufactured by Schering-Plough on September 24, 2004 (b) (4). The formula and batch numbers of the capsules were FM3887-1-1 and 80559-117, respectively.

Reviewer comment: Investigators did not test the proposed commercial formulation of boceprevir. Instead, they tested the original formulation of boceprevir available when this trial was conducted. The original and proposed commercial formulations underwent different manufacturing processes and contain different excipients. Nevertheless, since investigators used the same

formulation of boceprevir across all cohorts, the changes in PK exposures should be reflective of differences in absorption, distribution, and hepatic clearance of boceprevir secondary to hepatic dysfunction.

Drug Administration

On day -1, subjects arrived to the trial center. At night, subjects received a light snack prior to bedtime, but fasted for at least 6 hours before the administration of boceprevir the following morning.

On day 1, subjects received a single 400 mg [redacted] (b) (4)) dose of boceprevir in the morning, and then fasted for an additional 4 hours post dose. Lunch was available after the collection of the 4-hr PK blood sample. The timing and nutritional content of meals was similar across all treatment groups. Investigators prohibited snacking between meals, but permitted water intake except for 1 hour pre- and post boceprevir dose.

On Day 4, subjects went home after investigators collected the 72-hr blood sample.

Reviewer comment: Boceprevir was administered under fasting conditions. In previous clinical trials with boceprevir, food has been shown to increase the exposures of boceprevirin the proposed commercial formulation by as much as 65%. Hence, the exposures of boceprevir may be lower in this trial compared to exposures of boceprevir observed in other trials.

Rationale for Dose Selection

During trial design, boceprevir 800 mg was the highest dose tested in humans. Investigators decided to test 400 mg because boceprevir is heavily metabolized by CYP3A4 and AKR. Subjects with impaired liver function may have lower activity of hepatic CYP3A4 and AKR. Thus, subjects with decreased liver function may experience toxicities due to elevated concentrations of boceprevir. The 400 mg dose provided a safety window of 100% relative to 800 mg.

Pharmacokinetic Assessments

Investigators collected whole blood samples for PK analysis of boceprevir, SCH534128 and SCH534129 on days 1 through 4 beginning immediately prior to drug administration (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, and 72 hours after dosing. PK sampling was similar in all groups.

Bioanalytical Methods

Schering-Plough analyzed all plasma samples within the frozen stability timeframe for SCH534128, but not for SCH534129. Samples for SCH534129 expired before bioanalysis.

Initially, investigators used a chiral LC-MS/MS method (SN 04921) to measure the individual concentrations of SCH534128 and SCH534129 in non-acidified plasma. During method validation, investigators collected sufficient in-process and frozen storage stability for SCH534128, but not for SCH534129. Therefore, concentrations of SCH534129 were unreliable.

Subsequently, investigators used an achiral method (SN 03330) to measure the concentrations of boceprevir in non-acidified plasma. The method determined boceprevir concentrations, but it failed to resolve the two diastereomers SCH534128 and SCH534129. Because method 03330 was only used for Groups 1 and 2 (and one subject from Group 3), boceprevir concentrations cannot be used to make comparisons with the control group.

The plasma samples collected from this trial were analyzed as listed below:

Group	Subjects	1st Method	2nd Method
1	6/6	SN 03330	SN 04921
2	6/6	SN 03330	SN 04921
3	1/6	SN 03330	SN 04921
	5/6	SN 04921	-
4	6/6	SN 04921	-

Of note, all plasma samples were assayed with method SN 04921. Method SN 04921 reliably measured the concentrations of SCH534128 in all samples. Thus, data interpretation will be based on concentrations of SCH534128 only.

Reviewer comment: SCH534128 is the active diastereomer of boceprevir. The ratio of active to inactive diastereomer is 2:1. The ratio remained unchanged throughout clinical trials, and diastereomer interconversion is negligible in plasma. Thus, it is reasonable to use SCH534128 concentrations to evaluate the effect of hepatic impairment on the PK of boceprevir.

The lower and upper limits of quantification for SCH534128 were 1.31 ng/mL and 665 ng/mL, respectively using method SN 04921. All calibration standards and quality controls met the bioanalytical criteria. Investigators defined these criteria as precision (%CV) within ±15%, accuracy (%RE) ≤15%, and coefficient of determination (r^2) ≥0.98. The following table summarizes the precision and accuracy of the bioanalytical method.

Table 37 Precision (% CV) and accuracy (% relative error) of calibration standards and QC samples in human plasma

	Cal Std			QC	
Analyte	**%CV**	**%RE**	**R^2**	**%CV**	**%RE**
SCH534128	1.7 - 6.8	≤3.8	≥0.9959	3.7 – 10.8	≤5.7

Pharmacokinetic Analyses

This trial analyzed the following PK parameters for boceprevir, SCH534128, and SCH534129 in all groups: AUC(tf), AUC(I), C_{max}, T_{max}, t½, CL/F, and Vd/F. The PK parameters for boceprevir and SCH534129 were not used for data interpretation.

Statistical Analyses

Analysis of the log-transformed AUC and C_{max} of SCH534128 was performed using a one-way analysis of variance (ANOVA) model to extract the effects due to hepatic function. The mean differences in AUC and C_{max} were compared between subjects in groups 1, 2, and 3 versus subjects in group 4. The mean differences in exposures were associated with 90% confidence intervals.

Demographic Results

The trial enrolled 24 subjects with a mean age of 53.6 years (range, 43 to 65) and mean body mass index of 28.5 (range, 24.3 to 32.7). Twenty-one subjects (88%) were Caucasian and three subjects (12%) were Black. The median Child-Pugh scores for the mild, moderate, and severe hepatic impairment groups were 5, 7, and 10, respectively. Subjects in group 4 had similar demographics compared to subjects with liver impairment in groups 1, 2, and 3, except for body mass index. The mean body mass index for subjects in group 3 was 14% higher than subjects in group 4.

Pharmacokinetics results of SCH534128

The table below summarizes results for the statistical analysis for boceprevir and SHC534128.

Reviewer comment: Although this table lists concentrations of boceprevir, only concentrations of SCH534128 are reliable and available for all groups, and therefore should be used for data interpretation. Boceprevir concentrations are

only estimations of the true boceprevir concentrations for Groups 3 and 4.

Table 2 Ratio estimates and 90% confidence interval based on log-transformed AUC and C_{max} of boceprevir and SCH534128 following a single oral administration of 400 mg boceprevir to healthy subjects and to subjects with varying levels of hepatic impairment

Analyte	PK Parameter	Group	n	LS Mean[a]	Treatment Comparison	Ratio Estimate %	90% CI
Boceprevir	AUC(I) (ng·hr/mL)	1(Mild)	6	1623	Mild vs Healthy	88	60-130
		2(Moderate)	6	2008	Moderate vs Healthy	109	74-160
		3(Severe)	6	2619	Severe vs Healthy	142	97-209
		4(Healthy)	5[b]	1843		-	-
	AUC(tf) (ng·hr/mL)	1(Mild)	6	1587	Mild vs Healthy	91	63-131
		2(Moderate)	6	1981	Moderate vs Healthy	114	79-163
		3(Severe)	6	2591	Severe vs Healthy	149	104-213
		4(Healthy)	6	1743		-	-
	Cmax (ng/mL)	1(Mild)	6	509	Mild vs Healthy	100	62-161
		2(Moderate)	6	544	Moderate vs Healthy	107	66-172
		3(Severe)	6	822	Severe vs Healthy	161	100-260
		4(Healthy)	6	510		-	-
SCH 534128	AUC(I) (ng·hr/mL)	1(Mild)	6	1027	Mild vs Healthy	107	75-152
		2(Moderate)	6	1262	Moderate vs Healthy	131	93-187
		3(Severe)	6	1374	Severe vs Healthy	143	101-203
		4(Healthy)	6	960		-	-
	AUC(tf) (ng·hr/mL)	1(Mild)	6	1009	Mild vs Healthy	107	75-152
		2(Moderate)	6	1240	Moderate vs Healthy	132	93-187
		3(Severe)	6	1361	Severe vs Healthy	145	102-205
		4(Healthy)	6	941		-	-
	Cmax (ng/mL)	1(Mild)	6	295	Mild vs Healthy	115	71-188
		2(Moderate)	6	327	Moderate vs Healthy	128	79-208
		3(Severe)	6	413	Severe vs Healthy	162	99-263
		4(Healthy)	6	256		-	-

Hepatic impairment based on score by Pugh's Modification of Child's Classification of Severity of Liver Disease.

AUC(I) = area under the plasma concentration versus time curve to infinity; AUC(tf) = area under the plasma concentration versus time curve to the final measurable sampling time; CI = confidence interval; Cmax = maximum observed plasma concentration; LS = least square; PK = pharmacokinetic.

a: Model-based (least squares) geometric mean: ANOVA extracting the effects due to treatment.

b: AUC(I) missing for Subject 1/000405.

There was a trend toward higher SCH534128 exposures with severity in hepatic impairment. The mean AUC_{tf} values of SCH534128 for subjects with moderate and severe hepatic impairment were 32% and 45% higher relative to healthy subjects. The mean AUC_{tf} values were similar for subjects with mild hepatic impairment and healthy subjects. The mean C_{max} values of SCH534128 for subjects with mild, moderate, and severe hepatic impairment were 15%, 28%, and 62% higher relative to healthy subjects. The following table summarizes the

PK of SCH534128 across groups.

Reviewer comment: As mentioned previously, only concentrations of SCH534128 are reliable and should be used for data interpretation.

Table 3 Ratio estimates and 90% confidence interval based on log-transformed AUC and C_{max} of boceprevir and SCH534128 following single oral administration of 400 mg boceprevir to healthy subjects and to subjects with various levels of hepatic impairment

Group	Cmax (ng/mL) Mean (CV%)	Tmax (hr) Median (Min, Max)	AUC(tf) (ng·hr/mL) Mean (CV%)	AUC(I) (ng·hr/mL) Mean (CV%)	Vd/F (L) Mean (CV%)	CL/F (L/hr) Mean (CV%)	t½ (hr) Mean (CV%)
Boceprevir							
Mild (n=6)	532 (28)	1.75 (1.00, 3.00)	1700 (38)	1740 (38)	1670 (42)	266 (46)	5.04 (57)
Moderate (n=6)	600 (43)	1.75 (1.00, 2.50)	2030 (23)	2050 (22)	1400 (77)	204 (26)	4.77 (75)
Severe (n=6)	914 (42)	2.75 (1.00, 6.00)	2660 (24)	2690 (24)	1440 (90)	157 (28)	6.51 (89)
Healthy (n=6)	557 (43)	1.50 (1.00, 8.00)	1900 (43)	2020[a] (43)	2080[a] (16)	245[a] (61)	7.43[a] (44)
SCH 534128							
Mild (n=6)	305 (25)	1.75 (1.00, 3.00)	1070 (35)	1090 (35)	NA	NA	5.45 (49)
Moderate (n=6)	378 (57)	1.75 (1.00, 3.50)	1290 (30)	1310 (29)	NA	NA	5.67 (70)
Severe (n=6)	471 (49)	3.00 (1.00, 6.00)	1410 (29)	1420 (29)	NA	NA	5.24 (65)
Healthy (n=6)	269 (33)	1.50 (1.00, 8.00)	1010 (39)	1030 (39)	NA	NA	8.63 (86)

Hepatic impairment based on score by Pugh's Modification of Child's Classification of Severity of Liver Disease.

AUC(I) = area under the plasma concentration versus time curve to infinity; AUC(tf) = area under the plasma concentration versus time curve to the final measurable sampling time; CL/F = apparent total body clearance; Cmax = maximum observed plasma concentration; CV = coefficient of variation; Max = maximum; Min = minimum; NA = not available; t½ = terminal phase half-life; Tmax = time of maximum observed plasma concentration; Vd/F = apparent volume of distribution.

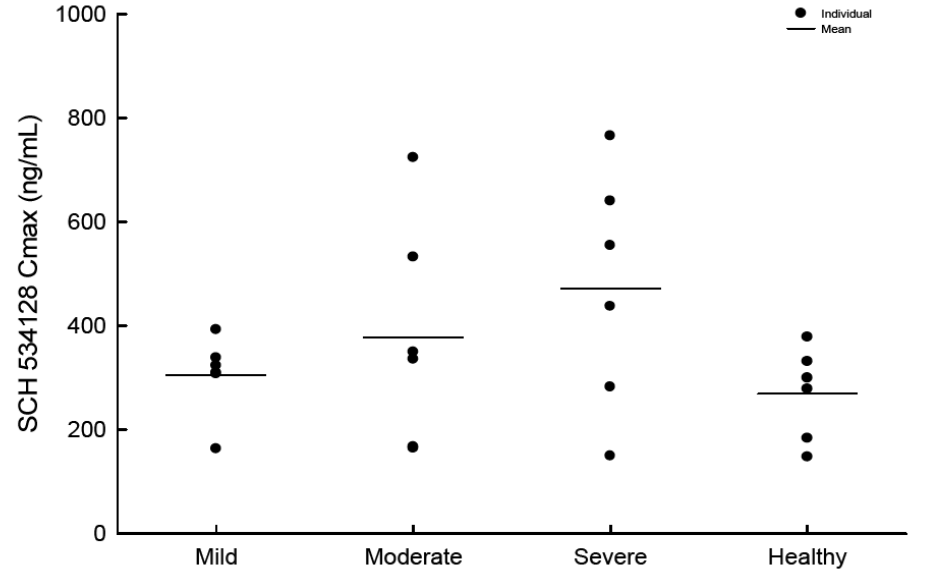
a: n=5; parameters in Subject 1/000405 are not reported since t½ could not be calculated.

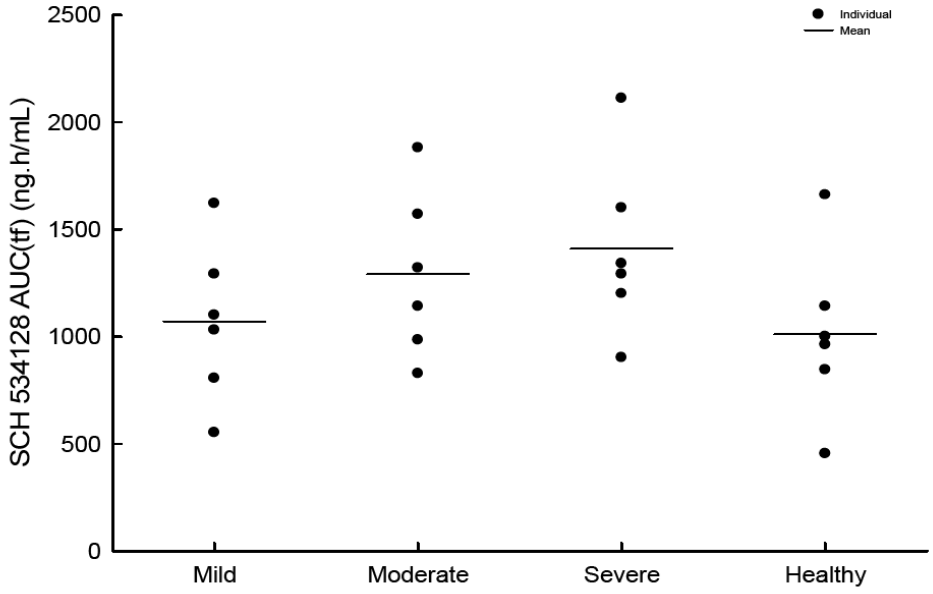
The mean half-life of SCH534128 was slightly longer in healthy subjects (8.6 hours) relative to subjects with hepatic impairment (range, 5.24 to 5.67 h). However, the half-life in healthy subjects had a large coefficient of variation (86%) suggesting that the half-life of SCH534128 may have been similar across all groups regardless of hepatic function.

Although the mean exposures (C_{max} and AUC) of SCH534128 were higher in subjects with hepatic impairment relative to healthy subjects, the individual plots of C_{max} and AUC_{tf} for SCH534128 showed a substantial overlap between the

groups. The figure below illustrates the individual and mean SCH534128 exposures across groups.

Figure 2 Individual and arithmetic mean SCH534128 exposures following single oral administration of 400 mg boceprevir to healthy subjects and healthy and subjects with various levels of hepatic impairment.





Safety results

Subjects safely tolerated a single 400 mg dose of boceprevir. Only one subject

(4%) in the severe impairment group reported mild vomiting possibly related to boceprevir during the trial. In the same group, two subjects had prolonged QTcF intervals no greater than 29 msec above 450 msec. Changes in QTcF occurred on day 4 when subjects were not taking boceprevir. Based on boceprevir half-life (~5 hr), the changes in ECG were likely due to daily variability in ECG readings rather than treatment with boceprevir. There were no deaths, serious adverse events, or other significant adverse events in the trial.

Discussion and Conclusions

Reliable boceprevir exposures were not available for all groups. Consequently, boceprevir concentrations were not used for data interpretation.

Investigators reliably measured SCH534128 in all plasma samples. SCH534128 is the active stereoisomer of boceprevir. The plasma ratio of SCH534128 to SCH534129 is 2:1, and has remained constant across clinical trials with boceprevir. Thus, it was reasonable to use the exposures of SCH534128 as a surrogate analyte for evaluating the effect of hepatic impairment on the PK of boceprevir.

Pharmacokinetic results showed a trend toward higher exposures of SCH534128 with severity of hepatic impairment. The mean C_{max} and AUC_{tf} ratios of SCH534128 in subjects with severe hepatic impairment were 62% and 45% higher relative to healthy subjects. Assuming the ratio of diastereomers was 2:1, the exposures of boceprevir may be ~33% higher than exposures of SCH534128. However, the relative difference of boceprevir in severe hepatic impairment versus healthy volunteers would be expected to be similar to that of SCH534128, given the stability of the 2:1 diasteriomer ratio.

Two previous clinical trials with boceprevir established the safety of boceprevir at doses as high as 1200 mg TID for up to 5 days. The C_{max} and AUC at this dose is 20% and 35% higher, respectively, than that at the therapeutic dose of 800 mg TID. At this higher dose, investigators did not observe severe toxicities that would warrant adjustments in the dose of boceprevir[1, 2]. In the thorough QT trial (P04489), one subject (107) had a mean exposure (AUC_{tau}) of SCH534128 of 6690 ng*hr/mL. This exposure is 84% higher than the mean SCH534128 exposure (AUC_{tau}= 3630 ng*hr/mL) produced by multiple doses of boceprevir 800 mg TID. Thus, it may be reasonable to conclude that a 45% higher SCH534128 exposure may not pose a safety risk in subjects with severe hepatic impairment.

Subjects safely tolerated a single dose of boceprevir 400 mg. Only one subject with severe hepatic impairment reported a mild case of vomiting possibly related to boceprevir. There were no deaths, serious adverse events, or other significant adverse events in the trial.

In conclusion, a 45% higher SCH534128 exposure (AUC_{tf}) may be clinically irrelevant and may not warrant dose adjustment in subjects with any degree of hepatic impairment. Exposures of boceprevir may be slightly higher (~33%) than those reported for SCH534128. Even so, the relative increase in boceprevir exposures would be expected to be similar to that observed for SCH534128 (~45%); thus, results may not warrant dose adjustment in subjects with any degree of hepatic impairment. Results of exposure-response analysis of the Phase 3 data may be used to further assess the safety implications of 45% higher exposure.

References

1. SCH503034: Rising multiple dose assessment of the safety, tolerability, pharmacokinetics, and pharmacodynamics of boceprevir in HCV positive genotype-1 interferon-α non-responders (P03516).

2. SCH503034: A thorough QT/QTc study to evaluate the cardiac safety for the HCV protease inhibitor SCH503034 in healthy volunteers (P04489).

Trial P05579

A trial to assess the safety, tolerability, and pharmacokinetics of boceprevir in subjects with renal insufficiency

Dates

August 13, 2008 to March 02, 2009

Trial Sites

1. Orlando Clinical Research Center, 5055 South Orange Avenue, Orlando, Florida 32809, USA.

2. New Orleans Center for Clinical Research-Knoxville, 1924 Alcoa Highway, 4 and 5 Northwest Knoxville, TN 37920, USA.

Summary of Reviewer Findings

Boceprevir exposures (AUC) were 10% lower in subjects with end stage renal disease (ESRD) relative to subjects with normal renal function. Clinicians should not adjust the dose of boceprevir in subjects with any degree of renal insufficiency.

ESRD subjects do not require a compensatory dose of boceprevir following hemodialysis. Hemodialysis removed less than 1% of boceprevir dose. Like so, hemodialysis may not be an adequate rescue method to treat an acute overdose of boceprevir.

ESRD does not affect the plasma protein binding of boceprevir. The fraction of unbound boceprevir (~20 to 30%) was similar in ESRD subjects relative to healthy subjects.

Trial Objectives

Primary: To evaluate the PK of boceprevir in subjects with different degrees of chronic renal insufficiency relative to matched subjects with normal renal function.

Secondary: To determine the safety and tolerability of boceprevir, the degree of boceprevir extraction by hemodialysis, and the extent of plasma protein binding of boceprevir in ESRD subjects relative to healthy subjects.

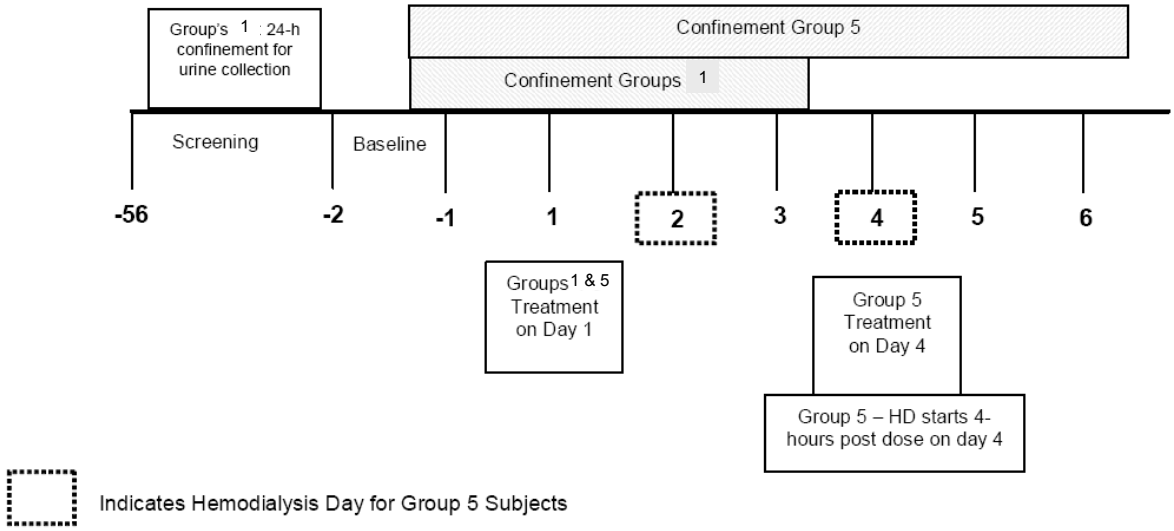
Trial Design

This was an adaptive, two-part, open-label, single-dose, non-randomized, parallel-group trial of boceprevir in subjects with normal and various degrees of renal insufficiency.

Investigators planned to conduct the trial in two parts. Part 1 would evaluate the effect of ESRD on the PK of boceprevir. Part 2 would evaluate the effect of mild, moderate, and severe renal impairment on the PK of boceprevir. Part 2 would begin only if the mean AUC of boceprevir was 2-times greater in ESRD subjects relative to healthy subjects in Part 1. ESRD decreased the exposure of boceprevir by 10%. Thus, this trial only completed Part 1.

Figure 1 below illustrates the trial design.

Figure 1 Trial Design



During screening, Group 1 reported to the clinic for laboratory assessments and measurement of urine and serum creatinine.

On day -1, Groups 1 and 5 arrived to the clinic and began confinement. Subjects ate a light snack prior to bedtime, but fasted for at least 10 hours before receiving a dose of boceprevir.

On day 1, Groups 1 and 5 received breakfast and a single oral dose of boceprevir 800 mg (4 X 200 mg capsules) with 240 mL of water. PK assessments began on day 1 until 48 hours post dose.

On day 4, Group 5 received an additional single oral dose of boceprevir 800 mg

to determine the effect of hemodialysis on the PK of boceprevir. The 4-hour hemodialysis session was initiated 4-hours post-dose. Dialysate samples were collected from 4 hours post boceprevir dose until 8 hours post dose. Venous and arterial blood samples were collected in 1-hour intervals during hemodialysis.

Reviewer's Comment: The FDA guidance recommends conducting an abbreviated trial in the worst-case population with renal insufficiency; that is, subjects with ESRD who are not receiving hemodialysis. However, the Sponsor conducted this trial in subjects with ESRD receiving hemodialysis. This is a potential review issue since trial results may not apply to severely renally impaired subjects not yet on dialysis.

Key Inclusion Criteria

Group 5 enrolled male or female subjects with ESRD of any race, between the ages of 18 and 79 years, and a body mass index (BMI) between 18 to 37 kg/m^2. Subjects were healthy based on physical examinations, ECGs, and laboratory tests, except for renal insufficiency and abnormalities related to this disease. All subjects in Group 5 required hemodialysis.

Group 1 enrolled male or female subjects with normal renal function who matched the race, age (±5 years), height (±8 cm), weight (±10 kg), and gender of subjects in Group 5.

Male and female subjects agreed to use an effective method of barrier contraception during the trial and 30 days after the last dose of boceprevir.

Key Exclusion Criteria

The trial excluded HIV, HBV, or HCV-infected subjects, illicit drug users, and subjects with medical conditions that may affect the ADME of boceprevir. Examples of such medical conditions were inflammatory bowel disease, gastrectomy, bowel resection, pancreatitis, liver disease, and urinary albumin.

Investigators prohibited the intake of prescription or over-the-counter medications at least 14 days before and during the trial. Inhibitors or inducers of aldo-keto reductase (AKR) and CYP3A4/5 enzymes were strictly prohibited. The only allowable medication was acetaminophen to treat potential adverse events.

Likewise, consumption of grapefruit, grapefruit juice, alcohol, and caffeinated beverages was strictly prohibited 48 hours before and during the trial. Subjects could smoke or use tobacco products at the discretion of the principal investigator.

Reviewer's comment: Investigators did not disclose the daily dose of acetaminophen. Acetaminophen is mainly metabolized by Phase II conjugation

and sulfation reactions. In vitro data suggests that boceprevir does not undergo glucuronidation. Therefore, boceprevir is unlikely to interact with acetaminophen. Investigators also allowed smoking and tobacco products during the trial. Smoking induces CYP1A2 but it is unlikely to affect the PK of boceprevir because CYP1A2 does not metabolize boceprevir.

Investigational Products

The trial used boceprevir 200 mg capsules in the commercial (b) (4) SLS-containing formulation, manufactured by Schering-Plough on October 18, 2007. Formula and batch numbers were FM005009-7-3 and K-H08667, respectively.

Reviewer's comment: The expiration date of the capsules is unknown. In previous clinical trials, investigators used boceprevir capsules before the expiration date (typically 1 to 3 years from manufacturing date). Thus, it is reasonable to believe that investigators used valid capsules in this trial.

Drug Administration

Boceprevir was given with meals. On days of boceprevir administration, subjects received a standard meal. Within 30 minutes of ingesting the meal, subjects received a dose of boceprevir along with 240 mL of water. Lunch was served after 4 hours post dose. The timing and nutritional content of meals was similar across groups.

Rationale for Dose Selection

The proposed commercial dose of boceprevir is 800 mg TID. In this trial, investigators tested a single 800 mg dose of boceprevir. A single dose of boceprevir is appropriate because it can predict multiple dose pharmacokinetics of boceprevir. In previous clinical trials (P04488 and P04489), single and multiple (TID) 800 mg doses of boceprevir produced mean AUC values of 5440 ng*hr/mL and 5320 ng*hr/mL, respectively, in healthy volunteers. Moreover, boceprevir displays linear pharmacokinetics between the doses of 200 mg and 800 mg. The mean half-life of boceprevir is ~4 hours, and minimally accumulates during multiple dosing. Based on these PK observations, investigators appropriately selected a single 800 mg dose for this trial.

Pharmacokinetic Assessments

The table below displays the schedule of sample collection for Groups 1 and 5.

	Group 1	Group 5
PK Samples	0 hour (pre-dose) and at 1, 2, 4, 6, 7, 8, 9, 10, 12, 24, 48-hours (post-dose)	(Day 1): 0 hour (pre-dose) and at 1, 2, 4, 6, 7, 8, 9, 10, 12, 24, 48-hours (post-dose) (Day 4): 0 hour (pre-dose) and at 1, 2, 4, 6, 7, 8, 9, 10, 12, 24, 48-hours (post-dose)
Arterial Blood Samples (Pre-dialyzer)	N/A	On Day 4: 5, 6, 7 and 8-hours (post-dose)
Venous Blood Samples (Post-dialyzer)	N/A	On Day 4: 5, 6, 7 and 8-hours, (post-dose)
Protein Binding	2-h post-dose on Day 1	2-h post-dose on Day 1 and pre-dialysis & post-dialysis on Day 4
Urine Collection	During Screening 24-h urine collection and 24-hours post boceprevir dose in 6-hour time blocks: (a) 0-6 hours, (b) 6-12 hours, (c) 12-18 and (d)18-24 hours.	N/A
Dialysate collection	N/A	On Day 4: Prior to dialysis (4 hours) and then in block samples at 4-5, >5-6, >6-7 and >7-8 hours after dosing with boceprevir.
Hemodialysis Sessions	N/A	Day 2 and Day 4
Confinement	Days -1 to 3	Day -1 to 6

Investigators collected:

1. Plasma samples to compare the PK of boceprevir and metabolite in healthy and ESRD subjects.

2. Venous and arterial blood samples to evaluate the amount of boceprevir removed by hemodialysis.

3. Dialysate samples to determine the percentage of boceprevir and metabolite removed by hemodialysis.

4. Urine samples to determine the percentage of boceprevir and its metabolite excreted in urine.

5. Plasma samples to determine the plasma protein binding of boceprevir and its metabolite.

Bioanalytical Methods

All biological samples were analyzed within the frozen stability period, except for the ultrafiltrate samples. The ultrafiltrate samples were processed 231 days after

collection, but the frozen stability period was 151 days.

Reviewer's comment: The actual storage period for several biological samples is missing. Investigators reported that samples were analyzed "within the storage stability period" recommended by Schering-Plough.

The limits of quantification for each analyte were the same across all LC-MS/MS methods.

Analyte	LLOQ (ng/mL)	ULQ (ng/mL)	LC-MS/MS Method
SCH534128	5.25	5250	DM27341 DM27655 DM27643 DM27662
SCH534129	4.75	4750	
SCH783004*	2.50	2500	
SCH783005*	2.50	2500	
SCH783006*	2.50	2500	
SCH783007*	2.50	2500	

*SCH619244, boceprevir's metabolite, is comprised of these four stereoisomers in a 1:1:1:1 ratio.

The precision (CV%) and accuracy (% relative error) of calibration standards and QC samples for the LC-MS/MS methods are listed below.

			Cal Std			QC	
Method	**Matrix**	**Analyte**	**%CV**	**%RE**	**R^2**	**%CV**	**%RE**
DM27341	Plasma	SCH534128	1.6 – 4.9	≤2.7	≥0.9968	2.5 – 6.5	≤2.3
DM27341	Plasma	SCH534129	2.2 – 5.3	≤3.2	≥0.9968	2.4 – 5.5	≤2.8
DM27341	Plasma	SCH783004	2.9 – 5.7	≤2.4	≥0.9947	2.8 – 6.9	≤3.2
DM27341	Plasma	SCH783005	1.6 – 5.5	≤1.6	≥0.9961	5.6 – 1.3	≤1.6
DM27341	Plasma	SCH783006	2.2 – 4.9	≤1.8	≥0.9968	1.6 – 6.7	≤1.3
DM27341	Plasma	SCH783007	2.0 – 5.8	≤1.4	≥0.9960	0.5 – 6.2	≤2.0
DM27655	Ultrafiltrate	SCH534128	2.2 – 12.0	≤2.9	≥0.9959	1.8 – 6.7	≤7.6
DM27655	Ultrafiltrate	SCH534129	0.8 – 11.7	≤5.5	≥0.9963	2.1 – 5.6	≤14.6
DM27655	Ultrafiltrate	SCH783004	0.0 – 12.2	≤3.2	≥0.9984	1.1 – 13.3	≤8.0
DM27655	Ultrafiltrate	SCH783005	0.7 – 9.4	≤3.6	≥0.9981	1.4 – 12.9	≤17.6*
DM27655	Ultrafiltrate	SCH783006	0.0 – 5.6	≤3.2	≥0.9991	1.4 – 12.9	≤17.6*
DM27655	Ultrafiltrate	SCH783007	0.0 – 12.2	≤3.2	≥0.9984	1.1 – 13.3	≤8.0
DM27643	Dialysate	SCH534128	1.6 – 5.4	≤2.4	≥0.9959	3.2 – 9.3	≤6.9
DM27643	Dialysate	SCH534129	1.8 – 9.6	≤3.6	≥0.9949	4.2 – 6.2	≤10.1
DM27643	Dialysate	SCH783004	1.8 – 6.8	≤2.6	≥0.9953	3.6 – 9.9	≤9.8
DM27643	Dialysate	SCH783005	1.7 – 6.2	≤3.5	≥0.9970	3.6 – 10.0	≤7.0
DM27643	Dialysate	SCH783006	1.6 – 5.6	≤2.6	≥0.9968	4.3 – 9.2	≤8.3
DM27643	Dialysate	SCH783007	1.5 – 4.2	≤2.8	≥0.9982	3.1 – 8.9	≤7.2
DM27662	Urine	SCH534128	2.3 – 7.3	≤7.3	≥0.9949	6.0 – 17.1*	≤12.9
DM27662	Urine	SCH534129	1.9 – 5.1	≤3.4	≥0.9971	3.7 – 18.8*	≤12.4
DM27662	Urine	SCH783004	1.9 – 6.9	≤2.0	≥0.9970	3.4 – 19.9*	≤11.2
DM27662	Urine	SCH783005	0.8 – 5.9	≤2.4	≥0.9980	2.4 – 16.0*	≤13.8

DM27662	Urine	SCH783006	1.7 – 6.6	≤3.6	≥0.9965	3.6 – 16.3*	≤13.8
DM27662	Urine	SCH783007	2.0 – 5.0	≤2.4	≥0.9974	3.0 – 22.6*	≤12.8

*Sample was diluted and re-analyzed.

All calibration standards and quality controls met the bioanalytical criteria. Investigators defined these criteria as precision (%CV) within ±15%, accuracy (%RE) ≤15%, and coefficient of determination (r^2) ≥0.98. Re-analyzed samples needed to be within ≤20% of the first value.

The following bioanalytical issues may have affected the PK results of boceprevir and its metabolite.

1. Bioanalysis of urine samples for renal elimination of boceprevir. Values for SCH629144 are only estimations of the actual concentrations because a large number (42%) of urine samples were diluted beyond acceptable levels.

Pharmacokinetic Analyses

The primary PK parameters for boceprevir, SCH534128, SCH534129, and SCH629144 were AUC(tf), C_{max}, T_{max}, Ae, AUC(I), CL/F, CLr, t½, and Vd/F.

Statistical Analyses

Investigators analyzed the log-transformed AUC and C_{max} of boceprevir, SCH534128, SCH534129, and SCH629144 using a one-way analysis of variance (ANOVA) model to extract the effects due to group (healthy or ESRD) and pair (matched healthy with ESRD subjects). Geometric mean ratios of AUC and C_{max} were reported with corresponding 90% confidence intervals.

Demographic Results

The following table summarizes the demographics of trial subjects

Demographic Characteristic	Group 1 Healthy Boceprevir 800 mg (n=6)	Group 5 ESRD Boceprevir 800 mg (n=8)	Total (n=14)
Sex (n,%)			
Male	6 (100)	8 (100)	14 (100)
Race (n, %)			
White	3 (50)	3 (38)	6 (43)
Non-white	3 (50)	5 (63)	8 (57)
Black or African American	3 (50)	5 (63)	8 (57)
Ethnicity (n, %)			
Hispanic or Latino	1 (17)	3 (38)	4 (29)
Not Hispanic or Latino	5 (83)	5 (63)	10 (71)
Age (yrs)			
Mean (SD)	43.5 (11.6)	44.1 (10.8)	43.9 (10.7)
Median	41.5	44.0	44.0
Range	32-57	29-57	29-57
Age (n, %)			
18-<65	6 (100)	8 (100)	14 (100)
Weight (kg)			
Mean (SD)	88.12 (10.87)	91.28 (15.94)	89.92 (13.60)
Median	88.90	89.95	88.90
Range	74.1-101.3	70.4-121.0	70.4-121.0
Height (cm)			
Mean (SD)	170.87 (2.56)	173.88 (4.89)	172.59 (4.22)
Median	170.50	173.00	171.00
Range	167.5-175.0	169.0-180.5	167.5-180.5
BMI (kg/m^2)			
Mean (SD)	30.25 (4.23)	30.20 (5.09)	30.22 (4.57)
Median	30.85	30.05	30.05
Range	24.2-35.3	21.7-37.1	21.7-37.1

Note: Two (2) end-stage renal disease (ESRD) subjects were enrolled and treated; however, they were not matched to healthy subjects due to their demographics.

SD = standard deviation; yrs = years; n = number; kg = kilograms; cm = centimeters; mg = milligrams

Fourteen male subjects enrolled in the trial, including 6 in Group 1 and 8 in Group 5. However, investigators excluded two ESRD subjects from data analysis because they did not meet the inclusion criteria.

Effects of ESRD on plasma concentrations of boceprevir, SCH534128, SCH534129, and SCH629144

The table below summarizes the geometric mean ratios of boceprevir, SCH534128, SCH534129, and SCH629144 exposures in Groups 1 and 5.

Table 38 Statistical results of the PK of boceprevir, SCH534128, SCH534129, and SCH629144 on day 1 following single oral dose of boceprevir 800 mg to healthy subjects (Group 1) and to ESRD subjects (Group 5).

	Parameter	Group	n	LS Mean[a]	GMR[b]	90% CI
Boceprevir	C_{max} (ng/mL)	Healthy ESRD	6 6	1472 1191	81	38 – 174
	AUC_{tf} (ng*hr/mL)	Healthy ESRD	6 6	5079 4572	90	47 – 173
	AUC_{I} (ng*hr/mL)	Healthy ESRD	6 6	5116 4613	90	47 – 174
SCH534128	C_{max} (ng/mL)	Healthy ESRD	6 6	830 707	85	40 – 182
	AUC_{tf} (ng*hr/mL)	Healthy ESRD	6 6	3033 2750	91	48 – 173
	AUC_{I} (ng*hr/mL)	Healthy ESRD	6 6	3059 2782	91	48 – 173
SCH534129	C_{max} (ng/mL)	Healthy ESRD	6 6	639 485	76	35 – 165
	AUC_{tf} (ng*hr/mL)	Healthy ESRD	6 6	2037 1817	89	45 – 175
	AUC_{I} (ng*hr/mL)	Healthy ESRD	6 6	2051 1835	89	46 – 176
SCH629144	C_{max} (ng/mL)	Healthy ESRD	6 6	2381 2107	89	41 – 192
	AUC_{tf} (ng*hr/mL)	Healthy ESRD	6 6	13539 13684	101	43 – 237
	AUC_{I} (ng*hr/mL)	Healthy ESRD	6 6	13629 13764	101	43 – 236

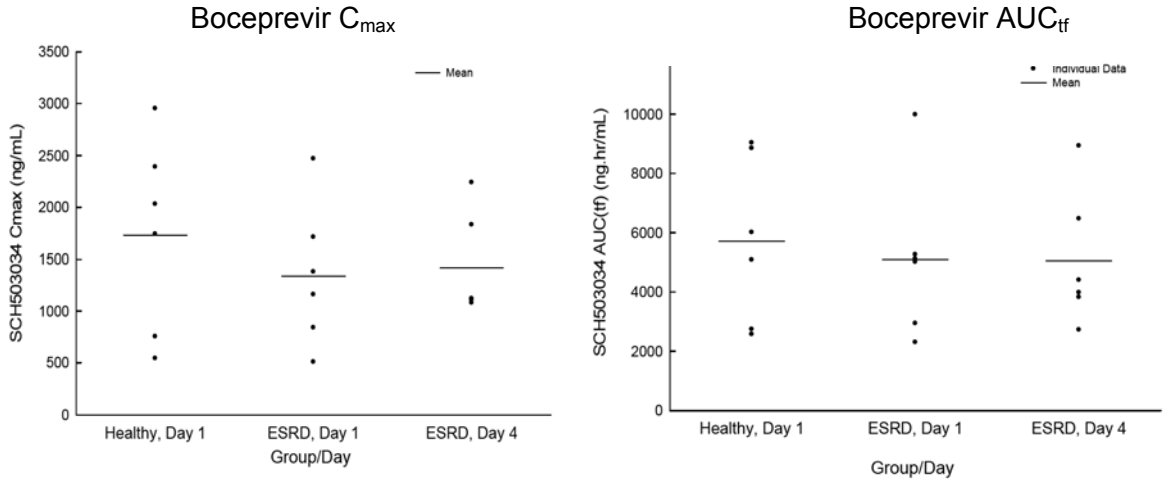
a. Model-based (least squares) geometric mean; ANOVA extracting the effects due to group and pair
b. Geometric mean ratio of ESRD subjects vs. healthy subjects
ESRD= End-stage renal disease; n= number; AUC(tf)= Area under the concentration-time curve from time 0 to the time of the final quantifiable sample; AUC(I)= Area under the concentration-time curve from time 0 to infinity; $t_{1/2}$= terminal phase half-life; Ae= amount of drug excreted in the urine; T_{max}= time to maximum observed plasma concentration; CV= coefficient of variation; C_{max}= maximum observed plasma concentration

Boceprevir exposures were lower in subjects with ESRD compared to subjects with normal renal function. For instance, the mean AUC and C_{max} of boceprevir were 10% and 19% lower in ESRD subjects relative to healthy subjects. However, the 90% confidence intervals associated with these ratios were wide (38% to 174%), possibly indicating an insufficient sample size to make a definitive conclusion. The mean AUC_{tf} ratios for SCH534128 and SCH534129 were similar to boceprevir. Overall, a 10% decrease in boceprevir exposure is unlikely to affect the antiviral activity of boceprevir.

The following figures display the individual and mean C_{max} and AUC_{tf} values for

boceprevir in normal and ESRD subjects.

Figure 2 Boceprevir C_{max} and AUC_{tf} values following a single oral dose of boceprevir 800 mg to healthy subjects (Group 1) and to subjects with ESRD (Group 5).



The table below summarizes the plasma PK of boceprevir, SCH534128, SCH534129, and SCH629144 in groups 1 and 5.

Table 2 Mean (CV, %) plasma PK of boceprevir, SCH534128, SCH534129, and SCH629144 following a single oral dose of boceprevir 800 mg to healthy subjects (Group 1) and to Subjects with ESRD (Group 5).

	Parameter	Healthy Subjects Group 1 (n=6)	ESRD Subjects Group 5 (n=6)	
			Day 1	Day 4
Boceprevir	T_{max}[a] (hr)	2.0 (2.0 – 4.0)	4.0 (1.0 – 6.0)	2.0 (1.3 – 2.0)
	C_{max} (ng/mL)	1730 (54)	1340 (52)	1420 (35)
	AUC_{tf} (ng*hr/mL)	5710 (50)	5100 (53)	5000 (43)
	AUC_I (ng*hr/mL)	5760 (50)	5150 (53)	5030 (43)
	$t_{1/2}$ (hr)	1.73 (21)	2.2 (60)	1.72 (43)
	CL/F (L/hr)	178 (55)	193 (50)	183 (38)
	Ae (mg)	19.2 (56)	-	-
	Ae (% dose)	2.40 (56)	-	-
	CLr (L/hr)	3.96 (54)	-	-
SCH534128	T_{max}[a] (hr)	2.0 (2.0 – 4.0)	4.0 (1.0 – 6.0)	2.0 (2.0 – 2.0)
	C_{max} (ng/mL)	968 (50)	801 (53)	807 (35)
	AUC_{tf} (ng*hr/mL)	3410 (49)	3050 (52)	3030 (42)
	AUC_I (ng*hr/mL)	3440 (49)	3090 (52)	3080 (42)
	$t_{1/2}$	1.69 (16)	2.17 (56)	2.63 (68)
	Ae (mg)	11.0 (55)	-	-
SCH534129	T_{max}[a] (hr)	2.0 (1.0 – 4.0)	3.0 (1.0 – 4.0)	2.0 (1.3 – 2.0)
	C_{max} (ng/mL)	768 (61)	546 (50)	615 (37)
	AUC_{tf} (ng*hr/mL)	2300 (51)	2050 (55)	1970 (46)
	AUC_I (ng*hr/mL)	2320 (51)	2070 (55)	1980 (46)
	$t_{1/2}$	1.95 (35)	2.05 (103)	1.34 (22)
	Ae (mg)	8.18 (56)	-	-
SCH629144	T_{max}[a] (hr)	4.0 (4.0 – 4.0)	4.0 (4.0 – 6.0)	4.0 (2.0 – 4.0)
	C_{max} (ng/mL)	2750 (52)	2510 (71)	2200 (50)
	AUC_{tf} (ng*hr/mL)	15700 (51)	18000 (97)	16100 (75)
	AUC_I (ng*hr/mL)	15800 (51)	18100 (97)	16200 (75)
	$t_{1/2}$	4.17 (24)	4.60 (34)	4.78 (34)
	Ae (mg)	25.9 (48)	-	-

a. Median range. n= number; AUC_{tf}= Area under the concentration-time curve from time 0 to the time of the final quantifiable sample; AUCI= Area under the concentration-time curve from time 0 to infinity; $t_{1/2}$= terminal phase half-life; CL/F= Apparent total body clearance or clearance; Ae= amount of drug excreted in the urine; CLr= renal clearance; C_{max}= maximum observed plasma concentration; T_{max}= time to maximum observed plasma concentration.

The half-life ($t_{1/2}$) values of boceprevir, SCH534128, and SCH534129 were similar in ESRD subjects relative to normal subjects. The half-life values ranged between 1.7 to 2.6 hours, and are consistent with values observed in previous clinical trials. Likewise, the mean apparent clearance (CL/F) of boceprevir was similar in both groups. Overall, these results suggest that the elimination of boceprevir is unaffected by ESRD.

Investigators recovered 2.4% of unchanged boceprevir dose in urine in Group 5 subjects. A similar amount (3%) of boceprevir was recovered in the mass balance trial in healthy subjects. These results support the finding that boceprevir is minimally excreted in urine.

Effects of hemodialysis on the PK of boceprevir, SCH534128, SCH534129 and SCH629144.

The table below summarizes the geometric mean ratios of boceprevir, SCH534128, SCH534129, and SCH629144 in ESRD subjects on day 1 and day 4 after hemodialysis.

Reviewer's comment: The geometric mean ratios are inverted; that is, the reference value was divided by the test value (GMR= Day 1/Day 4). The correct GMR is obtained by dividing the test value by the reference value (GMR= Day 4/Day 1).

Table 3 Statistical results for PK parameters of boceprevir, SCH534128, SCH53419, and SCH629144 on days 1 and day 4 following single oral doses of boceprevir 800 mg to subjects with ESRD undergoing hemodialysis.

	Parameter	Day	n	LS Mean[a]	GMR[b]	90% CI
Boceprevir	C_{max} (ng/mL)	1 4	6 6	1191 1355	88	63 – 123
	AUC_{tf} (ng*hr/mL)	1 4	6 6	4572 4654	98	81 – 119
	AUC_I (ng*hr/mL)	1 4	6 6	4613 4681	99	81 – 120
SCH534128	C_{max} (ng/mL)	1 4	6 6	707 771	92	64 – 132
	AUC_{tf} (ng*hr/mL)	1 4	6 6	2750 2831	97	81 – 117
	AUC_I (ng*hr/mL)	1 4	6 6	2782 2870	97	80 – 117
SCH534129	C_{max} (ng/mL)	1 4	6 6	485 584	83	61 – 113
	AUC_{tf} (ng*hr/mL)	1 4	6 6	1817 1810	100	81 – 125
	AUC_I (ng*hr/mL)	1 4	6 6	1835 1827	100	80 – 126

SCH629144	C_{max} (ng/mL)	1 4	6 6	2107 1994	106	91 – 123
	AUC_{tf} (ng*hr/mL)	1 4	6 6	13684 13365	102	86 – 121
	AUC_I (ng*hr/mL)	1 4	6 6	13764 13453	102	86 – 121

a. Model-based (least squares) geometric mean; ANOVA extracting the effects due to day and subject
b. Geometric mean ratio of day 1 vs. day 4

Reviewer's comment: Investigators did not weigh subjects immediately before and after hemodialysis to account for weight or fluid loss during hemodialysis. This may be a source of intersubject PK variability.

Hemodialysis did not affect the mean AUC_{tf} of boceprevir in ESRD subjects. The mean AUC_{tf} of boceprevir, SCH534128 and SCH534129 on day 4 relative to day 1 were 101.8%, 102.9%, and 99.6%, respectively. The mean apparent clearance of boceprevir was similar before (193 L/hr) and after (183 L/hr) hemodialysis.

Hemodialysis increased the mean C_{max} of boceprevir, SCH534128, and SCH534129 on day 4 relative to day 1 by 13.8%, 9.1%, and 20.4%, respectively. The increase in C_{max} of boceprevir is likely due to variability in absorption rather than hemodialysis. Hemodialysis typically affects the AUC and not the C_{max} of a drug. Nevertheless, a 20.4% increase in the C_{max} of boceprevir is unlikely to pose a safety concern to subjects.

Effect of hemodialysis on the PK of boceprevir, SCH534128, SCH534129, and SCH629144 in arterial and venous blood samples.

The assay (DM27655) for analysis of arterial and venous blood was appropriate. The table below summarizes the PK results of boceprevir, SCH534128, SCH534129, and SCH629144 in arterial and venous blood samples. Arterial samples represent blood entering the dialysis instrument. Venous samples represent blood leaving the instrument.

Table 4 Mean (CV,%) arterial and venous blood PK of boceprevir, SCH534128, SCH534129, and SCH629144 following a single oral dose of boceprevir 800 mg to subjects with ESRD (Group 5) on day 4.

Parameter	Boceprevir	SCH 534128	SCH 534129	SCH 629144
Arterial Blood (n=6) AUC(5-8hr) (ng·hr/mL)	816 (75)	567 (75)	249 (75)	4400 (80)
Venous Blood (n=6) [a] AUC(5-8hr) (ng·hr/mL)	745 (78)	513 (78)	232 (78)	3910 (88)

a: Venous AUC for two subjects was AUC(5-7hr)

ESRD = End-stage renal disease; n = number; AUC = Area under the concentration-time curve

The mean exposures ($AUC_{5\text{-}8h}$) of boceprevir, SCH534128, SCH534129, and SCH629144 were slightly lower in venous relative to arterial blood samples. Decreases in systemic exposures ranged from 7% to 12% across all analytes. However, these decreases in exposures are likely due to variability (78 – 88%) observed across values. Overall, results suggest that hemodialysis does not substantially remove systemic boceprevir diastereomers or metabolite.

PK of boceprevir, SCH534128, SCH534129, and SCH629144 in dialysate recovered during hemodialysis.

The table below summarizes the PK results of boceprevir, SCH534128, SCH534129, and SCH629144 in dialysate.

Table 5 Mean (CV,%) dialysate PK of boceprevir, SCH534128, SCH534129, and SCH629144 following a single oral dose of boceprevir 800 mg to subjects with ESRD (Group 5) on day 4.

Parameter	Boceprevir (n=6)	SCH 534128 (n=6)	SCH 534129 (n=6)	SCH 629144 (n=6)
Amount Recovered (4-8hr) (mg)	2.11 (68)	1.47 (70)	0.638 (66)	9.72 (57)
Amount Recovered (4-8hr) (%Dose)	0.263 (68)	NC	NC	NC

NC: Not calculated as % Dose is calculated on actual dose administered.

Investigators recovered less than 1% of the boceprevir 800 mg dose in dialysate. These results suggest that hemodialysis insignificantly removes boceprevir from the systemic circulation.

Effect of ESRD on plasma protein binding of boceprevir and SCH629144.

The ex vivo plasma protein binding assay conducted by the Sponsor is appropriate. The table below summarizes the results of boceprevir and SCH629144 plasma protein binding before and after hemodialysis.

Table 6 Mean (CV,%) percent protein binding for boceprevir and its metabolite following a single oral dose of boceprevir 800 mg to healthy (Group 1) and ESRD subjects (Group 5).

Analyte	Healthy Subjects (Group 1, n=6) Day 1-2hr	ESRD Patients (Group 5, n=6) Day 1-2 hr	Day 4-4 hr	Day 4-8 hr
Boceprevir	73.6 (3)	72.8 (7)	73.0 (3)	81.6[a] (NA)
SCH 629144	69.7 (4)	69.3 (6)	71.1 (4)	74.1[b] (4)

a: n=2

b: n=4

n = number: NA = not available: ESRD = end-stage renal disease: hr = hours

The mean percent plasma protein binding (PPB) values of boceprevir and SCH629144 were similar in healthy and in ESRD subjects. The percent PPB values observed in this trial are similar to *in vitro* PPB values for boceprevir (73.1% to 79.5%). The percent PPB at 8 hours on day 4 in ESRD subjects was slightly larger (81.6%) than the rest of the values across subjects. However, this increased PPB value may be due to lower number of subjects (n=2) available for assessment. Overall, ESRD did not affect the percent of plasma protein binding of boceprevir.

Safety results

Subjects safely tolerated a single dose of boceprevir 800 mg. All subjects completed the trial. Only two (14%) subjects in the ESRD group reported ventricular extrasystoles, flatulence, and catheter thrombosis. These treatment-emergent adverse events were moderate in severity, and likely unrelated to boceprevir administration. There were no serious or life-threatening adverse events in this trial.

Discussions and Conclusions

Previous *in vivo* experience with boceprevir suggested that renal insufficiency might not affect the PK of boceprevir. Boceprevir is primarily metabolized *in vivo* by hepatic enzymes and mainly (78%) eliminated in feces. In addition, approximately 1% of boceprevir dose is renally eliminated. The Sponsor conducted the trial because subjects infected with HCV and affected with renal

insufficiency are likely to be treated with boceprevir. Moreover, recent articles in the literature suggest that renal insufficiency may affect the PK of drugs, even if they do not undergo renal elimination. The following section discusses the trial results.

Effect of ESRD on plasma PK of boceprevir

In this trial, investigators compared the PK of boceprevir in plasma collected from subjects with ESRD versus healthy subjects. Subjects with ESRD had ~10% lower exposures (AUC_{tf}) of boceprevir relative to subjects with normal renal function. PK results were similar for SCH534128 and SCH534129. Overall, a 10% decrease in boceprevir exposure is unlikely to affect the antiviral activity of boceprevir.

The mean C_{max} values of boceprevir and its diastereomers were 15% to 24% lower in ESRD subjects relative to healthy subjects. However, the 90% confidence intervals associated with these mean C_{max} values were too wide to make a definitive conclusion.

The half-lives of boceprevir and its diastereomers ranged from 1.7 to 2.6 hours, and are consistent with values observed in previous clinical trials. Likewise, the mean apparent clearance (CL/F) of boceprevir was similar in ESRD subjects and healthy subjects. These results suggest that the elimination of boceprevir is unaffected by ESRD.

Overall, the findings of this trial support the recommendation that boceprevir does not need dose adjustment in subjects with any degree of renal insufficiency.

Effect of hemodialysis on the PK of boceprevir

Investigators evaluated whether hemodialysis affects the systemic exposures of boceprevir. Arterial blood, venous blood, and dialysate samples were collected to compare the PK exposures of boceprevir in subjects with ESRD versus healthy subjects.

Hemodialysis did not affect the plasma exposures (AUC) of boceprevir in ESRD subjects. The mean plasma AUC_{tf} values of boceprevir, SCH534128, and SCH534129 on day 4 relative to day 1 were unchanged at 101.8%, 102.9%, and 99.6%, respectively. The mean apparent clearance of boceprevir was also similar before and after hemodialysis. These results suggest that hemodialysis does not affect the overall exposure (AUC) of boceprevir in ESRD subjects.

Conversely, hemodialysis increased the mean plasma C_{max} of boceprevir, SCH534128, and SCH534129 on day 4 relative to day 1 by 13.8%, 9.1%, and

20.4%, respectively. However, the 90% confidence intervals associated with these values were too wide to make a definitive conclusion. The increase in C_{max} ratios is likely due to PK variability and not to hemodialysis because hemodialysis typically affects the overall exposure and not absorption of an oral drug.

Moreover, boceprevir exposures were similar in venous and arterial blood samples collected before and after hemodialysis. Investigators recovered less than 1% of the dose of boceprevir in dialysate.

These findings concur with the overall observation that hemodialysis does not affect the plasma concentrations of boceprevir.

Effect of ESRD on plasma protein binding of boceprevir

The trial also aimed to evaluate the effect of renal insufficiency on the plasma protein binding of boceprevir.

The mean percent plasma protein binding of boceprevir was similar in ESRD subjects relative to healthy subjects. The percent protein binding of boceprevir ranged from 73 to 82% across both groups. These findings are consistent with *in vitro* evaluations of protein binding with boceprevir.

Overall conclusion

In summary, clinicians should not adjust the dose of boceprevir in subjects with any degree of renal insufficiency. ESRD subjects do not require a compensatory dose of boceprevir following hemodialysis. Lastly, ESRD does not affect the plasma protein binding of boceprevir.

4.2.3 Extrinsic factors

Trial P04486

A Rising Multiple Dose Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics (PK) of High Dose Boceprevir Alone and Co-administered with Diflunisal in Healthy Female Subjects

Dates

November 28, 2005 to October 31, 2006

Trial Site

West Coast Clinical Trials, Long Beach, California

Summary of Reviewer Findings

Diflunisal 250 mg BID increased boceprevir exposures when dosed at 800 mg BID or TID. When boceprevir was dosed at 800 mg BID, diflunisal increased the mean C_{max}, AUC_{tau}, and C_{min} values of boceprevir by 16%, 31%, and 39%, respectively. When boceprevir was dosed at 800 mg TID, diflunisal increased only the mean C_{min} of boceprevir by 26%. Overall, investigators considered the increases in boceprevir exposures clinically irrelevant.

Conversely, boceprevir did not affect the PK of diflunisal.

Clinicians may co-administer boceprevir with aldo-keto reductase inhibitors like diflunisal and ibuprofen in a clinical setting.

Trial Objectives

The primary objectives of the trial were to determine

1. The highest dose of boceprevir for the thorough QTc study.

2. The safety and tolerability of the co-administration of boceprevir and diflunisal.

3. The effect of diflunisal on the trough concentrations (C_{min}) of boceprevir.

The secondary objectives of this trial were to evaluate

1. The PK of boceprevir (SCH503034).

2. The PK of boceprevir when co-administered with diflunisal.

Trial Design

This Phase 1 trial had a dose escalation, multiple doses, randomized (within each dose level), third-party blinded, placebo-controlled design. The trial consisted of five groups. Groups 1, 2, and 5 evaluated the PK of boceprevir given at various doses. Groups 3 and 4 evaluated the potential drug-drug interaction (DDI) between boceprevir and diflunisal.

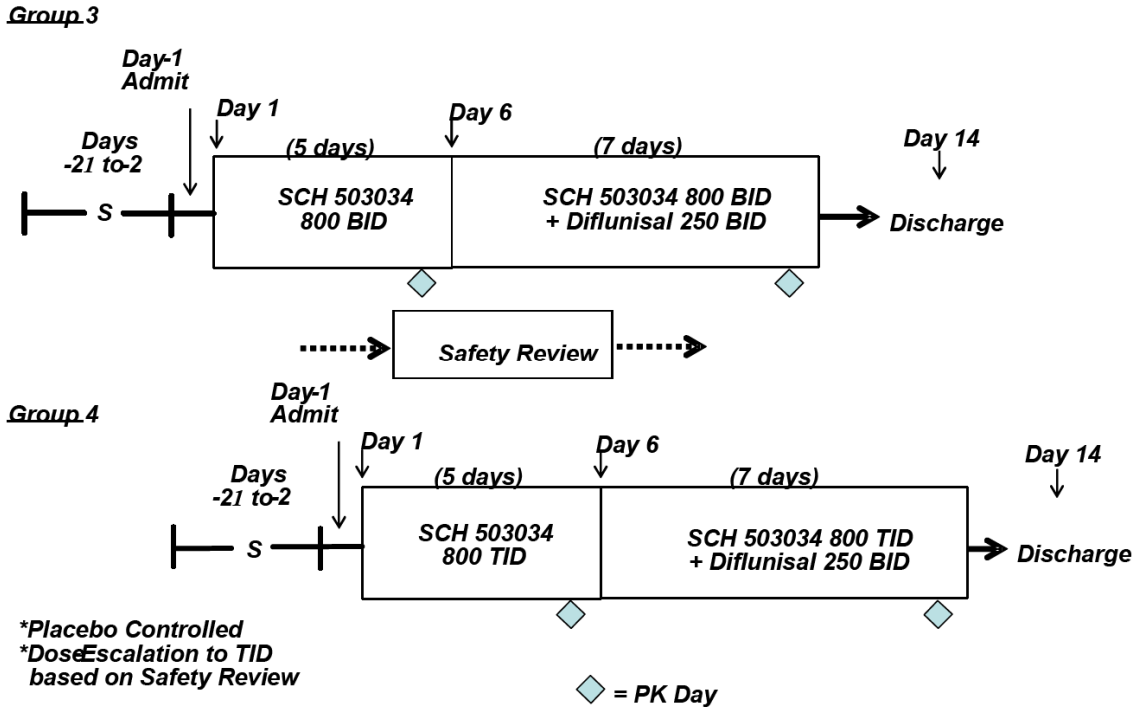
This report only reviews PK data from groups 3 and 4. Unfortunately, PK data from groups 1, 2, and 5 were unreliable because the Sponsor had difficulties assaying the plasma samples from these groups. Refer to the bioanalytical section for details.

In groups 3 and 4, investigators tested sequential, multiple-doses of boceprevir and diflunisal. Each group contained eight female subjects. Six subjects in each group received boceprevir and diflunisal. Two subjects in each group received placebo and diflunisal. Investigators evaluated the safety of drug co-administration in group 3 before dosing group 4. The treatments for groups 3 and 4 are summarized below. Figure 1 illustrates the trial design.

Group 3: Boceprevir 800 mg (4 X 200 mg capsules commercial formulation) or placebo BID for 11 consecutive days and one dose on day 12. Diflunisal 250 mg BID on days 6 through 14.

Group 4: Boceprevir 800 mg (4 X 200 mg capsules commercial formulation) or placebo TID for 11 consecutive days and one dose on day 12. Diflunisal 250 mg BID on days 6 through 14.

Figure 1 Trial Design



Key Inclusion Criteria

Prior to study enrollment, all subjects were healthy based on physical examinations and clinical laboratory tests. For instance, blood levels of AST, ALT, GGT, and bilirubin were within normal range at trial screening. Vital signs and ECG parameters were also within normal limits. All subjects were willing to use a barrier method of contraception in conjunction with spermicide during the trial and 30 days after the last dose of boceprevir.

Reviewer's comment: Boceprevir caused testicular degeneration in animals. As a safety precaution, male subjects did not participate in this trial. Investigators were conducting additional animal testing to evaluate testicular degeneration when this trial was conducted.

Key Exclusion Criteria

Subjects did not participate in the trial if they had an active viral infection (HIV-1, HIV-2, HBV, HCV), tested positive for illicit drugs, or smoked >10 cigarettes per day. Before the trial started, investigators instructed all subjects to refrain from

taking any drugs, herbal, or mineral supplements within 2 weeks prior to trial start. Subjects were not allowed to ingest alcohol and caffeine within 48 hours prior to and during the trial. Acetaminophen was the only drug allowed during the trial at doses ≤500 mg per day.

Reviewer's comment: Investigators neglected to specify the exclusion criteria for subjects with abnormal laboratory parameters.

Investigational Products

Subjects received the proposed commercial formulation of boceprevir as 200-mg capsules that contained a 1:1 mixture of two diastereomers, SCH534128 and SCH534129. SCH534128 is biologically active, whereas SCH534129 is inactive. The plasma ratio of SCH534128:SCH534129 is approximately 2:1.

Schering-Plough manufactured the capsules using boceprevir powder from 2 batches, 82408-020, and K-H07164. These batches were manufactured on June 03, 2005 and June 22, 2006, respectively.

(b) (4) manufactured the placebo capsules with batch number 79229-025.

Subjects received the commercial formulation of diflunisal as either a Canadian 250-mg tablet or a 500 mg tablet available in the United States. Investigators split the 500 mg tablets, if used.

Reviewer's comment: Investigators neglected to report the expiration dates of all the formulations used in the trial.

Drug Administration

All subjects were admitted to the trial site on day-1.

On day -1, subjects received a snack consisting of a sandwich, a piece of fruit, and a caffeine-free beverage approximately 10 to 12 hours prior to the first dose of boceprevir. The snack contained ≥120 calories, and excluded the intake of grapefruit and grapefruit juice. All subjects fasted overnight for at least 6 hours prior to the first dose of boceprevir. On day 1, subjects took boceprevir in the fasted state and were allowed to drink water 1 hour before and 1 hour after receiving boceprevir. Subjects fasted for an additional 4 hours after receiving boceprevir. On days 1 (second dose) to 12, subjects ingested regular meals 3 times daily, including snacks during the afternoon and evening dosing times.

Rationale for Dose Selection

In previous clinical trials, healthy and HCV-infected subjects safely tolerated single and multiple doses of boceprevir ranging from 800 mg up to 400 mg TID for 14 days. Therefore, investigators began this trial with 400 mg TID, and dose escalated until they found a higher tolerable dose. The boceprevir dose of 1200 mg TID was the highest dose tested in this trial. Additionally, investigators attempted to identify a dose that would deliver up to 5-fold higher exposures relative to the *in vitro* EC_{90}. The target average plasma concentration was 35 ng/mL and the efficacious AUC_{tau} at steady state was projected to be 840 ng*hr/mL. The dose of 400 mg TID met this target concentration.

Investigators dosed diflunisal at 250 mg BID based on the standard approved dose.

Pharmacokinetic Assessments

Investigators collected blood samples for PK of boceprevir, and boceprevir, SCH534128, SCH534129, and diflunisal. The table below shows the schedule of PK assessments in the trial.

Table 1 Schedule of blood sampling for PK of Boceprevir and Diflunisal

	Study day												
Group	**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Boceprevir													
3	0	0 (AM)	0 (AM)	0–12h				0 (AM)	0 (AM)	0 (AM)	0-12h	24h	
4	0	0 (AM)	0 (AM)	0-12h				0 (AM)	0 (AM)	0 (AM)	0–12h	24h	
Diflunisal													
3					0 (AM)	0 (AM)	0 (AM)	0 (AM)	0 (AM)	0 (AM)	0–12h	24h	48h
4					0 (AM)	0 (AM)	0 (AM)	0 (AM)	0 (AM)	0 (AM)	0-12h	24h	48h

Bioanalytical Methods

Faulty bioanalytical assays rendered the concentrations of boceprevir from Groups 1, 2, and 5 unreliable. After the first sample analysis, investigators observed unexpected concentrations of boceprevir. Suspicious of dilution errors, investigators re-analyzed the plasma samples only to discover that concentrations from the two runs did not meet the acceptable bioanalytical criteria (within ± 20% of the initial concentrations). What is more, some samples exceeded the frozen stability period for bioanalysis. Consequently, the concentrations of boceprevir from groups 1, 2, and 5 were unreliable.

Boceprevir concentrations from groups 3 and 4 are reliable. Investigators assayed the plasma samples from these groups using method DM27268 to determine the concentrations of SCH534128 and SCH534129 in acidified human plasma. Of note, boceprevir concentrations reported in groups 3 and 4 are derived from the sum of SCH534128 and SCH534129 concentrations.

Likewise, concentrations of diflunisal are also reliable. (b) (4) analyzed all plasma samples for diflunisal using a validated LC-MS/MS method DM27347. All standard samples were prepared using reference acquired from (b) (4) .

The table below lists the upper and lower limits of quantification for bioanalytical methods.

Table 2 Limits of quantification of LC-MS/MS bioanalytical methods used in the trial

Analyte	Matrix	LLOQ (ng/mL)	ULQ (ng/mL)	LC-MS/MS method
SCH534128	Acidified human plasma	1.3	655	DM27268
SCH534129	Acidified human plasma	1.2	595	DM27268
Diflunisal	Nonacidified human plasma	100	10000	DM27347

Group 3 and 4 calibration standards and quality controls met the bioanalytical criteria defined as precision (%CV) within ±15%, accuracy (%RE) ≤15%, and coefficient of determination (r^2) ≥0.98. The table below summarizes the precision and accuracy of the bioanalytical methods used by the investigators to determine the concentrations of all analytes in human plasma.

Table 3 Precision (% CV) and accuracy (% relative error) of calibration standards and QC samples in human plasma

		Cal Std			QC	
Method	Analyte	%CV	%RE	R^2	%CV	%RE
DM27268	SCH534128	1.6 – 4.7	≤1.5	≥0.9986	1.8 – 5.3	≤7.3
SN 04921	SCH534129	2.1 – 6.3	≤4.3	≥0.9961	4.1 – 7.1	≤6.4
DM27268	SCH534129	1.2 – 6.0	≤3.4	≥0.9963	3.4 – 5.0	≤9.3
DM27347	Diflunisal	2.0 – 7.7	≤4.2	≥0.9976	3.2 – 6.1	≤4.8

All plasma samples were analyzed within the frozen storage stability period. The frozen stabilities of SCH534128, SCH534129, and diflunisal in plasma were 301, 357, 316, and 274 days, respectively.

Pharmacokinetic and Statistical Analyses

Investigators compared differences in mean concentrations of boceprevir between the first portion of group 3 or group 4 (boceprevir alone) versus the corresponding second portion of group 3 or group 4 (boceprevir 800 mg BID + diflunisal 250 mg BID or boceprevir 800 mg TID + diflunisal 250 mg BID). Investigators computed 90% confidence interval estimates comparing the groups with and without diflunisal using an ANOVA method on log-transformed data, extracting the effects of subjects and treatment.

Demographic Results

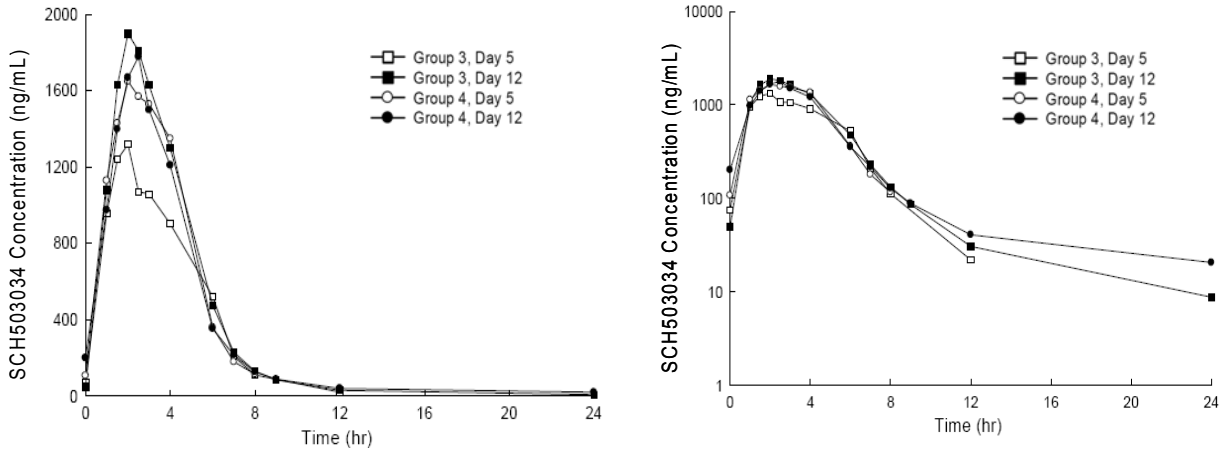
The table below lists the subject demographics.

	S503034 800 mg BID+ Dif 250 mg BID n=6	S503034 800 mg TID+ Dif 250 mg BID n=6
Sex (n,%)		
Female	6 (100)	6 (100)
Race (n,%)		
White	3 (50)	3 (50)
Non-White	3 (50)	3 (50)
American Indian or Alaskan Native	0	0
Asian	2 (33)	0
Black or African American	1 (17)	3 (50)
Native Hawaiian or Other Pacific Islander	0	0
Ethnicity (n,%)		
Hispanic or Latino	3 (50)	3 (50)
Not Hispanic or Latino	3 (50)	3 (50)
Age (yrs)		
Mean (SD)	28.7 (6.9)	30.5 (9.8)
Median	25.5	31.0
Range	23 - 38	19 - 47
Age (n,%)		
18 - <65	6 (100)	6 (100)
Weight (kg)		
Mean (SD)	62.82 (9.91)	75.00 (14.50)
Median	60.90	78.60
Range	49.2 - 77.4	48.3 - 91.0
Height (cm)		
Mean (SD)	160.48 (5.41)	164.97 (9.65)
Median	161.00	164.50
Range	154.1 - 168.4	150.7 - 181.0
BMI		
Mean (SD)	24.27 (2.57)	27.32 (3.23)
Median	24.35	28.35
Range	20.7 - 27.3	21.3 - 30.3

Pharmacokinetic results, Effect of diflunisal on the PK of boceprevir, Groups 3 and 4.

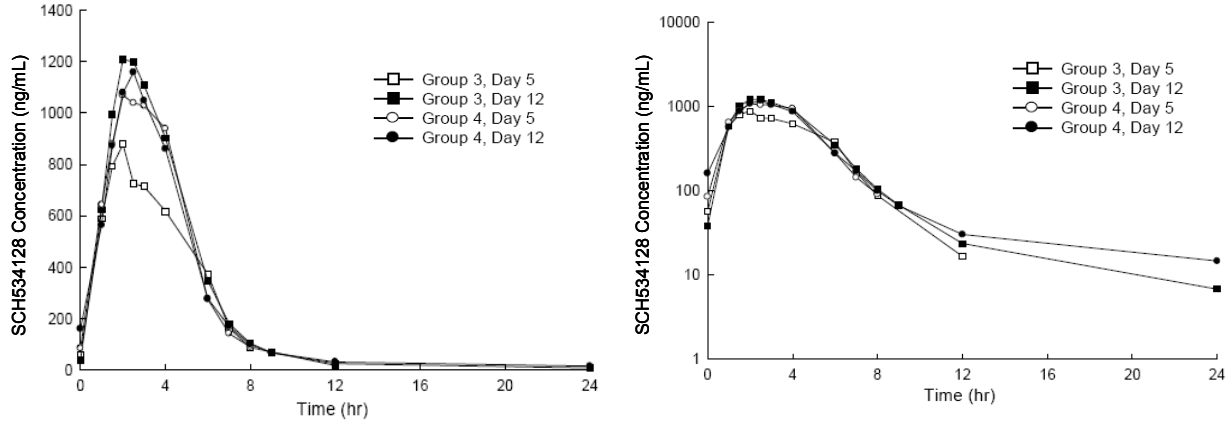
The concentration-time profiles of boceprevir were similar across dose cohorts. The figures below show concentration-time profiles of boceprevir in groups 3 and 4 in the presence (day 12) or absence (day 5) of diflunisal. The graph on the left is in linear-scale and the graph on the right is log-scale.

Figure 2 Mean plasma concentration-time profiles of boceprevir following single and multiple oral doses of boceprevir 800 mg BID (group 3) or boceprevir TID (group 4) with 250 mg diflunisal BID in healthy subjects.



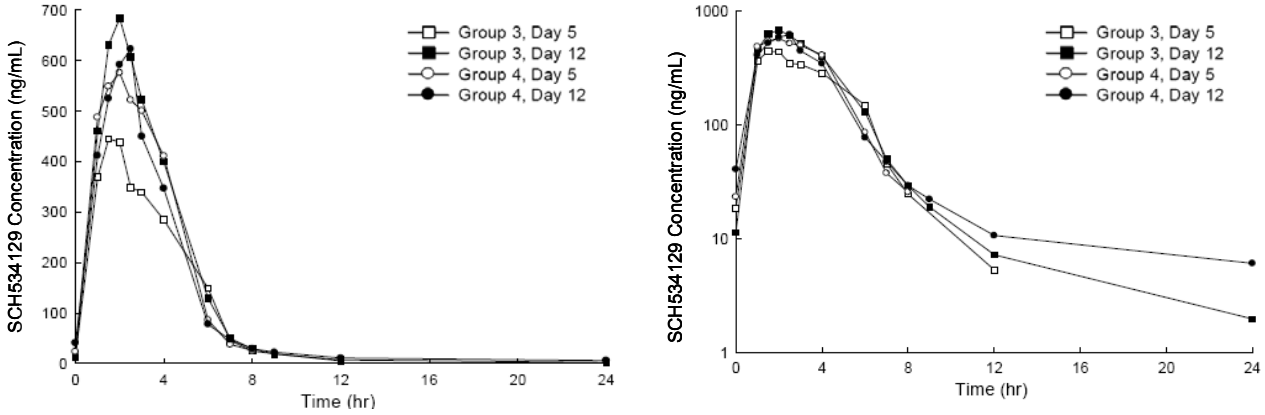
Diflunisal increased the systemic concentrations of SCH534128 in Group 3, but not in Group 4. The figures below show concentration-time profiles of SCH534128 in groups 3 and 4 in the presence (day 12) or absence (day 5) of diflunisal.

Figure 3 Mean plasma concentration-time profiles of active boceprevir diastereomer (SCH534128) following single and multiple oral doses of boceprevir 800 mg BID (group 3) or 800 mg TID (group 4) with 250 mg diflunisal BID in healthy subjects.



The figures below show concentration-time profiles of SCH534129 in groups 3 and 4 in the presence (day 12) and absence (day 5) of diflunisal.

Figure 4 Mean plasma concentration-time profiles of SCH534129 following single and multiple oral doses of boceprevir 800 mg BID (group 3) or 800 mg TID (group 4) with diflunisal 250 mg BID in healthy subjects.



The statistical results are summarized below.

Table 4 Statistical analysis of boceprevir in the presence (day 12) or absence (day 5) of diflunisal 250 mg BID.

				LS Means[a]		Treatment Comparison[a]		
Group	Analyte	Parameter	n	Day 5	Day 12	Comparison	Ratio	90% CI
3	SCH 503034a	Cmax	4[b]	1998	2315	Day 12 vs 5	116	90-148
		AUC(τ)		5974	7802	Day 12 vs 5	131	98-174
		Cmin		21	29	Day 12 vs 5	139	86-223
	SCH 534128	Cmax	4[b]	1321	1510	Day 12 vs 5	114	93-140
		AUC(τ)		4106	5236	Day 12 vs 5	128	99-164
		Cmin		16	22	Day 12 vs 5	138	89-214
	SCH 534129	Cmax	4[b]	679	874	Day 12 vs 5	129	101-165
		AUC(τ)		1862	2559	Day 12 vs 5	137	98-193
		Cmin		5	7	Day 12 vs 5	138	75-254
4	SCH 503034a	Cmax	5[c]	2259	1936	Day 12 vs 5	86	56-132
		AUC(τ)		6868	6597	Day 12 vs 5	96	79-117
		Cmin		83	108	Day 12 vs 5	131	104-165
	SCH 534128	Cmax	5[c]	1447	1292	Day 12 vs 5	89	56-142
		AUC(τ)		4602	4499	Day 12 vs 5	98	80-120
		Cmin		64	83	Day 12 vs 5	130	102-167
	SCH 534129	Cmax	5[c]	815	702	Day 12 vs 5	86	63-119
		AUC(τ)		2265	2095	Day 12 vs 5	92	76-112
		Cmin		19	23	Day 12 vs 5	126	104-152

SCH 503034a is the sum of SCH 534128 and SCH 534129.

a: Ratio and 90% CI are ANOVA model extracting the effect due to treatment and subject.

b: Subjects 1/000305 and 1/000307 were excluded from the analysis due to discontinuation.

c: Subject 1/000407 was excluded from the analysis due to discontinuation.

Group 3: SCH 503034 800 mg BID on Days 1 to 5 and SCH 503034 800 mg BID + diflunisal on Days 6 to 12. Group 4: SCH 503034 800 mg TID on Days 1 to 5 and SCH 503034 800 mg TID + diflunisal on Days 6 to 12.

ANOVA = analysis of variance; CI = confidence interval; LS = least-square.

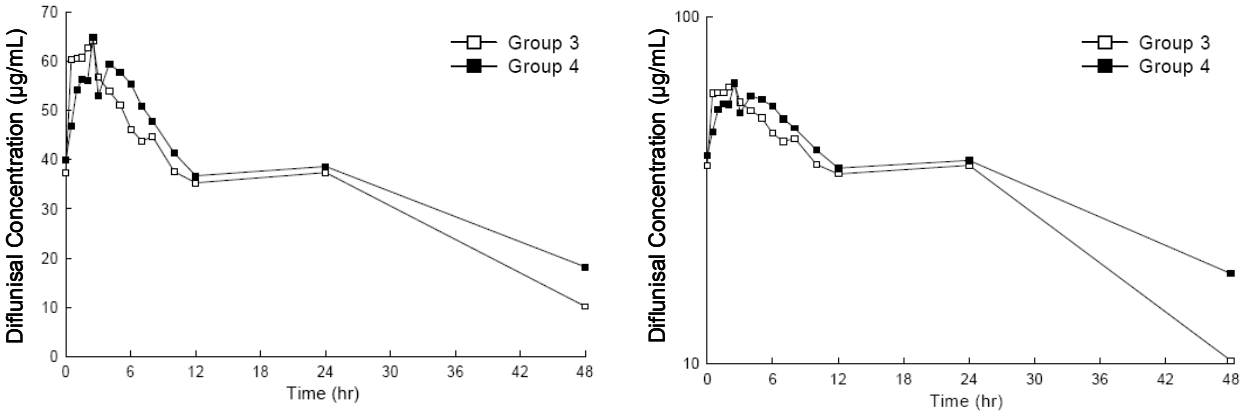
In group 3, diflunisal 250 mg BID increased the mean steady state C_{max}, AUC_{tau}, and C_{min} of boceprevir by 16%, 31%, and 39% respectively relative to boceprevir alone. Likewise, SCH534128 and SCH534129 exposures also increased by a similar magnitude in the presence of diflunisal relative to boceprevir alone.

In group 4, diflunisal 250 mg BID did not change the C_{max} and AUC_{tau} of boceprevir, SCH534128, and SCH534129 relative to boceprevir alone. Conversely, the mean C_{min} of all three analytes increased by 26% to 31% in the presence of diflunisal relative to boceprevir alone.

Pharmacokinetic results for diflunisal, Groups 3 and 4

Investigators did not evaluate the direct effect of boceprevir on the PK of diflunisal because PK samples for diflunisal were not collected in the absence of boceprevir. However, the impact of boceprevir on diflunisal was compared between 800 mg BID and TID. The figure below shows the concentration-time profiles of diflunisal in the presence of boceprevir. The graph on the left is in linear-scale and the graph on the right is log-scale.

Figure 5 Mean plasma concentration-time profiles of diflunisal following multiple (day 12) oral doses of diflunisal 250 mg in combination with boceprevir 800 mg BID (group 3) or 800 mg TID (group 4) in healthy subjects.



The following table summarizes the PK data of diflunisal in groups 3 and 4.

Table 5 PK parameters of diflunisal following multiple (day 12) oral doses of diflunisal with boceprevir in healthy subjects.

Parameters	SCH 503034 800 mg BID + Diflunisal Group 3 (n=4)[a]	SCH 503034 800 mg TID + Diflunisal Group 4 (n=5)[b]
Tmax[c] (hr)	1.50 (0.500-2.50)	2.50 (1.00-4.00)
Cmax (µg/mL)	73.5 (16)	68.0 (31)
Cmin (µg/mL)	34.7 (30)	35.6 (37)
AUC(τ) (µg·hr/mL)	579 (22)	609 (35)

Data presented as mean (CV).

a: Subjects 1/000305 and 1/000307 were excluded from the analysis due to discontinuation.

b: Subject 1/000407 was excluded from the analysis due to discontinuation.

c: Median (range).

Group 3: SCH 503034 800 mg BID for 11 consecutive days and one dose on Day 12; 250 mg diflunisal BID on Days 6 through 14.

Group 4: SCH 503034 800 mg TID for 11 consecutive days and one dose on Day 12; 250 mg diflunisal BID on Days 6 through 14.

BID = twice daily; CV = coefficient of variation; PK = pharmacokinetic(s); TID = three times daily.

The C_{max} and AUC_{tau} values of diflunisal were similar in groups 3 and 4. The package insert for Dolobid® (diflunisal) reports a mean C_{max} of 56 µg/mL following 8 days of diflunisal 250 mg BID. This value is similar to C_{max} values of diflunisal found in this trial.

Safety results

Twelve subjects enrolled, but only 10 completed the DDI sub-trial. One subject had a 2-fold increase in ALT relative to baseline levels. Another subject had gastroenteritis. The most common adverse event was headache during boceprevir administration alone and gastrointestinal disorders during administration of boceprevir with diflunisal.

Discussion and Conclusions

PK results, effect of diflunisal on the PK of boceprevir, groups 3 and 4.

Diflunisal 250 mg BID increased the steady state C_{min} of boceprevir and its

diastereomers during drug co-administration. In group 3, diflunisal increased the mean C_{max}, AUC_{tau}, C_{min}, of boceprevir by 16%, 31%, and 39%, respectively, relative to boceprevir alone. On the other hand, in group 4 diflunisal increased the C_{min} of boceprevir by 26% relative to boceprevir alone, without affecting C_{max} or AUC_{tau}. The increase in boceprevir exposures in the presence of diflunisal is likely clinically irrelevant.

Investigators were unable to monitor the formation of boceprevir metabolite SCH629144 due to a technical error in the trial protocol. This information may have helped determine if diflunisal inhibited the metabolism of boceprevir via the enzyme aldo-keto-reductase (AKR).

In the presence of diflunisal, the exposures of boceprevir, SCH534128, and SCH534129 increased when boceprevir was administered at 800 mg BID, but not at the 800 mg TID dose. This implies that the observed increase in boceprevir concentrations may have been due to diflunisal inhibition of AKR and not because of an imbalance in the diastereomer ratio. Diflunisal did not alter the 2:1 ratio of the diastereomers SCH534128 : SCH534129. However, any effect diflunisal has on the inhibition of boceprevir metabolism at 800 mg BID appears to be ameliorated at the higher boceprevir dose of 800 mg TID.

Overall conclusion

Diflunisal slightly increased the exposures of boceprevir. However, the increase in boceprevir exposure was clinically irrelevant. Conversely, boceprevir does not appear to affect the PK of diflunisal. Results suggest that clinicians may co-administer boceprevir with aldo-keto-reductase inhibitors like diflunisal and ibuprofen.

Trial P04624

A Study to Assess the Pharmacokinetics, Safety, and Tolerability of Boceprevir Administered in Combination with Ritonavir, Clarithromycin, or Diflunisal

Dates

June 29, 2006 to November 07, 2006

Trial Site

Parkway Research Center, Inc., North Miami Beach, Florida

Summary of Reviewer Findings

- The goal of the study was to identify an agent that would increase the steady state C_{min} of boceprevir to a clinically relevant extent by inhibiting its metabolism via CYP3A4 and/or AKR. They tested diflunisal, ritonavir, and clarithromycin as potential PK "boosters."

- Ritonavir 100 mg BID decreased the C_{min} of boceprevir by 48% relative to boceprevir alone, while ritonavir 100 mg QD did not affect the C_{min} of boceprevir. Similarly, the AUC_{tau} of boceprevir decreased in the presence of ritonavir 100 mg QD and BID by 19% and 28%, respectively compared to boceprevir alone. Overall, ritonavir 100 mg QD and BID decreased the exposures of boceprevir.

- Diflunisal 500 mg BID may have increased the C_{min} and AUC of boceprevir relative to boceprevir alone, but the overall trial results are inconclusive. The dosing intervals of boceprevir were different in the reference arm (400 mg TID) versus the test arms (400 mg BID) containing diflunisal. Thus, a change in dosing interval (AUC_{0-8h} vs. AUC_{0-12h}), and not a drug interaction, may be responsible for the observed change in the PK of boceprevir in this trial.

- The combination of clarithromycin 500 mg BID and diflunisal 500 mg TID did not affect the C_{min} of boceprevir relative to boceprevir alone. However, the drug combination increased the C_{max} and AUC_{tau} of boceprevir by 67% relative to boceprevir alone. The increase in boceprevir exposures is likely clinically irrelevant and may not require dose adjustment.

- None of the three agents tested increased boceprevir C_{min} by a clinically relevant extent.

Trial Objectives

The primary trial objectives were to determine the

1. Safety and tolerability of boceprevir administered in combination with ritonavir, diflunisal, or diflunisal with clarithromycin.

2. Effect of ritonavir on the trough concentration of boceprevir.

3. Effect of diflunisal on the trough concentration of boceprevir.

4. Effect of diflunisal in combination with clarithromycin on the trough concentrations of boceprevir.

The secondary trial objective was to determine

1. The AUC, C_{max}, T_{max}, and terminal $t_{1/2}$ of boceprevir.

Reviewer's Comment: The primary goal of this trial was to explore strategies for enhancing the PK profile of boceprevir (specifically trough concentrations). However, results from this trial inform the DDI potential and safety of boceprevir when combined with inhibitors of CYP3A4, P-gp and AKR.

Trial Design

This was a Phase 1, open-label, randomized, four-period, fixed-sequence, and multiple-dose trial of boceprevir in healthy subjects. The trial consisted of four periods. All periods were completed sequentially, though Periods 1 and 2 were combined (no washout). A total of 16 subjects were to be enrolled and were to participate in Periods 1, 2 and 3, while only 12 of the 16 were to participate in Part 4. In Period 1, all subjects were to receive Treatment A. In Period 2, subjects were to be randomized to Treatment B or C. In Period 3 all subjects were to receive Treatment D. In Period 4, only 12 of the 16 subjects were to receive Treatments E and F. All subjects received active treatment (no placebo). The following list summarizes the treatment periods. Figure 1 illustrates the trial design.

Period 1 (Days 1 to 5)
Treatment A: Boceprevir 400 mg TID (Q8º) after a meal or snack.

Period 2 (Days 6 to 17)
Treatment B: Boceprevir 400 mg TID (Q8º, Days 6 to 15) and ritonavir 100 mg QAM (Days 6 to 17) after a meal or snack.

Treatment C: Boceprevir 400 mg BID (Q12º, Days 6 to 15) and ritonavir 100 mg BID (Q12º, Days 6 to 17) after a meal or snack.

Period 3 (Days 1 to 10) after at least a 7 day washout period
Treatment D: Boceprevir 400 mg BID (Q12º, Days 1 to 7) and diflunisal 250

mg BID (Q12º, days 2 to 9) after a meal or snack.

Period 4 (Days 1 to 12) after at least a 14 day washout period

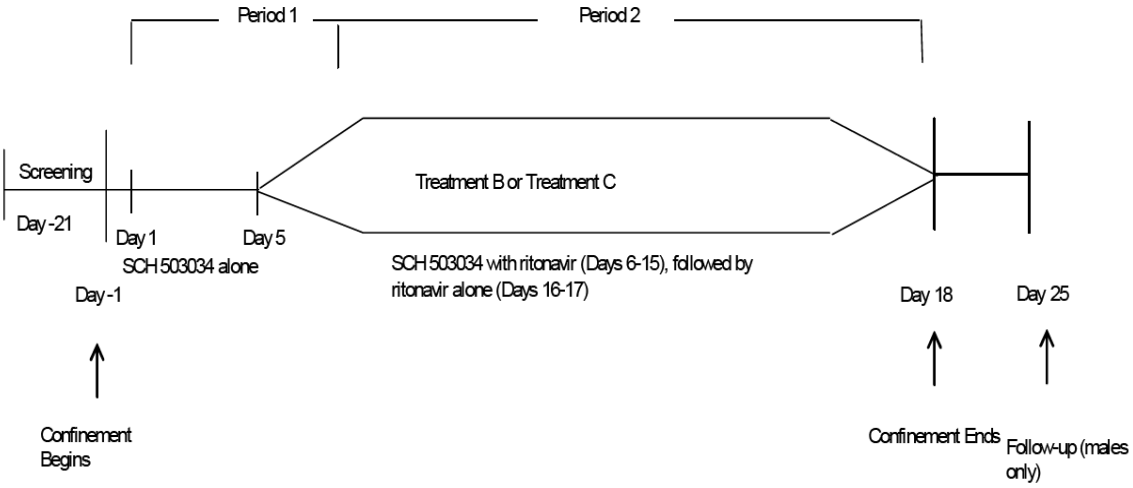
Treatment E: Boceprevir 400 mg BID (Q12º, Days 1 to 6) and diflunisal 500 mg BID (Q12º, Days 1 to 6) after a meal or snack.

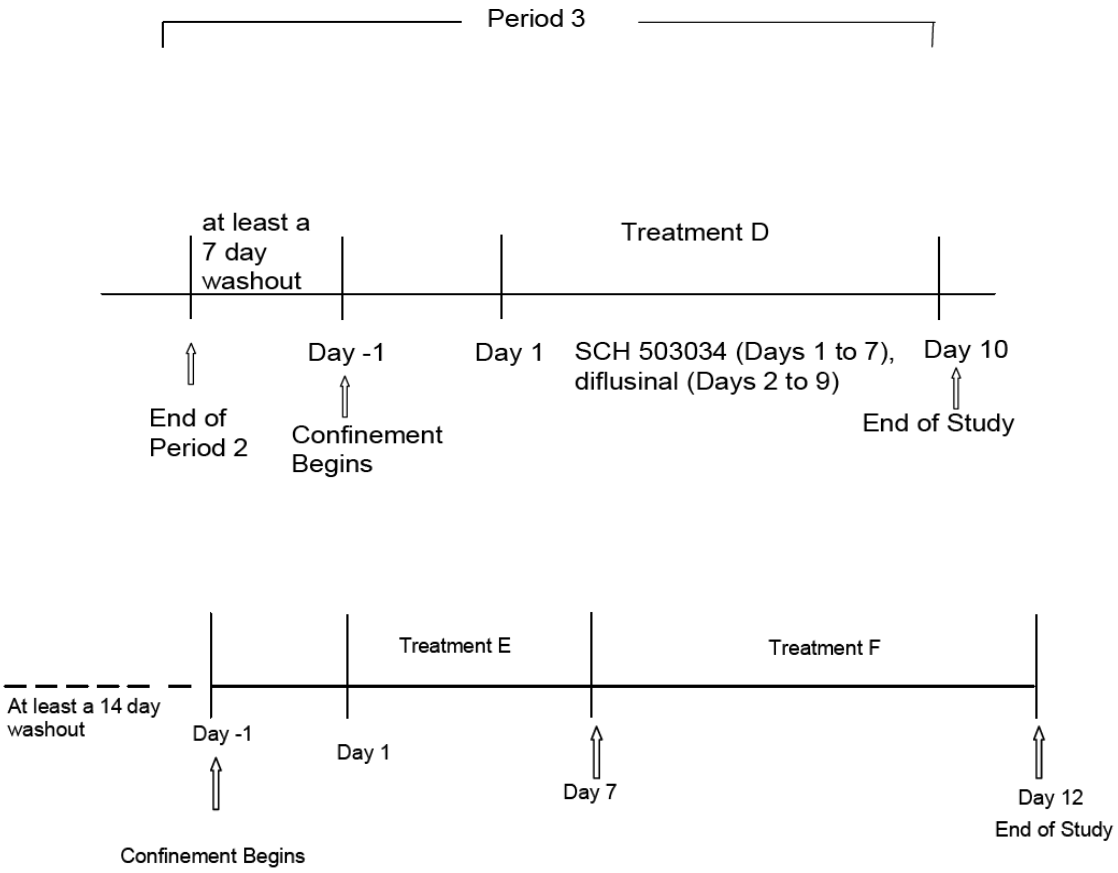
Treatment F: Days 7 to 9, boceprevir 400 mg BID (Q12º) with diflunisal 500 mg TID (Q8º) and clarithromycin 500 mg BID (Q12º) after a meal or snack.

Day 10, boceprevir 400 mg single dose (AM only) with diflunisal 500 mg TID (Q8º) and clarithromycin 500 mg BID (Q12º) after a meal or snack.

Day 11, diflunisal 500 mg TID (Q8º) and clarithromycin 500 mg BID (Q12º) after a meal or snack.

Figure 1 Trial diagram for periods 1, 2, 3, and 4





Key Inclusion Criteria

All subjects were between 18 and 65 years of age with BMIs ranging from 19 to 32 kg/m^2. Subjects had normal hepatic and renal function. Prior to study enrollment, all subjects were healthy based on physical examinations and clinical laboratory tests. Clinical laboratory tests included blood levels of AST, ALT, and GGT. Safety assessments included vital signs and ECG readings. All subjects used a barrier method of contraception in conjunction with spermicide during the trial and 30 days after the last dose of boceprevir.

Key Exclusion Criteria

Subjects did not participate in the trial if they had an active viral infection (HIV-1, HIV-2, HBV, HCV), tested positive for illicit drugs, or smoked >10 cigarettes per day. Investigators prohibited the use of any prescription or over-the-counter drugs, herbal, or mineral supplements two weeks before and during the trial, except acetaminophen. Subjects could ingest acetaminophen for the treatment of adverse events. Investigators prohibited alcohol and caffeine within 48 hours before starting and during the trial.

Reviewer's comment: The amount of acetaminophen allowed in the trial is unknown. Acetaminophen is mainly metabolized by Phase II conjugation and sulfation reactions. In vitro data suggests that boceprevir does not undergo glucuronidation; therefore, boceprevir is unlikely to interact with acetaminophen.

Investigational Products

Subjects received the commercial formulation of boceprevir provided as 200 mg capsules. Schering Plough manufactured the capsules in June 04, 2006 and capsules had an expiration date of (b) (4) The capsule batch number was K-H06953. Investigators stored the boceprevir capsules in a refrigerator between 2ºC and 8ºC until their use in this clinical trial.

Subjects received the commercially available formulations of ritonavir (Norvir®) 100-mg soft gelatin capsules (no longer marketed), diflunisal 250-mg tablet or split 500-mg tablet, and clarithromycin 250 mg tablets. Trial site investigators purchased and dispensed these drugs to subjects.

Reviewer's comment: Investigators did not provide lot numbers, expiration dates, and storage conditions for the ritonavir, diflunisal, and clarithromycin capsules or tablets used in this trial. However, it may be assumed the drugs were of good quality because investigators purchased them from US manufacturers.

Drug Administration

On day -1, all subjects entered the clinic. Their clinic stay ranged from 10 to 18 days depending on the treatment period.

Subjects received boceprevir, diflunisal, ritonavir, and clarithromycin with food. In all treatment periods, subjects had breakfast, lunch, an afternoon snack, dinner, and a late snack at approximately the same time each day. Main meals contained a minimum of 120 calories. Subjects consumed the entire meal within 20 minutes, and ingested drug treatment within 30 minutes after completing the meal.

Reviewer's comment: Food increases the exposures of boceprevir. The proposed label recommends taking boceprevir with meals. Food should not affect the bioavailability of ritonavir, clarithromycin and diflunisal to a significant extent, according to respective package inserts. The bioavailability of Norvir® (ritonavir) capsules is 13% higher when administered under fed relative to fasted conditions.

Rationale for Dose Selection

The doses of boceprevir tested in this trial were appropriate; however, they were lower than the proposed commercial dose of 800 mg TID. Investigators tested boceprevir 400 mg BID or TID based on safety and efficacy data at the time this DDI trial was completed. In previous clinical trial P04486, healthy subjects safely tolerated doses of boceprevir up to 1200 mg TID. Therefore, 400 mg BID or TID were acceptable from a safety standpoint. From an efficacy perspective, investigators selected doses of boceprevir that would deliver concentrations at least 5 times higher than the *in vitro* EC_{90}. Boceprevir 400 mg TID produced mean C_{min} and AUC levels that were 9.4 and 12.3-fold higher than the EC_{90}.

The doses of ritonavir, diflunisal, and clarithromycin tested in this trial were appropriate. Clinicians commonly use ritonavir 100 mg QD or BID doses for boosting concomitant HIV protease inhibitors. Furthermore, clarithromycin 500 mg BID and diflunisal 500 mg TID are the highest approved doses for each agent. Thus, these doses were appropriate for assessing maximal inhibition of CYP3A4, P-glycoprotein, and AKR, respectively.

Reviewer's Comment: The FDA guidance on design and conduct of DDI trials recommends Sponsors to test the commercial dose of the investigational drug. When this trial was conducted, the Sponsor had not identified 800 mg TID as the proposed commercial dose for boceprevir. Event though the Sponsor used 400 mg BID or TID in this trial, we may still gain valuable information on potential DDIs with boceprevir.

Pharmacokinetic Assessments

Investigators collected blood samples for PK of boceprevir (SCH503034), boceprevir diastereomers (SCH534128 and SCH534129), boceprevir metabolite (SCH629144), ritonavir, diflunisal, and clarithromycin. Table 1 lists the schedule of PK assessments.

Table 1 Schedule of blood sampling for PK of boceprevir, ritonavir, diflunisal, and clarithromycin.

			Trial Day																	
Period	Treatment	Drug	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1, 2	A, B, C	Boceprevir					0 – 8h										0-8h	24 h	48 h	72 h
	B, C	Ritonavir															12 h*	24 h		
3	D	Boceprevir	0-12 h			0h	0h	0h	0-12 h	24 h	48 h	72 h								
		Diflunisal		0	24	48	72													

				-12 h	h	h	h								
4	E, F	Boceprevir						0-12 h			0-12 h	24 h	48 h		
		Diflunisal						0-12 h	24 h	48 h					
		Clarithromycin									0-12 h	24 h	48 h		

* 12 hr sample only in period C

Bioanalytical Methods

Schering-Plough analyzed plasma samples for boceprevir stereoisomers (SCH534128 and SCH534129) and metabolite SCH629144 stereoisomers (SCH783004, SCH783005, SCH783006 and SCH783007) using validated LC-MS/MS method DM27341. Investigators acidified the plasma samples to identify and stabilize the diastereomer SCH534129.

(b) (4) analyzed plasma samples for ritonavir, diflunisal, and clarithromycin using validated methods SN03433, DM27347, and DM27431, respectively. Table 2 lists the upper and lower limits of quantification for all bioanalytical methods.

Table 2 Limits of quantification of LC-MS/MS bioanalytical methods used in the trial.

Analyte	LLOQ (ng/mL)	ULQ (ng/mL)	Method
SCH534128	5.24	5240	DM27341
SCH534129	4.76	4760	DM27341
SCH629144*	2.5	2500	DM27341
Diflunisal	100	100000	DM27347
Clarithromycin	20	10000	DM27431
Ritonavir	10	10000	SN03433

*SCH629144 is comprised of four stereoisomers: SCH783004, SCH783005, SCH783006, and SCH783007. All four analytes had the same LLOQ and ULQ listed in the table under SCH629144.

All calibration standards and quality controls met the bioanalytical criteria. Investigators defined these criteria as precision (%CV) within ±15%, accuracy (%RE) ≤15%, and coefficient of determination (r^2) ≥0.98. Table 3 summarizes the precision and accuracy of the bioanalytical methods.

Table 3 Precision (% CV) and accuracy (% relative error) of calibration standards and QC samples in human plasma.

		Cal Std			QC	
Method	**Analyte**	**%CV**	**%RE**	**R^2**	**%CV**	**%RE**
DM27341	SCH534128	0.7 – 5.2	≤2.9	≥0.9987	2.0 – 7.6	≤8.8
	SCH534129	0.7 – 5.9	≤3.7	≥0.9977	2.7 – 8.0	≤9.9
	SCH783004	2.8 – 6.6	≤1.5	≥0.9949	4.9 – 7.4	≤9.6
	SCH783005	3.2 – 5.5	≤1.2	≥0.9942	4.3 – 5.7	≤2.9
	SCH783006	2.7 – 4.9	≤2.7	≥0.9952	2.1 – 6.2	≤10.6
	SCH783007	2.9 – 6.0	≤3.6	≥0.9943	4.9 – 7.3	≤4.7
SN03433	Ritonavir	1.9 – 4.9	≤10.8	≥0.9970	2.0 – 4.0	≤11.3
DM27347	Diflunisal	1.9 – 7.7	≤4.2	≥0.9976	3.2 – 6.1	≤4.8
DM27431	Clarithromycin	1.8 – 4.9	≤10.8	≥0.9970	1.3 – 9.5	≤7.5

Investigators analyzed all plasma samples within the frozen stability timeframe provided by Schering-Plough. Investigators reported the storage period only for ritonavir samples (253 days). The storage period for SCH534128, SCH534129, and clarithromycin samples was only reported as "within storage period." Investigators did not mention the storage period for diflunisal samples.

Pharmacokinetic and Statistical Analyses

For all drugs, C_{min} was the primary PK parameter and C_{max} and AUC were the secondary PK parameters. Investigators conducted an ANOVA analysis on the log-transformed C_{min}, C_{max}, and AUC to extract the effects of treatment and subject. The analysis included the ratio estimates for C_{min}, C_{max}, and AUC along with 90% confidence intervals for Treatments B, C, or D vs. Treatment A. For the comparison of Treatment D vs. A, investigators conducted the analysis by treatment sequence (ABD and ACD).

For period 4, investigators compared the PK profile of boceprevir co-administered with diflunisal (Treatment E) to that of boceprevir co-administered with clarithromycin and diflunisal (Treatment F). They also compared Treatments E and F with Treatment D.

Demographic Results

Twelve female subjects enrolled in the trial. The number of subjects who received Treatments A, B, C, D, E, and F were 12, 6, 6, 12, 7, and 7, respectively. The majority of subjects (n=11) were Caucasian and Latino. The overall age range was 38 to 65 years. The mean ages for sequences ABD and ACD were 52.7 and 51.5 years. Subjects' BMI, weight, and height were similar between treatment sequences.

Reviewer's comment: Originally, the trial planned to enroll 16 male and female subjects, but enrolled only 12 female subjects. The enrollment period was curtailed because male subjects refused to enroll in the trial. Investigators speculated that male subjects might have hesitated to enroll in the trial due to boceprevir potential to cause testicular degeneration.

PK and statistical results: Effect of diflunisal and ritonavir on PK parameters of boceprevir

Investigators conducted a statistical analysis of the boceprevir ratio estimates for C_{min}, C_{max}, and AUC in the absence (Treatment A) and presence of ritonavir 100 mg QD (Treatment B) and diflunisal 250 mg BID (Treatment D). Table 4 below summarizes the statistical results for treatment sequence ABD.

Table 4 Relative systemic exposure of boceprevir, SCH534128, SCH534129, and SCH629144 following multiple oral administrations of boceprevir 400 mg TID, boceprevir 400 mg TID with ritonavir 100 mg QD, and boceprevir 400 mg BID with diflunisal 250 mg BID in healthy subjects (Sequence ABD).

			LS Means				Treatment Comparison[a]		
Analyte	Parameter	n	A	B	C	D	Comparison	Ratio	90% CI
SCH 503034	Cmin	6	65	68	-	122	B vs A	104	62-175
			-	-	-	-	D vs A	189	113-316
	Cmax	6	1372	1002	-	2079	B vs A	73	57-93
			-	-	-	-	D vs A	152	119-193
	AUC(τ)	6	3841	3121	-	5444	B vs A	81	73-91
			-	-	-	-	D vs A	142	127-158
SCH 534128	Cmin	6	47	49	-	94	B vs A	106	63-180
			-	-	-	-	D vs A	202	120-342
	Cmax	6	837	643	-	1246	B vs A	77	63-94
			-	-	-	-	D vs A	149	122-182
	AUC(τ)	6	2484	2109	-	3541	B vs A	85	78-93
			-	-	-	-	D vs A	143	130-156
SCH 534129	Cmin	6	18	18	-	28	B vs A	99	60-164
			-	-	-	-	D vs A	154	94-254
	Cmax	6	547	388	-	832	B vs A	71	52-97
			-	-	-	-	D vs A	152	112-207
	AUC(τ)	6	1356	1009	-	1885	B vs A	74	64-86
			-	-	-	-	D vs A	139	120-161
SCH 629144	Cmin	6	587	1299	-	641	B vs A	221	146-336
			-	-	-	-	D vs A	109	72-166
	Cmax	6	2421	4335	-	2868	B vs A	179	152-210
			-	-	-	-	D vs A	118	101-139
	AUC(τ)	6	10762	22599	-	13136	B vs A	210	182-242
			-	-	-	-	D vs A	122	106-141

a: Ratio and 90% CI are ANOVA model extracting the effect due to treatment and subject. The comparisons between B vs A and D vs A only includes the subjects in the sequence of ABD.

ANOVA = analysis of variance; BID = twice daily; CI = confidence interval; LS = lease-square; QAM = every morning; TID = three times daily

Treatment A: SCH 503034 400 mg TID
Treatment B: SCH 503034 400 mg TID (Days 6 to 15) and ritonavir 100 mg QAM (Days 6 to 17)
Treatment C: SCH 503034 400 mg BID (Days 6 to 15) and ritonavir 100 mg BID (Days 6 to 17)
Treatment D: SCH 503034 400 mg BID (Days 1 to 7) and diflunisal 250 mg BID (Days 2 to 9

During drug co-administration, diflunisal 250 mg BID increased the C_{min} of boceprevir by 89% relative to boceprevir alone. Likewise, diflunisal increased the C_{max} and AUC of boceprevir by 52% and 42%, respectively, relative to boceprevir alone. Of note, the doses of boceprevir were different between the reference arm (Treatment A, 400 mg TID) and the test arm (Treatment D, 400 mg BID). Even considering the difference in dosing interval, diflunisal likely still increases the exposures of boceprevir, though the magnitude of the increase observed in this study should be considered an approximation.

Ritonavir 100 mg QD did not affect the C_{min} of boceprevir in Treatment B relative to Treatment A. Conversely, ritonavir decreased the C_{max} and AUC of boceprevir by 27% and 19%, respectively, relative to boceprevir alone.

The following table summarizes the PK parameters of boceprevir, SCH514328, SCH514329, and SCH629144 collected during Treatments A, B, and C. The PK results during diflunisal coadministration are shown in Table 7 below.

Table 5 PK parameters of boceprevir, SCH534128, SCH534129, and SCH629144 following multiple oral administrations of boceprevir 400 mg BID or TID with co-administration of ritonavir 100 mg QD or BID in healthy subjects

Analyte	Period	Treat-ment	Day	n	AUC(τ) (ng·hr/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax[a] (hr)	t½ (hr)	CL/F (L/hr)	Vdss/F (L)	RAUC
SCH 503034	1	A	5	12	3800 (17)	1390 (23)	70.9 (47)	2.50 (1.00-5.00)	NA	NA	NA	NA
	2	B	15	6	3180 (22)	1070 (44)	87.1 (77)	1.75 (1.00-5.00)	4.13 (52)	131 (22)	792 (58)	NA
	2	C	15	6	3010 (17)	920 (34)	34.8 (31)	2.50 (1.50-3.00)	3.33 (76)[b]	142 (21)[b]	646 (71)[b]	NA
SCH 534128	1	A	5	12	2440 (17)	844 (21)	50.5 (49)	2.50 (1.50-5.00)	NA	NA	NA	NA
	2	B	15	6	2140 (20)	671 (35)	64.8 (78)	2.25 (1.50-5.00)	4.44 (54)	NA	NA	NA
	2	C	15	6	2020 (15)	591 (27)	25.3 (31)	2.50 (1.50-4.00)	4.30 (84)[b]	NA	NA	NA
SCH 534129	1	A	5	12	1360 (19)	559 (30)	20.4 (45)	2.50 (1.00-5.00)	NA	NA	NA	NA
	2	B	15	6	1040 (28)	427 (56)	22.3 (71)	1.75 (1.00-3.00)	2.86 (85)	NA	NA	NA
	2	C	15	6	999 (26)	347 (46)	9.54 (40)	2.00 (1.00-3.00)	1.54 (39)[b]	NA	NA	NA
SCH 629144	1	A	5	12	11300 (24)	2650 (26)	591 (42)	4.00 (2.00-5.00)	NA	NA	NA	3.03 (24)
	2	B	15	6	23200 (23)	4420 (21)	1480 (52)	4.00 (3.00-5.00)	13.8 (33)	NA	NA	7.41 (24)
	2	C	15	6	22300 (17)	3730 (21)	943 (29)	4.00 (3.00-6.00)	11.6 (29)[b]	NA	NA	7.65 (29)

Data presented as mean (CV).

a: Median (range)

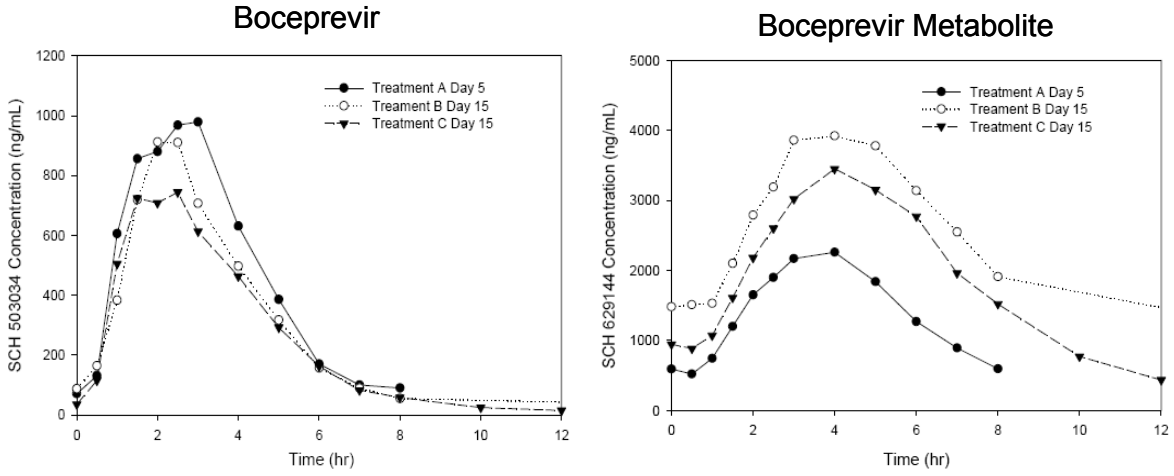
b: n=5

RAUC: Ratio=AUC(τ) SCH 629144/AUC(τ) SCH 503034; CV = coefficient of variance; NA = not applicable

The clearance and half-life values of boceprevir were similar for Treatments B and C. Although a direct comparison of the effect of different doses of ritonavir on the PK of boceprevir cannot be made, given the different boceprevir dosing regimens in Treatments B and C, in general, boceprevir exposure was similar between the two treatment groups. In addition, the ratio of metabolite to boceprevir AUC was similar for ritonavir 100 mg QD (7.4) and BID (7.6). The metabolite to boceprevir AUC ratio was ~2.5 times higher in Treatments B and C compared to Treatment A.

The figure below illustrates the concentration-time profile of boceprevir and SCH629144 in the presence and absence of ritonavir 100 mg QD and BID.

Figure 2 Mean plasma concentration-time profiles of boceprevir and its metabolite (SCH629144) following multiple oral doses of boceprevir alone or co-administered with ritonavir in healthy subjects.



Treatment A: SCH 503034 400 mg TID
Treatment B: SCH 503034 400 mg TID (Days 6 to 15) and ritonavir 100 mg QAM (Days 6 to 17)
Treatment C: SCH 503034 400 mg BID (Days 6 to 15) and ritonavir 100 mg BID (Days 6 to 17)

Investigators also conducted a statistical analysis of the boceprevir ratio estimates for C_{min}, C_{max}, and AUC in the absence (Treatment A) and presence of ritonavir 100 mg BID (Treatment C) and diflunisal 250 mg BID (Treatment D). The following table summarizes the statistical results for treatment sequence ACD.

Table 6 Relative systemic exposure of boceprevir, SCH534128, SCH534129, and SCH629144 following multiple oral administrations of boceprevir 400 mg TID, boceprevir 400 mg BID co-administered with ritonavir 100 mg BID, and boceprevir 400 mg BID co-administered with diflunisal 250 mg BID in healthy subjects (Sequence ACD).

Analyte	Parameter	n	LS Means				Treatment Comparison[a]		
			A	B	C	D	Comparison	Ratio	90% CI
SCH 503034	Cmin	6	64	-	33	50	C vs A	52	38-72
				-	-	-	D vs C	148	107-205
				-	-	-	D vs A	77	56-106
	Cmax	6	1329	-	876	1361	C vs A	66	56-78
				-	-	-	D vs C	155	131-184
				-	-	-	D vs A	102	86-122
	AUC(τ)	6	3646	-	2972	4146	C vs A	82	75-88
				-	-	-	D vs C	140	129-151
				-	-	-	D vs A	114	105-123
SCH 534128	Cmin	6	45	-	24	36	C vs A	54	38-76
				-	-	-	D vs C	150	106-212
				-	-	-	D vs A	81	57-114
	Cmax	6	813	-	573	788	C vs A	70	59-84
				-	-	-	D vs C	138	115-165
				-	-	-	D vs A	97	81-116
	AUC(τ)	6	2323	-	1995	2588	C vs A	86	79-93
				-	-	-	D vs C	130	119-141
				-	-	-	D vs A	111	103-121
SCH 534129	Cmin	6	19	-	9	13	C vs A	47	36-62
				-	-	-	D vs C	143	108-189
				-	-	-	D vs A	67	51-88
	Cmax	6	517	-	315	578	C vs A	61	51-73
				-	-	-	D vs C	183	154-219
				-	-	-	D vs A	112	94-133
	AUC(τ)	6	1314	-	964	1546	C vs A	73	67-80
				-	-	-	D vs C	160	147-175
				-	-	-	D vs A	118	108-129
SCH 629144	Cmin	6	504	-	910	331	C vs A	181	128-254
				-	-	-	D vs C	36	26-51
				-	-	-	D vs A	66	47-93
	Cmax	6	2717	-	3655	2013	C vs A	135	114-159
				-	-	-	D vs C	55	46-65
				-	-	-	D vs A	74	63-88
	AUC(τ)	6	11309	-	21985	9468	C vs A	194	165-229
				-	-	-	D vs C	43	36-51
				-	-	-	D vs A	84	71-99

a: Ratio and 90% CI are ANOVA model extracting the effect due to treatment and subject. The comparisons between C vs A, D vs A and D vs C only includes the subjects in the sequence of ACD.

ANOVA = analysis of variance; BID = twice daily; CI = confidence interval; LS = lease-square; TID = three times daily

Treatment A: SCH 503034 400 mg TID
Treatment B: SCH 503034 400 mg TID (Days 6 to 15) and ritonavir 100 mg QAM (Days 6 to 17)
Treatment C: SCH 503034 400 mg BID (Days 6 to 15) and ritonavir 100 mg BID (Days 6 to 17)
Treatment D: SCH 503034 400 mg BID (Days 1 to 7) and diflunisal 250 mg BID (Days 2 to 9

In treatment sequence ACD, ritonavir 100 mg BID decreased the C_{min} of boceprevir by 48% relative to boceprevir alone. Ritonavir 100 mg BID also decreased the C_{max} and AUC of boceprevir by 34% and 18% respectively. Of note, the boceprevir regimens were different in Treatments A (400 mg TID) and C (400 mg BID). Thus, the magnitude of the effect of ritonavir 100 mg BID should be interpreted with caution.

Diflunisal 250 mg BID decreased the C_{min} of boceprevir by 23% relative to boceprevir alone. Diflunisal did not affect the $C_{max,}$ but slightly increased the

AUC of boceprevir by 14% relative to boceprevir alone. Results should be interpreted with caution because the dosing intervals of boceprevir were TID in Treatment A and BID in Treatment D.

The following table summarizes the PK of boceprevir and SCH629144 in the presence and absence of diflunisal 250 mg BID collected during Treatment D. Given that no boceprevir accumulation is anticipated with repeat dosing of 400 mg BID, exposure on Day 1 can be compared with that of Day 7 to determine the effect of diflunisal on boceprevir within the same dosing regimen. Boceprevir AUC and C_{max} are increased ~50% and ~45%, respectively, from Day 1 to Day 7. However, this increase must be interpreted cautiously, given that Day 1 and steady-state exposure have not been directly compared for this boceprevir dosing regimen.

Table 7 PK parameters of boceprevir, SCH534128, SCH534129, and SCH629144 following boceprevir 400 mg BID alone (Day 1) and with co-administration of diflunisal 250 mg BID (Day 7) in healthy subjects

Analyte	Period	Treat-ment	Day	n	AUC(τ) (ng·hr/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax[a] (hr)	t½ (hr)	CL/F (L/hr)	Vdss/F (L)	RAUC
SCH 503034	3	D	1	12	3200 (23)	1230 (36)	0.00 (NA)	1.75 (1.00-3.00)	NA	NA	NA	NA
			7	12	4870 (22)	1780 (32)	104 (90)	2.00 (1.50-3.00)	3.47(87)	86.7 (27)	398 (74)	NA
SCH 534128	3	D	1	12	1920 (23)	675 (35)	0.00 (NA)	1.75 (1.00-3.00)	NA	NA	NA	NA
			7	12	3110 (23)	1050 (32)	79.8 (92)	2.00 (1.50-4.00)	3.87 (90)	NA	NA	NA
SCH 534129	3	D	1	12	1290 (24)	556 (39)	0.00 (NA)	1.75 (1.00-3.00)	NA	NA	NA	NA
			7	12	1750 (22)	739 (33)	24.4 (83)	2.00 (1.50-2.50)	3.52 (110)[b]	NA	NA	NA
SCH 629144	3	D	1	12	5850 (35)	1300 (39)	0.00 (NA)	3.00 (2.50-8.00)	NA	NA	NA	1.84 (27)
			7	12	11600 (27)	2530 (32)	532 (53)	3.00 (2.50-5.00)	8.44 (48)[c]	NA	NA	2.38 (16)

Data presented as mean (CV).

a: Median (range)

b: n=8

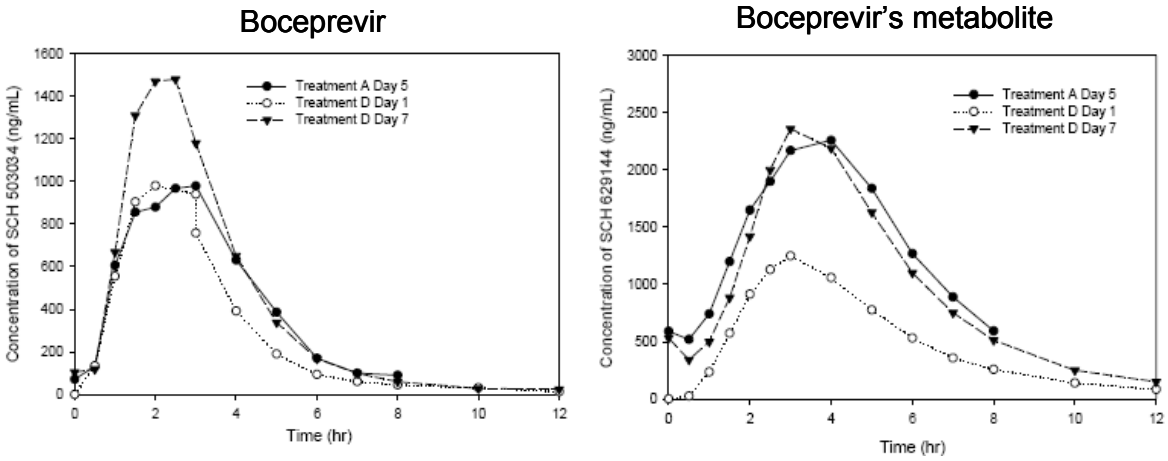
c: n=9

RAUC: Ratio=AUC(τ) SCH 629144/AUC(τ) SCH 503034; CV = coefficient of variance; NA = not applicable

Treatment D: SCH 503034 400 mg BID (Days 1 to 7) and diflunisal 250 mg BID (Days 2 to 9

The ratio of metabolite to boceprevir AUC slightly increased in the presence of diflunisal on day 7 (2.38) relative to day 1 (1.84). These results suggest that boceprevir metabolism to SCH629144 occurred despite diflunisal inhibition of AKR. However, the increase in ratio may be due to greater accumulation of the metabolite relative to the parent with repeat dosing. The figure below illustrates the concentration-time profile of boceprevir and SCH629144 in the presence and absence of diflunisal 250 mg BID.

Figure 3 Mean plasma concentration-time profile of boceprevir and SCH629144 following multiple oral administrations of boceprevir alone or in combination with diflunisal in healthy subjects.



Treatment A: SCH 503034 400 mg TID

Treatment D: SCH 503034 400 mg BID (Days 1 to 7) and diflunisal 250 mg BID (Days 2 to 9

PK and statistical results: Effect of diflunisal and clarithromycin on the PK parameters of boceprevir

The investigators conducted a statistical analysis of the boceprevir ratio estimates for C_{min}, C_{max}, and AUC in the absence (Treatment A) and presence of diflunisal 500 mg BID (Treatment E) or diflunisal 500 mg TID + clarithromycin 500 mg BID (Treatment F). The following table summarizes the statistical results for Treatments E and F.

Reviewer's comment: The table below was truncated and it is missing values for SCH534129 and SCH629144.

Table 8 Relative systemic exposure of boceprevir and SCH534128 following multiple oral administration of boceprevir 400 mg BID co-administered with diflunisal 500 mg BID and boceprevir 400 mg BID co-administered with diflunisal 500 mg TID and clarithromycin 500 mg BID in healthy subjects.

Analyte	Parameter	n	LS Means			Treatment Comparison [a]		
			A	E	F	Comparison	Ratio	90% CI
SCH 503034	Cmin	7	73	81	68	E vs A	110	79-154
			-	-	-	F vs A	94	67-131
			-	-	-	F vs E	85	61-119
	Cmax	7	1472	1810	2462	E vs A	123	94-161
			-	-	-	F vs A	167	128-219
			-	-	-	F vs E	136	104-178
	AUC(τ)	7	4029	5572	6733	E vs A	138	121-158
			-	-	-	F vs A	167	146-191
			-	-	-	F vs E	121	106-138
SCH 534128	Cmin	7	52	61	50	E vs A	116	85-160
			-	-	-	F vs A	96	70-132
			-	-	-	F vs E	82	60-113
	Cmax	7	898	1048	1434	E vs A	117	92-148
			-	-	-	F vs A	160	126-203
			-	-	-	F vs E	137	108-174
	AUC(τ)	7	2597	3492	4215	E vs A	134	118-153
			-	-	-	F vs A	162	143-185
			-	-	-	F vs E	121	106-137

a: Ratio and 90% CI are ANOVA model extracting the effect due to treatment and subject.
Subjects 101, 106, 109, 110, 111 were excluded in the analysis due to early withdraw.
ANOVA = analysis of variance; BID = twice daily; CI = confidence interval; LS = least-square; TID = three times daily

Treatment A: SCH 503034 400 mg TID

Treatment E (Days 1 to 6): SCH 503034 400 mg BID and diflunisal 500 mg BID

Treatment F (Day 10): SCH 503034 mg single dose (morning only), diflunisal 500 mg TID, and clarithromycin 500 mg BID, following a meal or snack

In Treatment E, diflunisal 500 mg BID did not change the C_{min} of boceprevir relative to boceprevir 400 mg TID alone. On the other hand, the C_{max} and AUC of boceprevir were higher by 23% and 38%, respectively, during Treatment E relative to Treatment A. Results should be interpreted with caution because the dosing intervals of boceprevir were BID in Treatment E vs. TID in Treatment A. Even considering the difference in boceprevir dosing interval, Treatment E likely still increased the exposures (C_{max} and AUC) of boceprevir relative to Treatment A.

In Treatment F, the combination of diflunisal and clarithromycin did not change the C_{min} of boceprevir relative to boceprevir 400 mg TID alone. In contrast, the clarithromycin and diflunisal increased both C_{max} and AUC of boceprevir by 67% relative to Treatment A. Of note, the dose of boceprevir was higher in Treatment A (400 mg TID) vs. Treatment F (400 mg BID), so the magnitude of the effect should be considered an estimate.

The following table summarizes the PK of boceprevir in Treatments E and F.

Table 9 PK parameters of boceprevir, SCH534128, SCH534129, and SCH629114 following multiple oral administrations of boceprevir 400 mg BID co-administered with diflunisal 500 mg BID and boceprevir 400 mg BID co-administered with diflunisal 500 mg TID and clarithromycin 500 mg BID in healthy subjects.

Analyte	Period	Treat-ment	Day	n	AUC(τ) (ng·hr/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax[a] (hr)	t½ (hr)	CL/F (L/hr)	Vdss/F (L)	RAUC
SCH 503034	4	E	6	7	5710 (24)	1940 (36)	85.1 (36)	2.50 (2.00-4.00)	NA	NA	NA	NA
		F	10	7	6840 (19)	2510 (21)	77.9 (66)	2.50 (2.00-3.00)	4.16 (63)	60.4 (19)	346 (56)	NA
SCH 534128	4	E	6	7	3570 (23)	1100 (32)	64.2 (36)	3.00 (2.00-5.00)	NA	NA	NA	NA
		F	10	7	4270 (18)	1460 (20)	56.9 (66)	3.00 (2.00-3.00)	4.68 (63)	NA	NA	NA
SCH 534129	4	E	6	7	2150 (26)	864 (38)	20.9 (37)	2.50 (1.50-4.00)	NA	NA	NA	NA
		F	10	7	2570 (21)	1090 (20)	21.1 (66)	2.50 (2.00-3.00)	3.31 (40)	NA	NA	NA
SCH 629144	4	E	6	7	10700 (39)	2190 (48)	497 (23)	4.00 (3.00-6.00)	NA	NA	NA	1.86 (23)
		F	10	7	18600 (18)	3750 (17)	726 (38)	4.00 (3.00-4.00)	7.18 (29)[b]	NA	NA	2.76 (16)

Data presented as mean (CV).

a: Median (range)

b n=6

RAUC: Ratio=AUC(τ) SCH 629144/AUC(τ) SCH 503034; CV = coefficient of variance; NA = not applicable

Treatment E (Days 1 to 6): SCH 503034 400 mg BID and diflunisal 500 mg BID

Treatment F (Day 10): SCH 503034 mg single dose (morning only), diflunisal 500 mg TID, and clarithromycin 500 mg BID, following a meal or snack

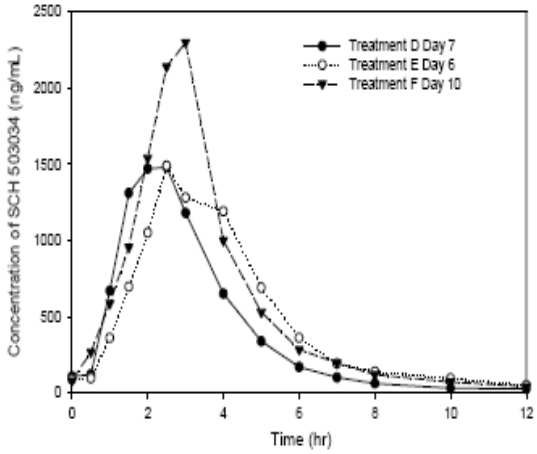
The ratio of metabolite to boceprevir AUC in Treatment F was slightly higher (2.76) compared to Treatment E (1.86). The results suggest that boceprevir metabolism via AKR was more pronounced in the presence of diflunisal and clarithromycin compared to diflunisal alone. This increase in the SCH629144 metabolite ratio from Treatment E to F occurred in spite of a diflunisal dose increase from 500 mg BID to 500 mg TID.

The following figure displays the concentration-time profiles of boceprevir and SCH629144 in Treatments D, E, and F.

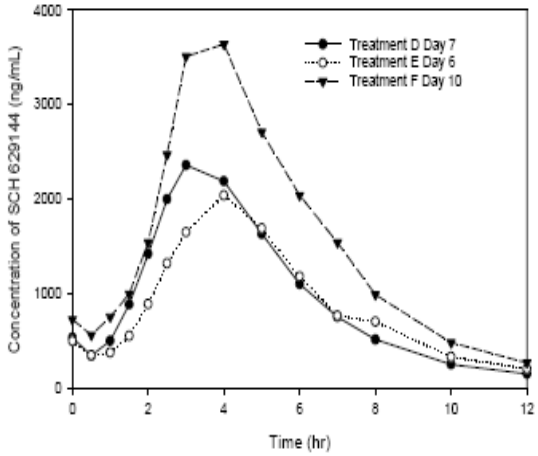
Figure 4 Mean plasma concentration-time profiles of boceprevir and SCH629144 following multiple oral administrations of boceprevir in combination with diflunisal or in

combination with diflunisal and clarithromycin in healthy subjects.

Boceprevir



Boceprevir's metabolite



Treatment D: SCH 503034 400 mg BID (Days 1 to 7) and diflunisal 250 mg BID (Days 2 to 9)

Treatment E (Days 1 to 6): SCH 503034 400 mg BID and diflunisal 500 mg BID

Treatment F (Day 10): SCH 503034 mg single dose (morning only), diflunisal 500 mg TID, and clarithromycin 500 mg BID, following a meal or snack

PK results: Effect of boceprevir on the PK of diflunisal and clarithromycin

The direct effect of boceprevir on the PK of diflunisal and clarithromycin was not evaluated. The reference PK values for diflunisal and clarithromycin were not available. Thus, exposures of diflunisal and clarithromycin observed in this trial were compared to historical values reported in their respective patient package inserts. The following table summarizes the PK of diflunisal and clarithromycin in the presence of boceprevir.

Table 10 PK parameters of clarithromycin and diflunisal following multiple oral administrations of boceprevir 400 mg BID with co-administration of diflunisal and/or clarithromycin in Period 3 and Period 4 to healthy adult subjects.

Analyte	Period	Treatment	Dose	Day	n	AUC(τ) (ng·hr/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax[a] (hr)
Clarithromycin	4	F	500 mg BID	10	7	32100 (9)	3480 (20)	2390 (12)	2.00 (1.00-4.00)
Diflunisal	3	D	250 mg BID	2	12	266000 (12)	39300 (18)	0.00 (NA)	3.00 (1.50-7.00)
Diflunisal	3	D	250 mg BID	7	12	755000 (17)	83100 (20)	50900 (20)	2.50 (1.00-7.00)
Diflunisal	4	E	500 mg BID	6	7	1610000 (11)[b]	155000 (12)	118000 (14)	4.00 (2.00-8.00)
Diflunisal	4	F	500 mg TID	10	7	1590000 (10)[c]	220000 (6)	176000 (12)	4.00 (2.00-8.00)

Data presented as mean (CV)

a: Median (range)

b: n=6

c: Missing value at 0 hour for Subject 102, and Subject 105 on Day 10 in Period 4. Next value (concentration at 1 hour) was carried in 0 hour to determine AUC(τ) for Subjects 102 and 105 on Day 10 in Period 4.

CV = coefficient of variance; NA = not applicable

Treatment D: SCH 503034 400 mg BID (Days 1 to 7) and diflunisal 250 mg BID (Days 2 to 9)
Treatment E (Days 1 to 6): SCH 503034 400 mg BID and diflunisal 500 mg BID
Treatment F (Day 10): SCH 503034 mg single dose (morning only), diflunisal 500 mg TID, and clarithromycin 500 mg BID, following a meal or snack

Boceprevir did not affect the PK of diflunisal. The mean C_{max} values of diflunisal observed in this trial are different from those listed in the package insert. However, the PK variability around the mean values overlap, suggesting that the mean values are similar. For instance, the package insert for Dolobid® reports that diflunisal 250 mg BID and 500 mg BID produced mean C_{max} values of 56 ± 14 µg/mL and 190 ± 33 µg/mL, respectively, following 4 - 8 days of treatment in healthy subjects. In comparison, the same doses of diflunisal produced mean C_{max} values of 83.1 ± 16 µg/mL and 155 ± 18.6 µg/mL, respectively, in this trial.

Boceprevir did not affect the PK of clarithromycin. The mean C_{max} values of clarithromycin observed in this trial were similar to those reported in the package insert. The package insert for Biaxin® reports that clarithromycin 500 mg BID produced a mean C_{max} of 3 to 4 µg/mL following 3 days of treatment in healthy subjects. In comparison, the same dose of clarithromycin produced a mean C_{max} of 3.5 µg/mL following 10 days of treatment in healthy subjects.

Safety results

Eight subjects experienced at least one treatment-emergent adverse event (TEAE) over the course of the trial. The most common TEAEs were gastrointestinal disorders (7/12, 58.3%). The second most common TEAEs were headaches (4/12, 33.3%). All other TEAEs occurred in one or less subjects except abdominal discomfort (n=3) and constipation (n=2). The majority of TEAEs occurred during Treatment F when subjects received boceprevir, diflunisal, and clarithromycin. No subjects withdrew from the trial due to an adverse event. Investigators did not report major fluctuations in hematology or laboratory parameters during the trial. Overall, subjects safely tolerated boceprevir alone and in combination with diflunisal, ritonavir, and clarithromycin.

Discussion and Conclusions

Boceprevir is primarily metabolized by AKR and undergoes minor metabolism by CYP3A4. Boceprevir is also a substrate and moderate inhibitor of p-glycoprotein and a strong inhibitor of CYP3A4. Given the poor *in vivo* relative bioavailability of boceprevir, investigators hoped to increase the systemic exposures of boceprevir by inhibiting its major metabolic pathways. In this trial, investigators assessed the effects of ritonavir, diflunisal, and clarithromycin on the PK of boceprevir, SCH534128, SCH534129, and SCH629144. Diflunisal is an inhibitor of AKR, ritonavir is a strong inhibitor of CYP3A4, and clarithromycin is a strong inhibitor of

CYP3A4 and P-glycoprotein. A discussion of the results and final conclusions from this trial are listed below:

Effect of ritonavir on the PK of boceprevir

- Ritonavir 100 mg QD did not affect the C_{min} of boceprevir relative to boceprevir alone, while boceprevir C_{max} and AUC_{tau} decreased 27% and 19%, respectively. Ritonavir 100 mg BID decreased the C_{max}, AUC_{tau} and C_{min} of boceprevir by 34%, 18%, and 48%, respectively, relative to boceprevir alone. Of note, the dosing interval of boceprevir was different in the 100 mg BID ritonavir arm (400 mg BID) versus the control arm (400 mg TID). Thus, the decrease in boceprevir C_{min} with ritonavir 100 mg BID may have been due at least in part to differences in dosing interval (8 hours vs. 12 hours) and may not be due entirely a drug-drug interaction. However, AUC_{tau} would have been expected to increase with a longer dosing interval.

- The ratio of SCH629144 to boceprevir AUC following ritonavir 100 mg BID was similar to that of ritonavir 100 mg QD, suggesting that ritonavir affected the PK of boceprevir similarly regardless of ritonavir dose.

- Overall, results indicate that ritonavir 100 mg QD did not alter the C_{min} of boceprevir, though ritonavir 100 mg BID may result in a lower boceprevir C_{min}. The C_{max} and AUC of boceprevir decreased in the presence of ritonavir relative to boceprevir alone. These results are counterintuitive because ritonavir should increase the exposures of boceprevir by inhibiting CYP3A4. However, the results make sense because boceprevir is only a minor substrate of CYP3A4 and most metabolism occurs via AKR. It appears that ritonavir increases the conversion of boceprevir to SCH629144 via induction of AKR. Although there is no information in the literature to suggest that ritonavir has been characterized as an inducer of AKR, it is a known inducer of other metabolic pathways, including CYP1A2 and UGT1A1. The CYP1A and UGT1A families are known to be under transcriptional control of the aryl hydrocarbon receptor (AhR). It has further been shown using rat hepatoma cell lines that AhR plays a role in the induction of enzymes in the AKR family.[1] This supports the hypothesis that ritonavir induces boceprevir metabolism via AKR. Boceprevir exposure may not have decreased to the same extent that SCH629144 increased due to ritonavir's inhibition of boceprevir's alternate CYP3A4 metabolic pathway.

Effect of Diflunisal on the PK of boceprevir

- Based on conflicting statistical results, the effect of diflunisal on the exposure of boceprevir is inconclusive. For instance, in sequence ABD diflunisal increased the C_{max}, AUC_{tau} and C_{min} of boceprevir by 52%, 42% and 89%,

respectively, relative to boceprevir alone. On the other hand, in sequence ACD diflunisal had largely no effect on boceprevir exposure relative to boceprevir alone. Further complicating treatment comparisons, the dose interval of boceprevir was different in Treatment A (boceprevir 400 mg TID) vs. Treatment D (boceprevir 400 mg BID).

- If it assumed that boceprevir does not accumulate with multiple doses of 400 mg BID, exposure on Day 1 of Treatment D (boceprevir alone) can be compared with that of Day 7 to determine the effect of diflunisal on boceprevir within the same dosing regimen. Boceprevir AUC and C_{max} are increased ~50% and ~45%, respectively, from Day 1 to Day 7. However, this increase must be interpreted cautiously, given that Day 1 and steady-state exposure have not been directly compared for this boceprevir dosing regimen.

- In Treatment E, diflunisal 500 mg BID slightly increased the C_{min} of boceprevir by 10% (CI: 79 to 154) relative to boceprevir alone (Treatment A). However, given the wide CI, the 10% increase in boceprevir C_{min} may be due to PK variability rather than a drug interaction. There was also a 38% increase in AUC_{tau} in Treatment E vs. A. Of note, the dosing interval of boceprevir is also different, 400 mg TID (A) compared to 400 mg BID (E). Thus, the magnitude of the increase in AUC_{tau} may be a reflection of the longer interval (12 hours vs. 8 hours). Diflunisal might have increased the C_{min} of boceprevir further in Treatment E, but the increase was indiscernible from Treatment A due to the difference in boceprevir dosing intervals.

- Overall, diflunisal alone did not increase the C_{min} of boceprevir during co-administration compared to boceprevir alone. The C_{max} and AUC_{tau} of boceprevir appeared to increase in the presence of diflunisal during Treatments D and E, but the magnitude of the increase should be used with caution, due to the difference in boceprevir dosing interval.

Effect of Diflunisal and Clarithromycin on the PK of boceprevir

- The combination of clarithromycin 500 mg BID and diflunisal 500 mg TID (Treatment F) did not alter the C_{min} of boceprevir relative to boceprevir alone (Treatment A), though C_{max} and AUC_{tau} increased 67%. The dosing interval of boceprevir was different in Treatment F (400 mg BID) from Treatment A (400 mg TID). Thus, an increased in C_{min} may have occurred in Treatment E but it was indiscernible due to the difference in boceprevir dosing interval.

- The ratio of metabolite to boceprevir AUC in Treatment F was slightly higher (2.76) compared to Treatment E (1.86). These results suggest that boceprevir metabolism via AKR was more pronounced in the presence of diflunisal and clarithromycin compared to diflunisal alone. This increase in the SCH629144 metabolite ratio from Treatment E to F occurred in spite of a

diflunisal dose increase from 500 mg BID to 500 mg TID. This finding is not unexpected, given clarithromycin's potent inhibition of the alternate CYP3A4 pathway. The metabolite ratio in Treatment E (2.8) during coadministration with diflunisal 500 mg BID was similar to that of Treatment D (2.4), when diflunisal 250 mg BID was coadministered.

- Overall, the combination of clarithromycin and diflunisal increased the exposure of boceprevir. These results are expected because together diflunisal and clarithromycin inhibit AKR, CYP3A4 and p-glycoprotein.

Effect of boceprevir on the PK of Diflunisal and Clarithromycin

- The effects of boceprevir on the PK of diflunisal and clarithromycin could not be directly evaluated in this trial. Investigators did not collect reference PK values of diflunisal and clarithromycin in the absence of boceprevir. Nevertheless, results from this trial were compared to historical values from respective package inserts.

- The mean exposures of diflunisal and clarithromycin remained unchanged in the presence of boceprevir relative to historical exposures reported in the package insert.

Overall Conclusions

- Ritonavir decreases boceprevir exposure, possibly via induction AKR.

- Diflunisal alone likely increases boceprevir exposure, but the magnitude of the interaction reported in this trial should not be considered conclusive, given the limitations of the trial design.

- Clarithromycin and diflunisal increased the C_{max} and AUC_{tau}, but not the C_{min} of boceprevir in this trial. However, given the limitations of the trial design, the results should be interpreted cautiously.

- Co-administration of boceprevir with strong inhibitors of AKR may be appropriate. However, further information is needed to support this conclusion, given the limitations of this trial.

References

[1] Vondracek J, Krcmar, P, Prochazkova J, et al. The role of aryl hydrocarbon receptor in the regulation of enzymes involved in the metabolic activation of polycyclic aromatic hydrocarbons in a model of rat liver progenitor cells. Chem Biol Interact. 2009;180:226.

Trial P05880

A Multi-Part Drug-Drug Interaction Trial to Characterize the Pharmacokinetic Properties of Boceprevir when Co-administered with Midazolam, Efavirenz, Tenofovir, and an Oral Contraceptive containing Drospirenone and Ethinyl Estradiol.

Dates

February 04, 2009 to December 01, 2009

Trial Site

PPD, Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin, TX 78744, USA

Summary of Reviewer Findings

- Boceprevir increased the mean C_{max} and $AUC_{0\text{-}24h}$ of midazolam by 177% and 430%, respectively, relative to midazolam alone. Results confirm that boceprevir is a strong inhibitor of CYP3A4. As such, clinicians should not co-administer boceprevir with sensitive substrates of CYP3A4.

- Boceprevir increased the mean C_{max} of tenofovir by ~32%, but did not affect the $AUC_{0\text{-}24h}$ and renal clearance of tenofovir. The mechanism by which boceprevir increased the C_{max} of tenofovir is unknown. Clinicians should be vigilant of tenofovir-induced adverse events during co-administration with boceprevir.

- Boceprevir increased the mean $AUC_{0\text{-}24h}$ of drospirenone by 99% relative to administration of Yaz® alone. Results confirm that boceprevir is an inhibitor of CYP3A4. In contrast, boceprevir decreased the $AUC_{0\text{-}24h}$ of ethinyl estradiol by 24% relative to administration of Yaz® alone. The mechanism by which boceprevir decreased the exposures of ethinyl estradiol is unknown. Results for drospirenone are concerning because higher levels of drospirenone may increase the risk of cardiovascular adverse events. Therefore, clinicians

should be cautious when recommending the use of hormonal contraceptives during boceprevir treatment. Clinicians should advise patients to use two barrier methods of contraception.

- Efavirenz decreased the mean C_{max}, AUC_{0-8h}, and C_{min} of boceprevir by 8%, 19%, and 44%, respectively, relative to boceprevir alone. Results confirm that boceprevir is a substrate of CYP3A4. In contrast, boceprevir increased the mean C_{max} and AUC_{0-24h} of efavirenz by 11% and 20%, respectively, relative to efavirenz alone. The mechanism by which boceprevir increased efavirenz exposures is unknown. Clinicians should avoid co-administration of boceprevir with strong inducers of CYP3A4.

Trial Objectives

The primary objectives of this trial were to determine the

1. Effects of boceprevir on the pharmacokinetic (PK) properties of midazolam.

2. Effects of efavirenz on the PK of boceprevir.

3. Drug-drug interaction between boceprevir and tenofovir (disoproxil fumarate).

4. Effect of boceprevir on the PK of Yaz®, an oral contraceptive containing drospirenone and ethinyl estradiol.

The secondary trial objectives were to evaluate the safety and tolerability of boceprevir when co-administered with midazolam, efavirenz, tenofovir, and an oral contraceptive containing drospirenone and ethinyl estradiol.

Trial Design

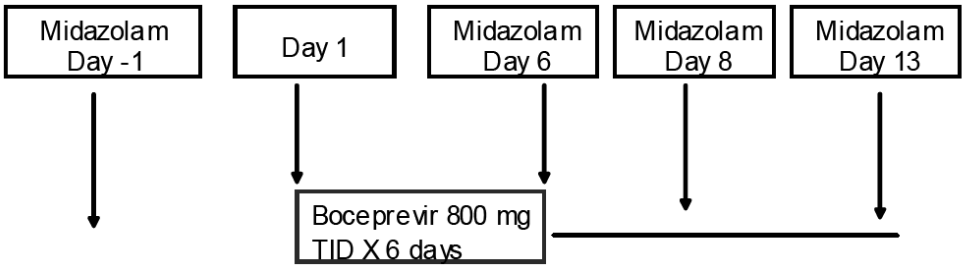
This phase 1 trial was a multi-part, open-label design. The trial aimed to evaluate the drug-drug interaction of boceprevir during co-administration with midazolam (Part 1), efavirenz (Part 2), tenofovir (Part 3), and drospirenone and ethinyl estradiol (Part 4) in healthy subjects. The trial consisted of four independent parts, each enrolling a separate cohort of healthy subjects. Fifty-eight subjects enrolled and participated in the trial. Parts 1, 2, 3, and 4 enrolled 12, 12, 18, and 16 male and female subjects respectively, though Part 4 only enrolled postmenopausal females. All subjects received active treatment (no placebo). The following section describes the trial parts.

Part 1 evaluated the co-administration of boceprevir with midazolam. On day -1, subjects received a single oral dose of midazolam 4 mg. From days 1 to 6, subjects received multiple daily doses of boceprevir 800 mg TID. In the morning

of day 6, subjects received boceprevir and a single dose of midazolam 4 mg. Treatment with boceprevir stopped on day 6. After a brief washout period, subjects received single doses of midazolam 4 mg on days 8 and 13.

Investigators collected blood samples for PK of midazolam and its metabolite on day -1 before boceprevir dosing, on day 6 at steady state during co-administration with boceprevir, and on days 8 and 13. The collection of blood samples for PK of boceprevir and its metabolite occurred on days 4, 5, and 6 at steady state during co-administration with midazolam. The figure below illustrates the design of part 1.

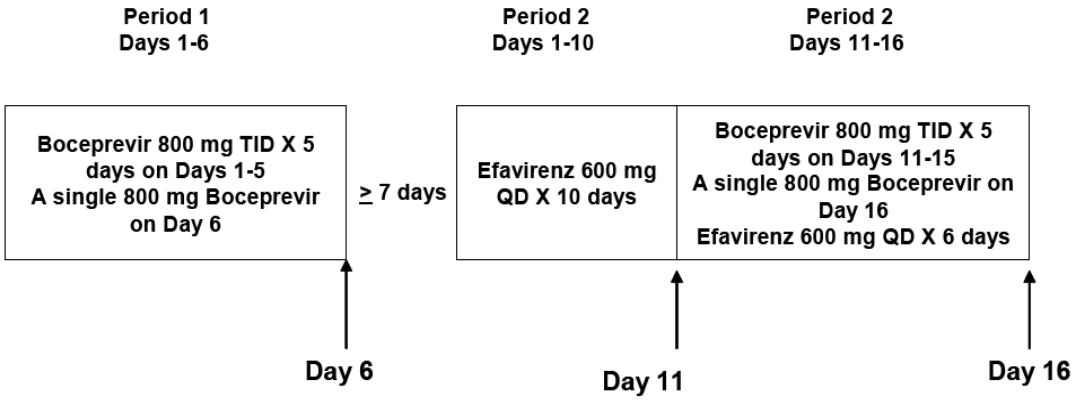
Figure 1 Trial design for part 1, co-administration of boceprevir with midazolam



Part 2 evaluated the co-administration of boceprevir with efavirenz. The sub-trial consisted of two periods with a fixed-sequence design. Period 1 evaluated the PK of boceprevir alone. Starting on day 1, subjects received boceprevir 800 mg TID for 5 days, and a single dose of boceprevir 800 mg on the morning of day 6. During period 1, investigators collected blood samples for PK of boceprevir and its metabolite on days 4, 5 and 6. At the end of period 1, subjects observed a 7-day washout before initiating period 2.

In period 2, subjects received efavirenz 600 mg QD alone for 10 days. From days 11 to 16, subjects received efavirenz 600 mg QD co-administered with boceprevir 800 mg TID. On the morning of day 16, subjects received a single dose of boceprevir 800 mg. Investigators collected blood samples for PK of boceprevir and its metabolite on days 14, 15, and 16. The collection of blood samples for PK of efavirenz occurred on days 7, 8, 9, 12, 13, and 14. The figure below illustrates the design of part 2.

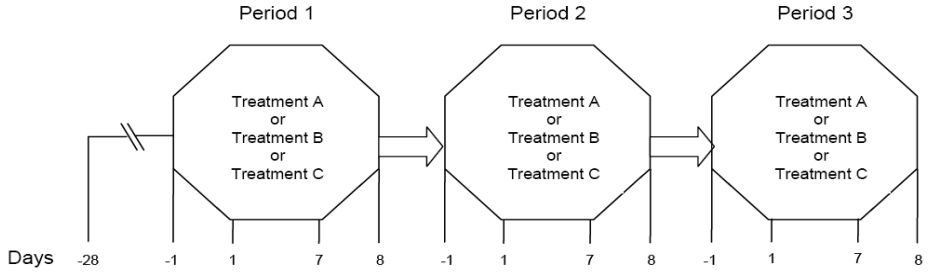
Figure 2 Trial design for part 2, co-administration of boceprevir with efavirenz



Part 3 evaluated the co-administration of boceprevir with tenofovir. Investigators randomized subjects into a three-period crossover sub-trial. In each period, subjects received either treatment A, B, or C. By the end of the trial, all subjects received the three active treatments (no placebo). Treatment A consisted of boceprevir 800 mg TID dosed for 7 days. Treatment B consisted of tenofovir 300 mg QD dosed for 7 days. Treatment C consisted of boceprevir 800 mg TID with tenofovir 300 mg QD dosed for 7 days. A 7-day washout occurred between each period.

Investigators collected blood samples for PK of boceprevir and its metabolite on day 7 in treatments A and C. Tenofovir plasma and urine samples were collected on day 7 of treatments B and C. The figure below illustrates the design of part 3.

Figure 3 Trial design for part 3, co-administration of boceprevir with tenofovir



Treatment A: ***800 mg boceprevir (4 X 200 mg capsules), TID, given orally for 7 days***

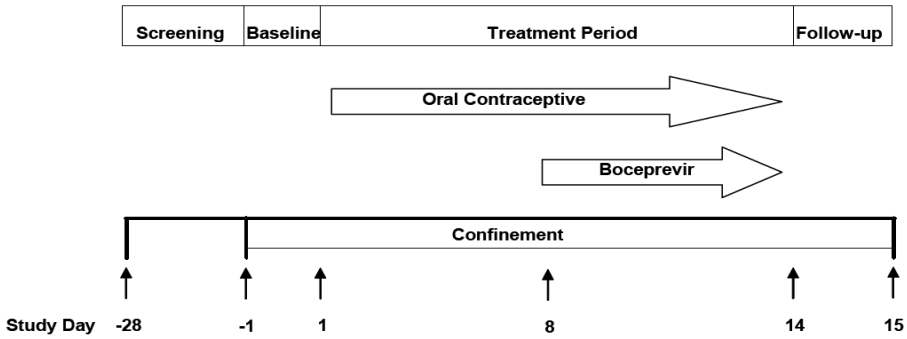
Treatment B: ***300 mg tenofovir (1 x 300 mg tablet), QD, given orally for 7 days***

Treatment C: ***800 mg boceprevir (4 X 200 mg capsules), TID, given orally and 300 mg tenofovir (1 x 300 mg tablet),QD, given orally for 7 days***

Dosing in each period must be separated by at least a 7 day interdose interval.

Part 4 evaluated the co-administration of boceprevir with Yaz®, an oral contraceptive containing drospirenone and ethinyl estradiol. This sequential, 14-day, multiple dose sub-trial did not include a washout period. In period 1, subjects received drospirenone 3 mg and ethinyl estradiol 0.02 mg QD for 7 days. In period 2, subjects co-administered drospirenone 3 mg and ethinyl estradiol 0.02 mg with boceprevir 800 mg TID from days 8 to 14. Investigators collected blood and urine samples for PK of drospirenone and ethinyl estradiol on days 7 and 14. Investigators did not collect blood samples for the PK of boceprevir. The figure below illustrates the design of part 4.

Figure 4 Trial design for part 4, boceprevir with drospirenone and ethinyl estradiol



- ***Treatment Administration***
  - ***Days 1 - 7: Oral contraceptive QD (Yaz®, drospirenone 3 mg/ ethinyl estradiol 0.02 mg)***
  - ***Days 8 - 14: Oral contraceptive QD (Yaz®, drospirenone 3 mg/ ethinyl estradiol 0.02 mg) coadministered with boceprevir 800 mg TID***

Key Inclusion Criteria

Male or female subjects of any race between 18 and 65 years of age with BMIs ranging from 19 to 32 kg/m^2. Part 4 enrolled only postmenopausal females between 18 and 65 years of age. All subjects were healthy based on physical examinations and clinical laboratory tests. Clinical laboratory tests included blood levels of AST, ALT, GGT, and serum creatinine. Safety assessments consisted of vital signs and ECG readings. All female subjects who were premenopausal and not surgically sterilized used a stable method of contraception for 90 days prior to trial screening, during the trial, and 90 days post last dose of trial medication. Acceptable methods of contraception included oral, transdermal, or injectable hormonal regimen for females, and condoms with spermicide for males.

Key Exclusion Criteria

Investigators excluded subjects who were infected with HIV, HBV, or HCV, tested positive for illicit drugs, or smoked >10 cigarettes per day. The trial also excluded subjects with medical conditions that may affect the absorption, distribution, metabolism, or excretion of any drug tested in the trial. For instance, subjects with inflammatory bowel disease, gastrectomy, bowel resection, pancreatitis, liver disease, or renal impairment did not enroll in the trial. Investigators prohibited the use of prescription and over-the-counter medications except acetaminophen. Medication intake stopped at least 14 days prior to trial start and during the trial. Dietary restrictions included the intake of grapefruit, grapefruit juice, alcohol, caffeinated beverages, and tobacco products for 48 hours prior to and during the trial.

Investigational Products

Schering-Plough manufactured the boceprevir 200 mg capsules on October 18, 2007 with batch number K-H08667. The capsules had an expiration date of (b) (4) The 200 mg capsules used are the proposed commercial formulation.

The trial used commercially available midazolam oral solution, efavirenz (Sustiva®) 200 mg capsules, tenofovir (Viread®) 300 mg tablets, and Yaz® tablets containing drospirenone 3 mg and ethinyl estradiol 0.02 mg.

Reviewer's comment: The trial report states that investigators were responsible for recording the lot number, storage, and expiry date of midazolam, efavirenz, tenofovir, and Yaz®. However, the report is missing this information. It may be assumed the drugs were of good quality because investigators purchased them from US manufacturers.

Drug Administration

Subjects received all of the trial drugs within 30 minutes of ingesting a meal or a snack with ~240 mL of water. Meals and snacks were of similar nutritional composition across all treatment periods. Drug intake occurred at approximately the same time everyday. Subjects received tenofovir, midazolam, drospirenone, and ethinyl estradiol in the morning. Efavirenz administration occurred in the evening, while boceprevir administration occurred every 8 hours throughout the day.

Special dietary restrictions occurred during days of serial PK sampling. On these days, subjects ate a snack at approximately 10 PM and then fasted overnight for at least 10 hours before the next day's dose of drug. The next morning,

investigators collected a predose blood sample, and subjects consumed a standard breakfast 30 minutes prior to receiving the drug. Subjects ingested the trial drugs within 30 minutes after consuming the meal. During drug intake, subjects could drink water as desired except for 1 hour after drug administration. Subjects were prohibited from eating for at least 4 hours post dose.

Reviewer's comment: Drug intake with food seems appropriate. However, food may have decreased the exposure of the oral contraceptive and may have increased the adverse events associated with efavirenz. According to the individual drug labels:

1. *Patients should take efavirenz capsules without food preferably at bedtime. Food increases the concentrations of efavirenz and may increase the frequency of adverse events[1]. In this trial, about 50% of subjects reported nausea during boceprevir co-administration with efavirenz.*

2. *Patients may take midazolam tablets with or without food. In this trial, investigators tested midazolam syrup instead of tablets. According to the label, the effect of food on the PK of midazolam HCl syrup has not been evaluated in a clinical trial[2]. In this trial, subjects took midazolam with food at baseline and during co-administration with boceprevir. Hence, the effect of food on midazolam may be similar across both treatment sessions.*

3. *Patients may take tenofovir tablets with or without food[3].*

4. *Subjects may take Yaz® tablets with or without meals. However, the rate of absorption of drospirenone and ethinyl estradiol following single administration of Yaz® was slower under fed (high fat meal) conditions with the serum C_{max} being reduced by about 40% for both components. The extent of absorption of ethinyl estradiol was reduced by about 20% under fed conditions[4]. Subjects took Yaz® with food at baseline and during co-administration with boceprevir.*

5. *Patients should take boceprevir with food.*

Rationale for Dose Selection

The dose of boceprevir evaluated in this study (800 mg TID) is the dose proposed for approval.
The dose of midazolam 4 mg tested in this trial was reasonable. Efavirenz 600 mg QD is the maximum recommended dose for adults infected with HIV. Investigators dosed efavirenz for 16 days to optimize the induction of CYP3A4.

Tenofovir 300 mg QD is the maximum recommended dose for the treatment of HIV and HBV. The literature reports that tenofovir might be a substrate of p-gp.

Boceprevir is both a substrate and a potential inhibitor of p-gp *in vitro*. Thus, boceprevir may affect the permeability of tenofovir by inhibiting p-gp in the intestines.

Yaz® is a commercially available oral contraceptive containing drospirenone 3 mg and ethinyl estradiol 0.02 mg. The dose of Yaz® tested in this trial was appropriate. Drospirenone and ethinyl estradiol are both minor substrates of CYP3A4. Boceprevir is a strong inhibitor of CYP3A4 and may increase the concentration of drospirenone and ethinyl estradiol.

Pharmacokinetic Assessments

Investigators collected plasma samples for PK of boceprevir, SCH534128, SCH534129, SCH629144, midazolam, 1-OH-midazolam, efavirenz, tenofovir, drospirenone, and ethinyl estradiol. Urine samples were collected for PK of tenofovir and ethinyl estradiol. The table below lists the schedule of PK collection.

Table 1 Schedule of plasma and urine sampling for PK of boceprevir, midazolam, efavirenz, tenofovir, drospirenone, and ethinyl estradiol.

		Days														
Part	**Analyte**	**-1**	**1**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**13**	**14**	**15**	**16**	**17**
1	Boceprevir	-		0h	0h	0-8h	-									
	Midazolam	0-12h	0h (24h)	-		0-12h	0h (24h)	0-12h	0h (24h)	-		0-12h	0h (24h)	-		
2	Boceprevir	-		0h	0h	0-12h	0h (24h)	-					0h	0h	0-12h	0h (24h)
	Efavirenz	-					0h	0h	0-12h	0h (24h)	0h	0h	0-12h	0h (24h)	-	
3	Boceprevir[a]	-					0-8h	-								
	Tenofovir plasma[b]	-					0-12h	0h (24h)	-							
	Tenofovir urine[b]	-					0-6h 6-12h 12-18h 18-24h	-								
4	Drospirenone and ethinyl estradiol	-					0-12h	0h (24h)	-				0-12h	0h (24h)	-	
	Ethinyl estradiol urine[c]	-					0-6h 6-12h 12-18h 18-24h	-					0-6h 6-12h 12-18h 18-24h	-		

a. Boceprevir PK samples collected during Treatments A and C.
b. Tenofovir samples collected during Treatments B and C. Urine samples collected in 4 intervals.
c. Ethinyl estradiol urine samples collected in 4 intervals.

Bioanalytical Methods

Six different laboratories analyzed the plasma and urine samples collected from this trial. The following table lists the analytes, validated bioanalytical methods, lower and upper limits of quantification, and the parties responsible for sample bioanalysis.

Table 2 Analytes, limits of quantification, LC-MS/MS methods, and parties responsible for the bioanalysis of samples.

Analyte	LLOQ (ng/mL)	ULQ (ng/mL)	LC-MS/MS Method	Party Responsible for Bioanalysis
SCH629144*	2.5	2500	DM27341	Schering-Plough
SCH534128	5.25	5250	DM27341	Schering-Plough
SCH534129	4.75	4750	DM27341	Schering-Plough
Midazolam	0.1	50	DM27802	(b) (4)
1-OH-midazolam	0.1	50	DM27802	
Efavirenz	10	8000	DM27810	
Tenofovir plasma	5.0	1000	DM28025	
Tenofovir urine	50	5000	DM28026	
Drospirenone	0.5	200	DM28024	
Ethinyl estradiol	0.001	0.2	DM28023	

*SCH629144 is comprised of four steroisomers: SCH783004, SCH783005, SCH783006, and SCH783007. All stereoisomers shared the same LLOQ and ULQ values.

All calibration standards and quality controls met the bioanalytical criteria. Investigators defined these criteria as precision (%CV) within ±15%, accuracy (%RE) ≤15%, and coefficient of determination (r^2) ≥0.98. The following table summarizes the precision and accuracy of the bioanalytical methods.

Table 3 Precision (% CV) and accuracy (% relative error) of calibration standards and QC samples in human plasma and urine.

	Cal Std			QC	
Analyte	%CV	%RE	R^2	%CV	%RE
SCH534128	1.1 - 5.4	≤2.4	≥0.9976	1.0 - 17.6	≤5.3
SCH534129	1.1 - 4.8	≤2.6	≥0.9978	1.2 - 17.6	≤5.0
SCH783004	2.0 - 6.1	≤1.0	≥0.9948	2.9 - 7.1	≤6.4
SCH783005	1.9 - 5.4	≤1.7	≥0.9956	2.9 - 7.1	≤6.4
SCH783006	2.2 - 4.8	≤1.6	≥0.9965	1.0 - 11.1	≤3.2
SCH783007	2.6 - 5.1	≤2.8	≥0.9947	0.8 - 11.5	≤3.6
Midazolam	2.7 - 8.9	≤6.0	≥0.9931	3.6 - 7.5	≤5.0
1-OH-midazolam	2.2 - 7.5	≤3.5	≥0.9945	4.6 - 7.9	≤1.5
Efavirenz	0.6 - 7.2	≤11.8	≥0.9936	3.1 - 7.3	≤9.7
Tenofovir plasma	2.1 - 5.7	≤3.8	≥0.9984	2.2 - 6.9	≤4.7
Tenofovir urine	3.5 - 6.6	≤5.0	≥0.9915	5.5 - 7.7	≤3.3
Drospirenone	1.2 - 6.8	≤3.2	≥0.9972	1.9 - 5.5	≤2.7
Ethinyl estradiol	2.9 - 6.5	≤3.1	≥0.9937	1.1 - 5.3	≤6.2

Investigators analyzed all plasma and urine samples within the frozen stability timeframe provided by Schering-Plough.

PK and Statistical Analyses

Part 1: The log-transformed AUC and C_{max} of midazolam and 1-OH-midazolam were analyzed using an analysis of variance (ANOVA) model extracting the effects of treatment and subject. The primary endpoint was the geometric mean ratio (GMR) of the relative bioavailability of the PK of midazolam during co-administration with boceprevir relative to the PK of midazolam alone. GMR estimates were associated with 90% confidence intervals.

Part 2: The log-transformed AUC and C_{max} of boceprevir and its metabolite were analyzed using an ANOVA model extracting the effects of treatment and subject. The primary endpoint was the GMR of relative bioavailability of the PK of boceprevir and its metabolite during co-administration with efavirenz relative to the PK of boceprevir alone. GMR estimates were associated with 90% confidence intervals. Although not specified in the protocol, investigators also performed a similar analysis on the PK of efavirenz.

Part 3: The log-transformed AUC and C_{max} of boceprevir and its metabolite were analyzed using an ANOVA model extracting the effects of treatment, period, sequence, and subject. The primary endpoint was GMR of relative bioavailability of the PK of boceprevir and its metabolite during co-administration with tenofovir relative to the PK of boceprevir alone. GMR estimates were associated with 90% confidence intervals. Investigators also performed a similar analysis on the PK of tenofovir.

Part 4: The log-transformed AUC and C_{max} of drospirenone and ethinyl estradiol were analyzed using an ANOVA model extracting the effects of treatment and subject. The primary endpoint was GMR of relative bioavailability of the PK of drospirenone and ethinyl estradiol co-administered with boceprevir relative to the PK of drospirenone and ethinyl estradiol alone. GMR estimates were associated with 90% confidence intervals.

Demographic Results

The trial planned to enroll 46 subjects, but ended up enrolling 58 subjects. The following section breaks down subject enrollment per trial part:

Part 1 enrolled seven males and five females. The mean age of subjects was 39.1 years (range, 22 – 60 years), and the mean BMI was 25.6 kg/m^2 (range, 20.6 – 31.3 kg/m^2). All subjects completed part 1.

Part 2 enrolled six males and six females. The mean age of subjects was 34.3 years (range, 23 – 54 years), and the mean BMI was 27.9 kg/m^2 (range, 24.3 – 32.0 kg/m^2). All subjects completed part 2.

Part 3 enrolled fifteen males and three females. The mean age of subjects was 30.4 years (range, 19 – 49 years), and the mean BMI was 25.7 kg/m^2 (range, 19.5 – 31.0 kg/m^2). Two subjects discontinued due to adverse events in part 3.

Part 4 enrolled sixteen postmenopausal women. The mean age of subjects was 53.4 years (range, 40 – 63 years), and the mean BMI was 27.2 kg/m^2 (range, 19.6 – 32.0 kg/m^2). All subjects completed part 4.

Part 1. Drug interaction between boceprevir and midazolam

Pharmacokinetics results for boceprevir and SCH629144 in the presence or absence of midazolam.

The effect of midazolam on the PK of boceprevir was not evaluable because the trial did not include a control arm for boceprevir. However, exposures of boceprevir collected during co-administration with midazolam (day 6) were compared to exposures of boceprevir alone collected in part 3 of this trial (tenofovir sub-trial). Overall, midazolam did not affect the PK of boceprevir and SCH629144 during co-administration (Day 6) relative to boceprevir alone in part 3. The table below compares the PK of boceprevir and SCH629144 in the presence of midazolam on day 6 relative to boceprevir alone in part 3 of this trial.

Table 4 Indirect comparison of boceprevir and SCH629144 PK obtained during co-administration of boceprevir 800 mg TID with midazolam 4 mg on Day 6 relative to the PK of boceprevir alone in Part 3 (tenofovir sub-trial).

	Boceprevir + midazolam	Boceprevir alone (from tenofovir sub trial)	SCH629144 + midazolam	SCH629144 alone (from tenofovir sub trial)
Parameter	Part 1, day 6 (n=12)	Part 3 (n=16)	Part 1, day 6 (n=12)	Part 3 (n=16)[c]
T_{max}[a] (h)	3.0 (0-4)	3.0 (1-4)	4.0 (1-6)	4.0 (3-6)
C_{max} (ng/mL)	1610 (30)	1580 (22)	5510 (29)	4860 (26)
C_{min}[b] (ng/mL)	107 (71)	88.5 (52)	1160 (35)	1180 (41)
AUC_{0-8h} (ng*hr/mL)	5730 (29)	5100 (21)	26700 (28)	23200 (29)
$t_{1/2}$ (h)	1.3 (31)	1.3 (36)	-	
CL/F[b] (L/h)	150 (29)	164 (23)	-	

[a] Median (range)
[b] C_{min} and CL/F calculated based on sample collection over 8 hours

PK values of boceprevir and SCH629144 collected during parts 1 and 3 were similar. These results suggest that midazolam did not affect the PK of boceprevir during co-administration.

Pharmacokinetic results for midazolam and 1-OH-midazolam in the

presence or absence of boceprevir

Boceprevir increased the mean C_{max} and $AUC_{0\text{-}24h}$ values of midazolam by 177% and 430%, respectively, during co-administration (day 6) relative to midazolam alone (day -1). On the other hand, the mean C_{max} and $AUC_{0\text{-}24h}$ of 1-OH midazolam decreased by 71% and 44%, respectively, in the presence of boceprevir relative to midazolam alone. The exposures of midazolam and 1-OH-midazolam returned to baseline levels (day -1) after boceprevir was discontinued on days 8 and 13. These results confirm that boceprevir is a strong inhibitor of CYP3A4. The following table summarizes the statistical results of midazolam and 1-OH-midazolam in the presence or absence of boceprevir.

Table 5 Statistical results for PK of midazolam and 1-OH-midazolam following single oral doses of midazolam (MDZ) 4 mg administered alone or co-administered with multiple oral dose of boceprevir (BOC) 800 mg TID to healthy subjects in part 1.

Parameter	Treatment	n	LS Mean [a]	Ratio Estimate (%)[b]	90%CI
MDZ					
Cmax (ng/mL)	MDZ Alone (Day -1)	12	9.96	277	236-325
	MDZ + BOC (Day 6)	12	27.6		
	MDZ Alone (Day 8)	12	9.82		
	MDZ Alone (Day 13)	12	8.94		
AUC(0-24hr) (ng·hr/mL)	MDZ Alone (Day -1)	12	52.94	530	466-603
	MDZ + BOC (Day 6)	12	280.7		
	MDZ Alone (Day 8)	12	56.10		
	MDZ Alone (Day 13)	12	43.83		
1-OH-MDZ					
Cmax (ng/mL)	MDZ Alone (Day -1)	12	3.76	29	24-35
	MDZ + BOC (Day 6)	12	1.09		
	MDZ Alone (Day 8)	12	2.48		
	MDZ Alone (Day 13)	12	3.80		
AUC(0-24hr) (ng·hr/mL)	MDZ Alone (Day -1)	12	18.95	56	50-63
	MDZ + BOC (Day 6)	12	10.63		
	MDZ Alone (Day 8)	12	13.78		
	MDZ Alone (Day 13)	12	18.48		

ANOVA = analysis of variance; AUC(0-24hr) = area under the plasma concentration-time curve from time 0 to 24 hours; BOC = boceprevir; CI = confidence interval; Cmax = maximum observed plasma concentration; LS = least squares; MDZ = midazolam; 1-OH-MDZ = 1-hydroxy-midazolam; TID = three times daily

a: Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and subject.

b: Geometric mean ratio of MDZ + BOC (Day 6) vs MDZ alone (Day -1).

On day 6, boceprevir decreased the mean apparent clearance of midazolam by 85% and prolonged the mean half-life of midazolam by 97% relative to midazolam values at baseline (day -1). In the absence of boceprevir (days 8 and 13), the clearance and half-life of midazolam returned to baseline (day -1). Results suggest that boceprevir increased the PK parameters of midazolam by inhibiting CYP3A4 metabolism. The following table summarizes the PK of

midazolam and 1-OH-midazolam in the presence and absence of boceprevir.

Table 6 Mean (CV%) plasma PK of midazolam and 1-OH-midazolam following single oral doses of midazolam (MDZ) 4 mg administered alone or co-administered with multiple oral doses of boceprevir (BOC) 800 mg TID to healthy subjects in part 1.

Parameter	MDZ Alone (Day -1) (n=12)	MDZ + BOC (Day 6) (n=12)	MDZ Alone (Day 8) (n=12)	MDZ Alone (Day 13) (n=12)
MDZ				
Tmax [a] (hr)	2.00 (1.00-2.00)	2.50 (1.00-4.00)	2.00 (0.500-4.00)	1.00 (0.500-2.00)
Cmax (ng/mL)	10.3 (25)	28.5 (26)	10.3 (34)	9.15 (22)
AUC(0-24hr) (ng·hr/mL)	56.4 (40)	285 (19)	59.2 (37)	45.4 (28)
t½ (hr)	4.98 (38)	9.79 (33)	5.22 (38)	4.86 (44)
CL/F (L/hr)	78.8 (36)	12.0 (16)	73.3 (34)	92.9 (28)
1-OH-MDZ				
Tmax [a] (hr)	2.00 (0.500-2.00)	2.00 (1.00-8.00)	2.00 (0.500-3.00)	1.50 (1.00-2.00)
Cmax (ng/mL)	3.86 (23)	1.15 (34)	2.85 (72)	4.07 (42)
AUC(0-24hr) (ng·hr/mL)	19.3 (22)	10.9 (31)	14.3 (40)	19.1 (29)
t½ (hr)	3.92 (56)	9.21 (38)	3.80 (76)	4.11 (50)

AUC(0-x) = area under the plasma concentration-time curve from time 0 to x hours; BOC = boceprevir; CL/F = apparent total body clearance; Cmax = maximum observed plasma concentration; CV = coefficient of variation; MDZ = midazolam; 1-OH-MDZ = 1-hydroxy-midazolam; t½ = elimination half-life; TID = three times daily; Tmax = time to maximum observed plasma concentration

a: Median (range).

Part 2. Drug interaction between boceprevir and efavirenz

Pharmacokinetics results for boceprevir, SCH534128, SCH534129, and SCH629144 in the presence or absence of efavirenz.

Efavirenz decreased the mean C_{max}, AUC_{0-8h}, and C_{min} of boceprevir by 8%, 19%, and 44%, respectively, during co-administration relative to boceprevir alone. These results were expected because efavirenz in an inducer of CYP3A4. However, efavirenz unexpectedly decreased the mean C_{max} and AUC_{0-8h} of SCH629144 by 39% and 53%, respectively. The reason for this decrease in SCH629144 exposures is unknown. The following table summarizes the statistical results of boceprevir in the presence and absence of efavirenz.

Table 7 Statistical results for PK parameters of boceprevir, SCH534128, SCH534129, and SCH629144 following multiple oral doses of boceprevir (BOC) 800 mg TID administered alone or co-administered with multiple oral doses of efavirenz (EFV) 600 mg QD to healthy subjects in part 2.

	Parameter	Treatment	n	LS Mean[a]	Ratio Estimate (%)[b]	90% CI
Boceprevir	C_{max} (ng/mL)	BOC alone BOC + EFV	12 12	2038 1871	92	78 – 108
	AUC_{0-8h} (ng*hr/mL)	BOC alone BOC + EFV	12 12	6913 5630	81	75 – 89
	C_{min} (ng/mL)	BOC alone BOC + EFV	12 12	94.4 52.5	56	42 – 74
SCH534128	C_{max} (ng/mL)	BOC alone BOC + EFV	12 12	1307 1186	91	78 – 106
	AUC_{0-8h} (ng*hr/mL)	BOC alone BOC + EFV	12 12	4659 3702	79	73 – 86
SCH534129	C_{max} (ng/mL)	BOC alone BOC + EFV	12 12	749 688	92	76 – 112
	AUC_{0-8h} (ng*hr/mL)	BOC alone BOC + EFV	12 12	2236 1922	86	78 – 95
SCH629144	C_{max} (ng/mL)	BOC alone BOC + EFV	12 12	6149 3730	61	52 – 70
	AUC_{0-8h} (ng*hr/mL)	BOC alone BOC + EFV	12 12	30769 14435	47	40 – 56

[a] Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and subject.
[b] Geometric mean ratio of BOC + EFV vs. BOC alone.

Efavirenz slightly increased (20%) the apparent clearance (CL/F) of boceprevir relative to boceprevir alone. However, the $t_{1/2}$, and T_{max} of boceprevir remained unchanged during co-administration with efavirenz relative to boceprevir alone. The table below summarizes the PK of boceprevir (SCH534128 + SCH534129) and SCH629144 in the presence or absence of efavirenz.

Table 8 Mean (CV%) plasma PK parameters of boceprevir, SCH534128, SCH534129, and SCH629144 following multiple oral doses of boceprevir (BOC) 800 mg TID administered alone or co-administered with multiple oral doses of efavirenz (EFV) 600 mg QD to healthy subjects in part 2.

	Boceprevir		SCH534128		SCH534129		SCH629144	
Parameter	BOC (n=12)	BOC + EFV (n=12)	BOC (n=12)	BOC + EFV (n=12)	BOC (n=12)	BOC + EFV (n=12)	BOC (n=12)	BOC + EFV (n=12)
T_{max}[a] (hr)	2.5 (1 – 4)	3 (1 – 4)	2.5 (2 – 4)	3 (1 – 4)	2 (0 – 4)	2.5 (1 – 4)	3.5 (3 – 6)	4 (2 – 8)
C_{max} (ng/mL)	2100 (25)	1920 (23)	1340 (25)	1220 (23)	776 (28)	709 (25)	6480 (33)	3850 (26)
C_{min} (ng/mL)	111 (69)	54.3 (29)	83.5[b] (69)	40.5[b] (29)	26.8 (70)	13.8 (37)	1790 (59)	518 (31)
AUC_{0-8h} (ng*hr/mL)	7070 (22)	5700 (17)	4760 (22)	3750 (18)	2300 (25)	1950 (18)	32500 (33)	15000 (30)
AUC_{0-24h} (ng*hr/mL)	7620 (22)	6040 (17)	5150 (22)	4000 (17)	2450 (26)	2030 (19)	40300 (40)	17700 (28)
$t_{1/2}$ (hr)	3.53[c] (59)	3.22[c] (84)	-		-		-	
CL/F[b] (L/hr)	118 (22)	144 (15)	-		-		-	

[a] Median (range)
[b] C_{min} and CL/F values were calculated over an 8-hour interval for all treatments
[c] The $t_{1/2}$ calculation was based on sample collection over 24 hours

Pharmacokinetic results for efavirenz in the presence or absence of boceprevir

Boceprevir increased the mean C_{max} and AUC_{0-24h} of efavirenz by 11% and 20%, respectively, during co-administration relative to efavirenz alone. The results were expected because efavirenz is a substrate of CYP3A4. The following table summarizes the statistical results of efavirenz in the presence or absence of boceprevir.

Table 9 Statistical results for PK of efavirenz following multiple oral doses of efavirenz (EFV) 600 mg QD administered alone or co-administered with multiple oral doses of boceprevir 800 mg TID to healthy subjects in part 2.

Parameter	Treatment	n	LS Mean [a]	Ratio Estimate (%)[b]	90%CI
Cmax (ng/mL)	EFV Alone	12	4573	111	102-120
	EFV + BOC	12	5077		
AUC(0-24hr) (ng·hr/mL)	EFV Alone	12	78667	120	115-126
	EFV + BOC	12	94655		

ANOVA = analysis of variance; AUC(0-24hr) = area under the plasma concentration-time curve from time 0 to 24 hours; BOC = boceprevir; CI = confidence interval; Cmax = maximum observed plasma concentration; EFV = efavirenz; LS = least squares; QD = once daily; TID = three times daily

a: Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and subject.

b: Geometric mean ratio of EFV + BOC vs EFV alone.

Boceprevir decreased the mean apparent clearance (CL/F) of efavirenz by 16%

during co-administration relative to efavirenz alone. Moreover, boceprevir prolonged the median T_{max} of efavirenz from 6 hours to 9 hours during co-administration compared to administration of efavirenz alone. The following table summarizes the PK of efavirenz in the presence or absence of boceprevir.

Table 10 Mean (CV%) plasma PK of efavirenz following multiple oral doses of efavirenz (EFV) 600 mg QD administered alone or co-administered with multiple oral doses of boceprevir 800 mg TID to healthy subjects in part 2.

Parameter	EFV Alone (n=12)	EFV + BOC (n=12)
Tmax [a] (hr)	6.00 (4.00-10.0)	9.00 (4.00-12.0)
Cmax (ng/mL)	4630 (16)	5210 (24)
Cmin (ng/mL)	2400 (21)	3010 (25)
AUC(0-24hr) (ng·hr/mL)	80000 (19)	97200 (23)
CL/F (L/hr)	7.77 (21)	6.52 (26)

AUC(0-x) = area under the plasma concentration-time curve from time 0 to x hours; BOC = boceprevir; CL/F = apparent total body clearance; Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; CV = coefficient of variation; EFV = efavirenz; QD = once daily; TID = three times daily; Tmax = time to maximum observed plasma concentration

a: Median (range).

Part 3. Drug interaction between boceprevir and tenofovir

Pharmacokinetics results of boceprevir, SCH534128, SCH534129, and SCH629144 in the presence or absence of tenofovir.

Tenofovir did not affect the PK of boceprevir during co-administration relative to boceprevir alone. Investigators observed a slight increase (~10%) in the exposures (C_{max} and AUC) of SCH629144 during co-administration with tenofovir. However, the increase in SCH629144 is likely due to PK variability rather than a drug interaction with tenofovir. The following table summarizes the statistical results of boceprevir in the presence or absence of tenofovir.

Table 11 Statistical results for PK parameters of boceprevir, SCH534128, SCH534129, and SCH629144 following multiple oral doses of boceprevir (BOC) 800 mg TID administered alone or co-administered with multiple oral doses of tenofovir (TFV) 300 mg QD to healthy subjects in part 3.

	Parameter	Treatment	n	LS Mean[a]	Ratio Estimate (%)[b]	90% CI
Boceprevir	C_{max} (ng/mL)	BOC alone BOC + TFV	16 17	1536 1607	105	98 – 112
	AUC_{0-8h} (ng*hr/mL)	BOC alone BOC + TFV	16 17	5041 5441	108	102 – 114
	C_{min} (ng/mL)	BOC alone BOC + TFV	16 17	80 87	108	97 – 120
SCH534128	C_{max} (ng/mL)	BOC alone BOC + TFV	16 17	984 1027	104	98 – 111
	AUC_{0-8h} (ng*hr/mL)	BOC alone BOC + TFV	16 17	3330 3619	109	104 – 114

SCH534129	C_{max} (ng/mL)	BOC alone BOC + TFV	16 17	562 592	105	97 – 115
	AUC_{0-8h} (ng*hr/mL)	BOC alone BOC + TFV	16 17	1706 1816	106	100 – 113
SCH629144	C_{max} (ng/mL)	BOC alone BOC + TFV	16 17	4610 5114	111	101 – 122
	AUC_{0-8h} (ng*hr/mL)	BOC alone BOC + TFV	16 17	21899 24156	110	101 – 121

[a] Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment, period, sequence, and subject.
[b] Geometric mean ratio of boceprevir + tenofovir vs. boceprevir alone.

Tenofovir did not affect the mean apparent clearance (CL/F), T_{max} and $t_{1/2}$ of boceprevir during co-administration relative to boceprevir alone. The following table summarizes the PK of boceprevir, SCH534128, SCH534129, and SCH629144 during part 3.

Table 12 Mean (CV%) plasma PK parameters of boceprevir, SCH534128, SCH534129, and SCH629144 following multiple oral doses of boceprevir (BOC) 800 mg TID administered alone or co-administered with multiple oral doses of tenofovir (TFV) 300 mg QD to healthy subjects in part 3

	Boceprevir		**SCH534128**		**SCH534129**		**SCH629144**	
Parameter	BOC (n=16)[a]	BOC + TFV (n=17)[a]	BOC (n=16)[a]	BOC + TFV (n=17)[a]	BOC (n=16)[a]	BOC + TFV (n=17)[a]	BOC (n=16)[a]	BOC + TFV (n=17)[a]
T_{max}[b] (hr)	3 (1 – 4)	3 (2 – 4)	3 (2 – 4)	3 (2 – 4)	2.5 (1 – 4)	3 (2 – 4)	4 (3 – 6)	4 (3 – 4)
C_{max} (ng/mL)	1580 (22)	1650 (19)	1010 (20)	1050 (18)	582 (23)	607 (21)	4860 (26)	5230 (20)
C_{min} (ng/mL)	88.5 (52)	101 (53)	65.9 (52)	76 (52)	21.7 (56)	24.2 (57)	1180 (41)	1370 (34)
AUC_{0-8h} (ng*hr/mL)	5100 (21)	5610 (22)	3370 (21)	3720 (21)	1730 (24)	1890 (26)	23200 (29)	24800 (20)
$t_{1/2}$ (hr)	1.25 (36)	1.27 (30)	-		-		-	
CL/F (L/hr)	164 (23)	149 (23)	-		-		-	

[a] Subject 1/000309 and subject 1/000314 (both in part 3) discontinued the trial early, and therefore, did not have all PK samples available for the analyses.
[b] Median (range)

Pharmacokinetic results for tenofovir in the presence or absence of boceprevir.

Boceprevir increased the mean C_{max} of tenofovir by 32% during co-administration compared to tenofovir alone. However, the AUC of tenofovir was unchanged in the presence or absence of boceprevir. The following table summarizes the statistical results for tenofovir in the presence or absence of boceprevir.

Table 13 Statistical results for PK of tenofovir following multiple oral doses of tenofovir 300 mg QD administered alone or co-administered with multiple oral doses of boceprevir

800 mg TID to healthy subjects in part 3.

Parameter	Treatment	n	LS Mean [a]	Ratio Estimate (%)[b]	90%CI
Cmax (ng/mL)	TFV Alone	18	315	132	119-145
	TFV + BOC	17	415		
AUC(0-24hr) (ng·hr/mL)	TFV Alone	18	3248	105	101-109
	TFV + BOC	17	3403		

ANOVA = analysis of variance; AUC(0-24hr) = area under the plasma concentration-time curve from time 0 to 24 hours; BOC = boceprevir; CI = confidence interval; Cmax = maximum observed plasma concentration; LS = least squares; QD = once daily; TFV = tenofovir; TID = three times daily

a: Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment, period, sequence (as fixed effects), and subject within sequence (as random effect).

b: Geometric mean ratio of TFV + BOC vs TFV alone.

The mean apparent plasma (CL/F) and renal clearance (CLr) of tenofovir remained relatively unchanged in the presence or absence of boceprevir. Similarly, the amount of tenofovir excreted in the urine (Ae) over 24 hours at steady state was similar during co-administration with boceprevir relative to tenofovir alone. These results suggest that boceprevir did not affect the renal elimination of tenofovir. The T_{max} of tenofovir was similar in the presence and absence of boceprevir. The following table summarizes the PK of tenofovir in the presence or absence of boceprevir.

Table 14 Mean (CV%) PK of tenofovir following multiple oral doses of tenofovir 300 mg QD administered alone or co-administered with multiple oral doses of boceprevir 800 mg TID to healthy subjects in part 3.

Parameter	TFV Alone (n=18)[a]	TFV + BOC (n=17)[a]
Tmax[b] (hr)	3.00 (2.00-4.00)	2.00 (1.00-4.00)
Cmax (ng/mL)	324 (22)	426 (23)
Cmin (ng/mL)	63.9 (20)	69.1 (22)
AUC(0-24hr) (ng·hr/mL)	3320 (20)	3490 (21)
t½ (hr)	12.0 (20)	15.6 (21)
CL/F (L/hr)	94.4 (22)	89.8 (23)
Ae (% Dose)	15.8 (19)	15.9 (20)
CLr (L/hr)	14.6 (19)	14.1 (22)

Ae = amount excreted in the urine; AUC(0-x) = area under the plasma concentration-time curve from time 0 to x hours; BOC = boceprevir; CL/F = apparent total body clearance; CLr = renal clearance; Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; CV = coefficient of variation; PK = pharmacokinetics; QD = once daily; t½ = elimination half-life; TFV = tenofovir; TID = three times daily; Tmax = time to maximum observed plasma concentration

a: Subject 1/000314 (in Part 3) discontinued the study early, and therefore, did not have all PK samples available for the analyses.

b: Median (range).

Part 4. Drug interaction between boceprevir, drospirenone, and

ethinyl estradiol

Pharmacokinetic results for drospirenone and ethinyl estradiol in the presence or absence of boceprevir.

Boceprevir increased the mean C_{max}, AUC_{0-24h} and C_{min} of drospirenone by 57%, 99%, and 143%, respectively, during co-administration relative to Yaz® alone. Boceprevir probably increased the exposures of drospirenone by inhibiting CYP3A4.

In contrast, boceprevir decreased the mean AUC_{0-24h} and C_{min} of ethinyl estradiol by 24% and 31%, respectively, but the C_{max} remained unchanged during co-administration relative to Yaz® alone. The decrease in ethinyl estradiol AUC was consistent across all subjects (Fig. 5). The results are unexpected because ethinyl estradiol primarily undergoes CYP3A4 metabolism.

The following table summarizes the statistical results of drospirenone and ethinyl estradiol in the presence or absence of boceprevir.

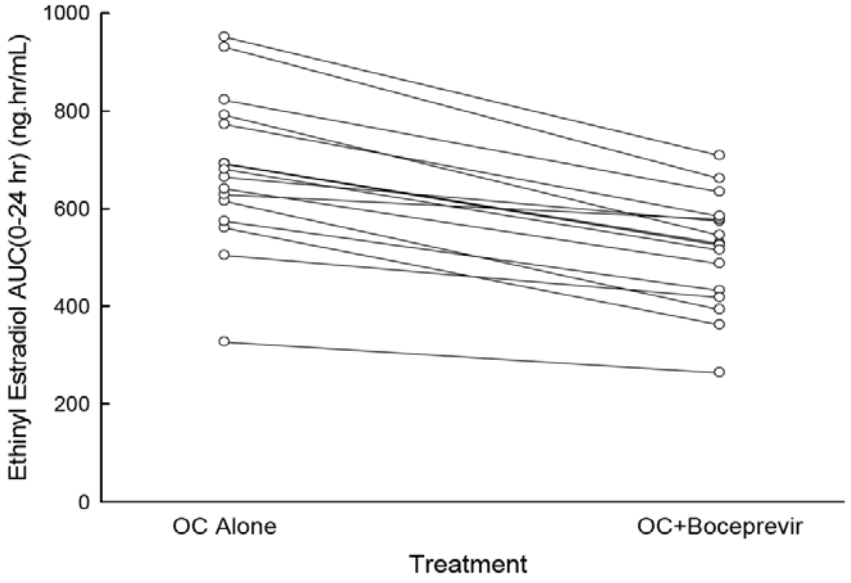
Table 15 Statistical results for PK of drospirenone and ethinyl estradiol following multiple oral daily doses of Yaz® (drospirenone 3 mg and ethinyl estradiol 0.02 mg) alone or co-administered with boceprevir 800 mg TID to healthy postmenopausal women in part 4.

Parameter	Treatment	n	LS Mean[a]	Ratio Estimate (%)[b]	90% CI
Drospirenone					
C_{max} (pg/mL)	OC Alone OC + BOC	16 16	46 73	157	146 – 170
AUC_{0-24h} (pg*hr/mL)	OC Alone OC + BOC	16 16	655 1304	199	187 – 211
C_{min} (pg/mL)	OC Alone OC + BOC	16 16	19 46	243	225 – 262
Ethinyl Estradiol					
C_{max} (ng/mL)	OC Alone OC + BOC	16 16	54 54	100	91 – 110
AUC_{0-24h} (ng*hr/mL)	OC Alone OC + BOC	16 16	659 499	76	73 – 79
C_{min} (ng/mL)	OC Alone OC + BOC	16 16	14 9	69	65 - 73

a: Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and subject. b: Geometric mean ratio of OC + BOC vs. OC alone

Figure 2 Individual ethinyl estradiol AUC_{0-24} Values Following Multiple Oral Doses of Oral

Contraceptive (OC) Alone and with Boceprevir.



Boceprevir decreased the mean apparent clearance (CL/F) of drospirenone by 50% during co-administration relative to Yaz® alone. Conversely, boceprevir increased the mean CL/F of ethinyl estradiol by 32% during co-administration relative to Yaz® alone. The following table summarizes the PK of drospirenone and ethinyl estradiol in the presence or absence of boceprevir.

Table 16 Mean (CV%) plasma PK of drospirenone and ethinyl estradiol following multiple oral daily doses of Yaz® (drospirenone 3 mg and ethinyl estradiol 0.02 mg) alone or co-administered with boceprevir 800 mg TID to healthy postmenopausal women in part 4.

Parameter	OC Alone (n=16)	OC + BOC (n=16)
DRSP		
Tmax [a] (hr)	3.00 (1.00-6.00)	4.00 (2.00-4.00)
Cmax (ng/mL)	47.0 (18)	74.4 (21)
Cmin (ng/mL)	19.4 (29)	46.7 (22)
AUC(0-24hr) (ng·hr/mL)	672 (24)	1330 (21)
CL/F (L/hr)	4.69 (23)	2.35 (22)
EE		
Tmax [a] (hr)	3.00 (1.00-6.00)	2.00 (1.00-6.00)
Cmax (ng/mL)	55.1 (24)	55.6 (29)
Cmin (ng/mL)	14.3 (29)	9.82 (28)
AUC(0-24hr) (ng·hr/mL)	677 (23)	513 (23)
t½ (hr)	14.9 (24)	15.5 (22)
CL/F (L/hr)	31.4 (30)	41.4 (29)

AUC(0-x) = area under the plasma concentration-time curve from time 0 to x hours; BOC = boceprevir; CL/F = apparent total body clearance; Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; CV = coefficient of variation; DRSP = drospirenone; EE = ethinyl estradiol; OC = oral contraceptive; QD = once daily; t½ = elimination half-life; TID = three times daily; Tmax = time to maximum observed plasma concentration

a: Median (range).

<u>Reviewer's comment:</u> Investigators collected urine samples to evaluate the amount of ethinyl estradiol excreted over a 24-hr interval during co-administration of oral contraceptive with boceprevir. However, investigators did not report the concentrations of ethinyl estradiol recovered in urine.

The oral contraceptive was only administered for 7 days in each treatment period, without a washout period. According to the package insert for Yaz®, drospirenone concentrations reach steady state after 8 days of dosing and EE reaches steady state during the second half of the treatment cycle. Thus, there was initial concern that drospirenone and ethinyl estradiol may not have reached steady state when PK samples were collected. If so, then changes in the PK of drospirenone and ethinyl estradiol may have been partly due to insufficient time to reach steady state.

The following table shows that drospirenone and ethinyl estradiol reached steady state trough levels during PK sampling in the presence and absence of boceprevir. Therefore, the changes in exposures of drospirenone and ethinyl estradiol are likely caused by drug interactions with boceprevir, instead of insufficient time to reach steady state exposures.

Table 17 Mean (CV%) steady state C_{min} values of drospirenone and ethinyl estradiol in the presence or absence of boceprevir.

	OC Alone		OC + BOC	
	Day 7 (0h)	Day 8 (24h)	Day 14 (0h)	Day 15 (24h)

Drospirenone	C_{min} (pg/mL)	20100 (29)	21200 (31)	48500 (25)	51700 (23)
Ethinyl Estradiol	C_{min} (ng/mL)	15.6 (28)	15.1 (30)	10.5 (28)	9.9 (29)

Safety results

The trial did not report deaths, life-threatening, or severe adverse events. Two subjects discontinued the trial during part 3 (tenofovir) due to vomiting and viral infection. The next section lists the safety findings observed in each part.

Part 1 (Midazolam + boceprevir). Six (50%) subjects experienced at least one treatment emergent adverse event (TEAE). Gastrointestinal disorders (5 subjects, 42%) and dysgeusia (3 subjects, 25%) were the most common TEAEs associated with boceprevir treatment alone. One subject reported ear pain, dermatitis, and cough on day -1 during midazolam treatment.

Part 2 (Efavirenz + boceprevir). Ten subjects (83%) experienced at least one TEAE. All TEAEs were evenly distributed across boceprevir and efavirenz treatments. The most common TEAEs were gastrointestinal (7 subjects, 58%), nervous system (6 subjects, 50%), and skin and subcutaneous tissues (6 subjects, 50%) disorders. Six subjects (50%) reported nausea. Five subjects reported dermatitis and rash during treatment with efavirenz alone. All adverse events were mild in severity except one case of moderate maculopapular rash during treatment with efavirenz alone.

Part 3 (Tenofovir + boceprevir). Thirteen subjects (72%) experienced at least one TEAE. A higher number of subjects reported TEAEs during treatments with boceprevir alone (9, 53%) and boceprevir + tenofovir (7, 41%) than during treatment with tenofovir alone (5, 28%). The highest incidences of TEAEs were gastrointestinal (8, 44%) and nervous system disorders (7, 39%). All adverse events were mild in severity with the exception of one case of moderate vomiting and another case of viral infection. These two subjects discontinued the trial.

Part 4 (Yaz® + boceprevir). Twelve subjects (75%) experienced at least one TEAE. More subjects reported TEAEs during co-administration of boceprevir and oral contraceptive (12, 75%) than during treatment with oral contraceptive alone (3, 19%). The highest incidences of TEAEs were gastrointestinal (10, 63%) and nervous system disorders (7, 44%). The most commonly reported TEAEs were nausea (5, 31%) and mild dysgeusia (5, 31%).

Discussion and Conclusions

Boceprevir and midazolam

Boceprevir is a strong inhibitor of CYP3A4. In this trial, boceprevir substantially increased the single-dose C_{max} and AUC_{0-24} of midazolam by 177% and 430%, respectively, during co-administration relative to midazolam alone. Boceprevir inhibited the metabolism of midazolam, as demonstrated by the 44% decrease in 1-OH midazolam exposures observed during co-administration with boceprevir. Furthermore, the exposures of midazolam and 1-OH-midazolam returned to baseline levels upon discontinuation of boceprevir. These results suggest that boceprevir is a strong inhibitor of CYP3A4. Therefore, clinicians should avoid co-administering boceprevir with sensitive substrates of CYP3A4. If co-administration is unavoidable, clinicians should consider reducing the dose of the sensitive substrate of CYP3A4.

Midazolam did not affect the pharmacokinetics of boceprevir during co-administration.

Boceprevir and efavirenz

Boceprevir is a substrate of CYP3A4. In this trial, efavirenz decreased the mean C_{max}, AUC_{0-8h}, and C_{min} of boceprevir by 8%, 19%, and 44%, respectively, during co-administration relative to boceprevir alone. Efavirenz is a moderate inducer of CYP3A4. Therefore, a decrease in boceprevir exposures in the presence of efavirenz was expected. It is unknown if the 44% decrease in boceprevir C_{min} will have a negative effect on the antiviral efficacy of boceprevir. Of note, efavirenz is only a moderate inducer of 3A4. Considering trial results, one may expect even lower boceprevir exposures in the presence of rifampin, a stronger inducer of CYP3A4. For this reason, clinicians should be cautious when co-administering boceprevir with strong inducers of CYP3A4. These drugs may further decrease the exposures of boceprevir; thereby, potentially decreasing the efficacy of boceprevir.

Boceprevir increased the mean C_{max} and AUC_{0-24h} of efavirenz by 11% and 20%, respectively, during co-administration relative to efavirenz alone. These results were expected because efavirenz is substrate of CYP3A4. Clinicians should be wary of potential efavirenz-induced adverse events during co-administration with boceprevir.

Boceprevir and tenofovir

Boceprevir increased the C_{max} of tenofovir by 32% during co-administration relative to tenofovir alone, but did not affect the mean AUC and renal clearance of tenofovir. The increase in C_{max} of tenofovir in the presence of boceprevir is unexpected because tenofovir does not undergo metabolism via CYP450

enzymes. Investigators speculate that boceprevir increased the C_{max} of tenofovir by inhibiting p-glycoprotein in the gut. However, *in vitro* study results suggest that boceprevir is unlikely to be a clinically relevant inhibitor of P-gp (I_u/IC_{50} < 0.1).

Other uncharacterized gut transporters (e.g. BCRP) may also have contributed to the observed increase in tenofovir's C_{max}. For instance, tenofovir is also a substrate of the renal transporters OAT1 and OAT2. However, the clearance of tenofovir remained unchanged during co-administration with boceprevir relative to tenofovir alone. These results suggest that boceprevir may not affect OAT1 and OAT2.

Tenofovir had no clinically relevant effect on the PK of boceprevir.

Overall, clinicians may co-administer boceprevir with tenofovir without dose adjustment, but should monitor the development of adverse events due to tenofovir.

Boceprevir and drospirenone/ethinyl estradiol

Boceprevir increased the mean C_{max}, AUC_{0-24h}, and C_{min} of drospirenone by 57%, 99%, and 143%, respectively, during co-administration relative to Yaz® alone. These results were expected because boceprevir is a strong inhibitor of CYP3A4, the enzyme responsible for metabolizing drospirenone. The interaction between boceprevir and drospirenone is concerning because an increase in drospirenone exposure may lead to higher incidences of hyperkalemia, cardiovascular events, nausea, and vomiting.

In contrast, boceprevir decreased the mean AUC_{0-24h} and C_{min} of ethinyl estradiol by 24% and 31%, respectively, during co-administration relative to Yaz® alone. The results were unexpected because ethinyl estradiol is a substrate of CYP3A4. However, the drug also undergoes metabolism by UGT enzymes. It is currently unknown if boceprevir is an inducer of UGT. A study conducted in neonate/juvenile rats indicated boceprevir caused some induction of UGT1A1/6 and UGT2B2, particularly in females, though the results were not consistent in all rats. The observed decrease in ethinyl estradiol may lead to breakthrough bleeding. It is not entirely clear to what extent ethinyl estradiol contributes to the contraceptive efficacy of combined oral contraceptives; thus, it is difficult to predict how a 24% decrease in exposure may affect efficacy.

The oral contraceptive was only administered for 7 days in each treatment period, without a wash-out period. According to the package insert for Yaz, drospirenone concentrations reach steady state after 8 days of dosing and EE reaches steady state during the second half of the treatment cycle. A comparison of Ctrough values from Days 7 and 8 and Days 14 and 15 indicate

that drospirenone and ethinyl estradiol reached steady state at the time of PK sampling. Therefore, the changes in exposures of drospirenone and ethinyl estradiol are likely caused by drug interactions with boceprevir, instead of insufficient time to reach steady state exposures.

Overall, investigators recommend that subjects use alternative contraceptives besides Yaz® during treatment with boceprevir. However, boceprevir may also increase the exposures of the progesterone component of other oral contraceptives (e.g. norethindrone). Thus, it may be appropriate to recommend subjects to avoid hormonal contraceptives during boceprevir treatment. Instead, subjects should use two methods of barrier contraception during treatment with boceprevir.

References

1. Sustiva® label, Bristol-Myers Squibb, 2010.
2. Midazolam HCl syrup label, Paddock laboratories, 2006.
3. Viread® label, Gilead Sciences, 2009.
4. Yaz® label, Bayer Healthcare Pharmaceuticals, 2010.

4.3 Review of *in vitro* experiments

03208 – Identification of Human Drug-Metabolizing Enzymes Responsible for the Metabolism of Boceprevir, and Further Characterization of Enzymology

Study initiated May 9, 2003 at Schering-Plough Research Institute, Kenilworth, NJ

Objective:
Identify the CYP450 enzymes capable of metabolizing boceprevir. Based on unexpected metabolic profiling of boceprevir in humans, an additional objective was added to further characterize the enzymology of boceprevir.

Methods:
^{14}C-boceprevir was incubated with cDNA-expressed recombinant human P450 enzymes or human liver microsomes (HLM) in the presence and absence of NADPH and selective inhibitors of P450 enzymes. Based on the results of an early single ascending dose trial conducted in healthy volunteers, in which M28 and M31 were detected as the major metabolites of boceprevir in plasma and urine, further exploration of enzymology was conducted with human liver subcellular fractions (S9, cytosol and mitochondria), flavin monooxygenase (FMOs) and other recombinant cytosolic enzymes. In addition, the individual isomers of boceprevir, SCH534128 and SCH534129, were incubated with human liver subcellular fractions and cytosolic enzymes.

In the metabolic profiling method used for most of the experiments in this study, M31 coeluted with SCH534128; therefore, formation of this metabolite could not be quantified. However, its presence was confirmed by LC-MS/MS. Only the human liver cytosol experiments used a modified LC-MS/MS method that separated both M28 and M31.

HLM
All test systems, including HLM, S9, cytosol, mitochondria and P450 Supersomes® were obtained from commercial sources (b) (4). Pooled HLM (1 nmol P450/mL) were incubated with 0.5, 1, 10 and 50 µM C-boceprevir for 120 min. in the presence of an NADPH-generating system and 3 mM $MgCl_2$ in potassium phosphate buffer, pH 7.4. The incubation mixture was pre-incubated for 2 min. prior to addition of drug. After 120 min. at 37 degrees C, the reaction was terminated by 0.5 mL ice-cold acetonitrile with 1% acetic acid. The mixture was then vortexed and supernatants analyzed by HPLC coupled with Flow Scintillation Analysis (FSA). Separate HLM experiments were also performed with selective inhibitors of the various P450 enzymes. HLM were pre-incubated separately with various inhibitors for 15 min. at room temperature,

followed by the addition of buffer, cofactor and substrate.

Supersomes®
Reactions with 19 human P450 Supersomes (1A1, 1A2, 2A6, 2B1, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, 4F2, 4F12, 4F3A and 4F3B) were initiated by the addition of ^{14}C-boceprevir following a 2 min. incubation. After incubation with drug for 120 min at 37 degrees C, reactions were terminated and supernatants analyzed by LC-MS/MS. Supernatants were also concentrated and analyzed by LC-MS/FSA. The level of enzyme activity in HLM and Supersomes was determined using previously described substrates as controls.

Human Liver S9/cytosol/mitochondria fractions
Incubations with S9, cytosol or mitochondria fractions were conducted with the protein (1.6 or 3.2 mg/mL) and ^{14}C-boceprevir (20 µM) for 120 min. S9 fractions were also incubated for 30 and 60 min. All incubations contained an NADPH-generating system, $MgCl_2$ and potassium phosphate buffer, pH 7.4. Reactions without NADPH were used as controls. Incubations of ^{14}C-boceprevir and SCH629144 with cytosol were conducted using various cofactors (NADH, NADP and NADPH) as well. Inhibition of ^{14}C-boceprevir was evaluated after pre-incubation with selective inhibitors of cytosolic enzymes, as outlined below:

Cytosolic Enzymes	Inhibitors Used
Carbonyl Reductase (CBR) Aldehyde Oxidase	Menadione
Carboxylesterase Amidase	bis(4-nitrophenyl) phosphate (BNPP)
Monamine Oxidase (MAO A and B)	Pargyline
Carbonyl Reductase	Quercetin
Xanthine Oxidase	Allopurinol
Aldo-keto Reductase	Flufenamic acid Mefenamic acid Phenolphthalein

Cross-species comparisons with mouse, rat, monkey and human subcellular fractions were also conducted. The results of the non-human evaluations are not described further in this review.

Aldo-Keto Reductase (AKR)
Six cell lines expressing a variety of recombinant enzymes belonging to the AKR family and a reductase were obtained from a commercial source, as follows:

3alpha-HSD type 1 (AKR1C4)
3alpha-HSD type 3 (AKR1C2)
17beta HSD type 5 (3alpha-HSD type 2 or AKR1C3)
17beta HSD type 1
17beta HSD type 2
17beta HSD type 3
5alpha-reductase type 2
Control, cells expressing the transfection vector without any enzyme

The cells were propagated in appropriate tissue culture medium supplemented with 10% fetal bovine serum, penicillin-streptomycin stock solution and Geneticin. Following growth to confluency, the cells were rinsed and collected by centrifugation and suspended in a buffer containing a cocktail of protease inhibitors and sonicated on ice to lyse the cells. The cell lysate was then centrifuged and the resultant supernatant collected as the S9. Incubations were performed with the S9 fractions and ^{14}C-boceprevir, ^{14}C-SCH534128 and ^{14}C-SCH534129 (all at 20 µM). Samples were analyzed by HLPC/FSA and confirmed by LC-MS. Inhibition experiments were also performed using various inhibitors of AKR. Inhibition studies were also conducted with selective substrates to assess the interaction potential of boceprevir.

Results:

The results of the activity determination of HLM and Supersomes using positive controls confirmed the activity of both systems. Based on preliminary experiments, a 30-min. incubation at a P450 concentration of 1 nmol/mL and substrate concentration of 20 µM was selected for ideal formation of oxidative metabolite M11.

^{14}C-boceprevir was metabolized extensively in HLM to several radioactive metabolites when incubated with NADPH, with 99% and 56% of the parent compound converted at 5 and 20 µM, respectively. No metabolite was formed in the absence of NADPH. In vitro incubation with Supersomes indicated the formation of hydroxylated metabolites via oxidation by recombinant CYP3A4 and 3A5. Characterization of metabolites formed in HLM and Supersomes demonstrated that ~100% and 43% of metabolites of boceprevir were produced by CYP3A4 at 5 and 20 µM, respectively. CYP3A5 yielded 97% and 42% of metabolites at 5 and 20 µM, respectively. The results of enzyme characterization are shown below in Table 1.

Table 1. Metabolites Formed by cDNA-Expressed Human P450 Isoenzymes

ID	Rt (min)[a]	m/z	Human Plasma Level	% Conversion (% of total radioactivity profile)									
				3A4		3A5		2D6	2C19	1A2	1A1	2B6	4F3A
				5 µM	20 µM	5 µM	20 µM	5 µM	5 µM	5 µM	5 µM	5 µM	5 µM
M1	13.7[b]	552	ND[c]	ND	0.33	2.68	ND	ND	ND	ND	ND	ND	ND
M2	14.3[b]	552	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M3	16.2	554	Trace[d]	5.20	ND	ND	ND	ND	ND	ND	ND	ND	ND
M4	16.6	368	Trace	4.57	0.58	2.22	<0.81	ND	0.29	0.29	0.33	0.22	0.24
M5	17.6	552	Trace	3.81	0.80	0.90	ND	ND	ND	ND	ND	ND	ND
M6	17.6	554	Trace	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M7	18.3	538	Trace	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M8	19.2	538	Trace	ND	ND	ND	ND	ND	0.49	ND	ND	ND	ND
M9	19.7	552	Trace	4.99	1.59	3.01	ND	ND	ND	ND	ND	ND	ND
M10	20.2	554	Trace	ND	5.35	ND	ND	ND	ND	ND	ND	ND	ND
M11 (SCH 641574)	20.3	536	Trace	1.12		21.32	10.67	2.74	ND	ND	ND	ND	ND
M13	21.3	538	Trace	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M14	21.7	552	Trace	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M15	22.2	367	Minor[e]	<3.45	<4.64	15.74	2.87	1.90	ND	1.37	2.90	2.06	0.61
M16 (SCH 641574)	22.5	536	Trace						ND	ND	ND	ND	ND
M17	22.6	538	Trace	ND		ND	ND	ND	ND	ND	ND	ND	ND
M18	22.9	552	Trace	3.24	ND	1.32	ND	ND	ND	ND	ND	ND	ND
M19	24.1	538	Trace	ND	ND	ND	ND	ND	0.11	ND	ND	ND	ND
M20	25.5	552	Trace	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M21	26.9	536	Trace	0.32	<4.56	15.34	9.38	ND	ND	ND	ND	ND	ND
M22	27.2	538	Minor	ND	ND	ND	ND	ND	0.83	ND	ND	ND	ND
M23 (SCH 564649)	29.9	536	Minor	1.12	<7.99	<7.94	<6.02	0.38	ND	ND	ND	ND	ND
M24 (SCH 564649)	33.1	536	Minor	0.25	1.27	6.96	2.39	ND	ND	ND	ND	ND	ND
M25	34.2	536	Trace	ND	ND	0.82	0.25	ND	ND	ND	ND	ND	ND
M26	36.1	580	Trace	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M27	38.2	580	Trace	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M28 (SCH 629144)	40.1	522	Major[f]	ND	BIT[g]	ND	BIT	0.56	0.38	0.34	0.57	0.90	1.78
M29	40.5	580	Trace	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M30[h] (SCH 629144)	41.2	522	Major	ND	ND	ND	BIT	ND	ND	ND	ND	ND	ND
SCH 503034	42.8	520	Major	BIT	37.98	0.98	38.77	57.22	60.30	59.66	56.46	56.54	57.31
M31[i] (SCH 629144)	43.1	522	Major	ND	(M31 is minor)	ND	ND	ND	ND	ND	ND	ND	ND
SCH 503034	44.6	520	Major	BIT	18.98	2.19	19.67	31.66	30.71	31.72	33.40	33.77	34.35
M32	48.8	463	Trace	ND	0.97	0.11	0.88	ND	1.06	2.18	2.32	1.29	0.65
Sum				28.07	<85.04	81.53	91.71	94.46	94.17	95.56	94.98	94.78	94.94
Sum of SCH 503034 Left				BIT	56.96	3.17	58.44	88.88	91.01	91.38	88.86	90.31	91.66

a: Unless otherwise noted, retention times were taken from P02727 Metabolite Profiling Report (Table 1).

b: Retention time was taken from P02727 Metabolite Profiling Report (Table 2).

c: ND = Not detected.

d: Trace is defined as the percent ratio of XIC area for the metabolites (all known isomers) to that for parent (two isomers) is ≤10%.

e: Minor is defined as the percent ratio of XIC area for the metabolites (all known isomers) to that for parent (two isomers) is between 10-50%.

f: Major is defined as the percent ratio of XIC area for the metabolites (all known isomers) to that for parent (two isomers) is ≥50%.

g: BIT = Below integration threshold of radiometric detector, but detected by mass spectrometer.

h: Although SCH 629144 (3 diastereomers, M28, M30 and M31, combined) is a major circulating metabolite in human plasma, the level of M30 is the lowest of the 3 diastereomers.

i: If M31 (SCH 629144) was detected, it co-eluted with the 2nd diastereomer of SCH 503034.

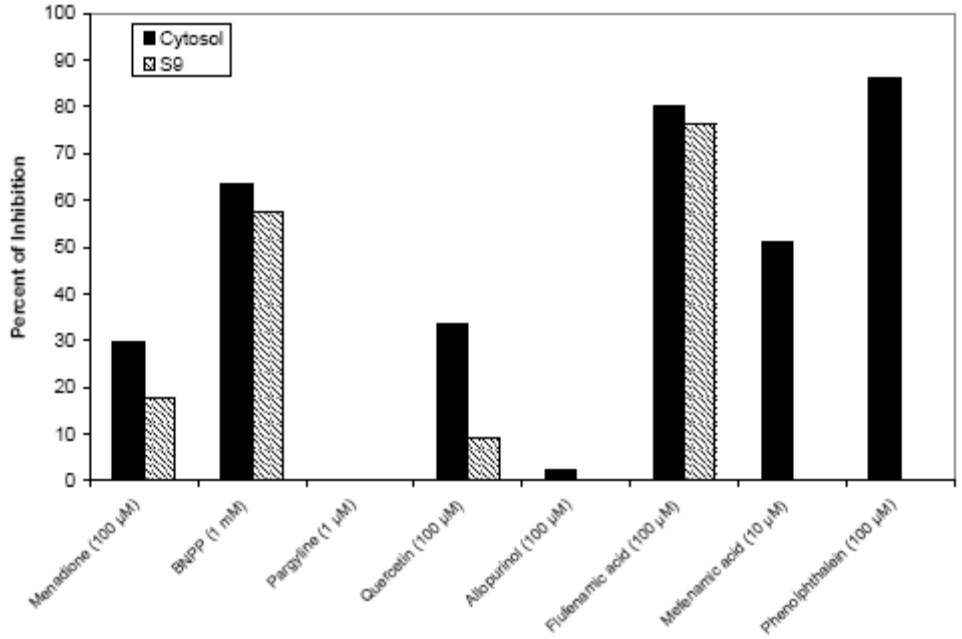
Results of incubation of HLM with chemical inhibitors indicated ketoconazole and azamulin, both potent CYP3A4/5 inhibitors, inhibited formation of major oxidative metabolites of boceprevir . Ketoconazole (2 µM) inhibited formation of M11 by 40%, M14/15/16 by 61%, M21 by 44% and M23 by 51%. Ritonavir also inhibited boceprevir metabolism (~100%) at 2 µM. Inhibition of other P450 enzymes indicated no inhibition of boceprevir metabolism.

Studies in human liver subcellular fractions evaluating the enzymology of M28

(SCH629144 diastereomer) indicated the greatest enzyme activity results from studies in liver S9 and cytosol fractions in the presence of an NADPH system. The major metabolites formed were M28 and M31 (diastereomers of SCH629144), also the primary circulating metabolites in humans. The effect of cofactors on the potential conversion of SCH629144 back to the parent was explored; however, no significant back-conversion was detected.

The relative contribution of AKRs and carbonyl reductase (CBR) to boceprevir metabolism were determined using known chemical inhibitors and the S9 and cytosol fractions (Figure 1). The results showed menadione (CBR and aldehyde oxidase inhibitor) inhibited M28 formation by 30 and 18% in human cytosol and S9 fractions, respectively. Similarly, quercetin (CBR inhibitor) inhibition M28 formation by 33 and 9% in cytosol and S9, respectively. Pargyline (MAO-A/B inhibitor) and allopurinol (xanthine oxidase inhibitor) showed no inhibition. Flufenamic acid (selective AKR inhibitor) inhibited M28 formation by 80 and 77% in cytosol and S9, respectively, indicating the likely involvement of AKRs in boceprevir metabolism. Similarly, phenolphthalein and mefenamic acid (both AKR-selective inhibitors) inhibited M28 formation.

Figure 1. Effect of Inhibitors of Cytosolic Enzymes on the Formation of M28 from Boceprevir (20 µM) in Human Liver S9 and Cytosolic Fractions



The formation of M28 and M31 was evaluated using various concentrations of boceprevir (0.5 to 20 µM) in human liver cytosol. The Km for M28 and M31 were determined to be 13.0 and 12.5 µM, respectively. The Vmax/Km values of M28 (2.2) and M31 (2.8) suggest that the intrinsic clearance of the two metabolites are similar. Thus, the biotransformation of boceprevir to each metabolite would be

expected to be similar. When the intrinsic clearance of each boceprevir diastereomer was evaluated separately, the Vmax/Km for M31 formation from SCH534129 (30.9) was higher than that of M28 formation from SCH534128 (10.2), indicating the clearance of SCH534129 may be faster than SCH534128 in humans. Human jejunum cytosol was also evaluated and found to generate M28 (9.5%) from boceprevir.

Results from the recombinant AKR experiments showed that both AKR1C2 and AKR1C3 generated M28 and M31. AKR1C4 was not involved in the formation of either metabolite. AKR1C3 preferentially metabolized SCH534128, the active isomer, while AKR1C2 preferentially metabolized SCH534129, the inactive isomer. Furthermore, the intrinsic clearance estimate for formation of M28 was higher for AKR1C3 than for AKR1C2, suggesting that AKR1C3 may be the preferred biotransformation pathway for the formation of M28 in human liver cytosol.

Incubation of boceprevir with various inhibitors of AKR in pooled human cytosol indicated diazepam, phenolphthalein, and flufenamic acid were all potent inhibitors of the formation of M28 in cytosol at 100 µM (Table 2). Ibuprofen inhibited formation by 70% at 1 mM. Midazolam, flunitrazepam and nirazepam inhibited M28 formation to a lesser extent. CYP3A inhibitors ketoconazole and ritonavir had no effect on M28 formation. Naproxen (100 µM) and celecoxib (50 µM) also inhibited M28 formation by 45 and 21%, respectively.

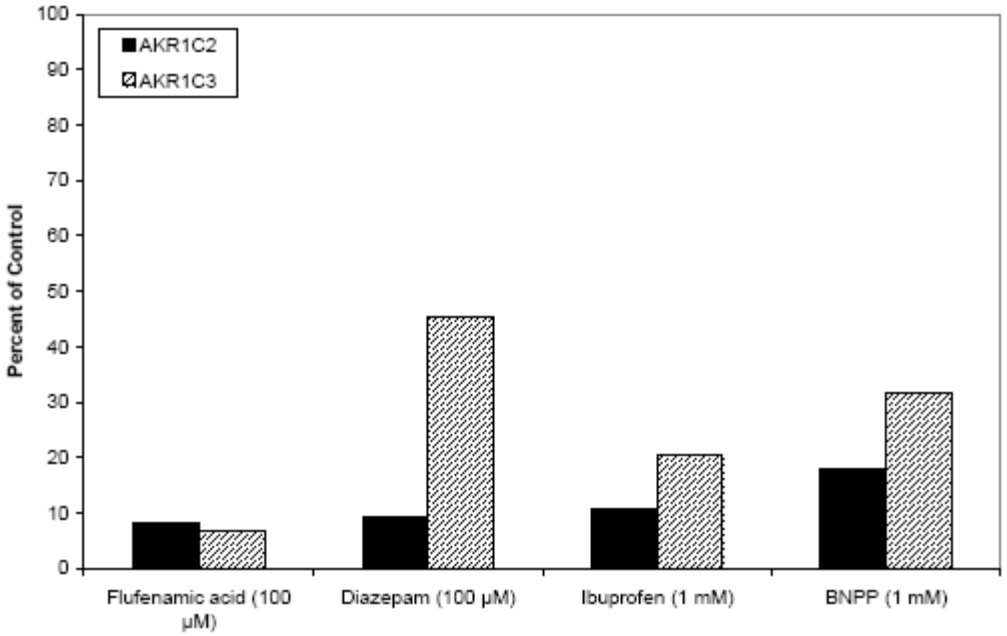
Table 2. Effect of Inhibition of the Formation of M28 from Boceprevir (20 µM) Using Pooled Human Liver Cytosol (1.6 mg/mL)

Inhibitors	Conc (μM)	% of Inhibition
Diazepam	2	15.7
	10	40.3[a]
	100	75.1
Ibuprofen	50	31.3
	100	33.4
	1000	70
Ibuprofen[b]	100	25.9
Diazepam + Ibuprofen[b]	10 + 100	43.7
Midazolam	60	37
Flunitrazepam	60	51
Nitrazepam	50	24
Celecoxib	50	20.5
Naproxen	100	44.7
Ribavirin	10	1.76
	30	0
Ketoconazole	2	0
Ritonavir (coincubation)	2	0
Ritonavir (preincubation)	2	0
Indomethacin	100	19
Gemfibrozil	100	27.4
Phenobarbital	100	0
Testosterone	40	48.2

a: Average of duplicate determinations
b: Experiments done on the same day

The effect of inhibitors on the formation of M28 in recombinant AKR enzymes showed that flufenamic acid, diazepam and ibuprofen are potent inhibitors of AKR1C2, while flufenamic acid and ibuprofen are also potent inhibitors of AKR1C3 (Figure 2).

Figure 2. Effect of AKR Inhibitors on the Formation of M28 from Boceprevir via AKR1C2 and 1C3



Incubation of SCH534128 and SCH534129 with human plasma, plasma ultrafiltrate, boiled plasma and buffer showed some conversion with all matrices at all incubation durations (Table 3). The conversion of SCH534129 to SCH534128 was faster than the reverse in plasma (12.6% at 10 min. and 55% at 120 min.). Interconversion of the two isomers in boiled plasma and plasma ultrafiltrate suggests no enzymes are involved in the interconversion. In plasma, equilibrium appears to be reached at a SCH534128:SCH534129 ratio of ~1.5:1.

Table 3. Time-Dependent Inter-Conversion of SCH534128 and SCH534129 in Human Plasma, Ultrafiltrate, Boiled Plasma and Buffer (PBS)

Matrix Time (min) Conversion	Percent of Profiled Radioactivity											
	10		30		60		120		180		240	
	128[a]	129[b]	128	129	128	129	128	129	128	129	128	129
Plasma (fresh)												
SCH 534128	100	0	75.44	17.78	64.90	29.49	60.69	34.02	61.76	38.24	57.92	37.35
SCH 534129	12.65	82.07	23.68	72.18	37.94	57.05	54.78	39.21	56.88	37.77	57.58	36.43
Plasma Ultrafiltrate												
SCH 534128	86.74	13.26	87.61	10.68	83.65	16.35	72.16	27.84	64.59	35.41	58.87	41.13
SCH 534129	7.39	92.61	11.03	88.97	17.62	82.38	29.84	70.16	40.67	59.33	51.34	48.66
Boiled Plasma												
SCH 534128	86.02	10.68	82.43	13.67	76.56	18.95	66.75	29.52	59.26	36.59	57.82	38.58
SCH 534129	8.06	89.14	10.39	87.42	18.97	79.18	31.74	62.63	42.25	54.28	47.53	49.33
PBS (pH 7.4)												
SCH 534128	89.07	10.93	89.08	10.91	88.69	11.31	88.00	12.00	83.45	14.10	82.76	13.32
SCH 534129	0	100	0	100	5.16	94.85	7.02	92.98	7.29	92.76	8.26	88.92

SCH 534128/534129 conc. = 2 µM; 50 µL injected on HPLC
a: SCH 534128
b: SCH 534129

Conclusions

The results of this study indicate CYP3A4 and CYP3A5 are responsible for

producing a large number of minor oxidative metabolites from boceprevir. Ketoconazole (2 μM) inhibited the formation of oxidative metabolites by 40-63%. The two primary circulating metabolites in humans, M28 and M31, are preferentially formed by AKR1C3 and AKR1C2, respectively. The formation of M28 was inhibited by 100 μM of flufenamic acid (80.3%) and phenolphthalein (86.1%), known inhibitors of AKR (cytosolic enzyme), suggesting its formation is through the carbonyl reduction pathway. Formation of M28 was also inhibited by 100 μM diazepam (75.1%) and 1 mM of ibuprofen (70%).

The conversion of SCH534129 to SCH534128 was faster than the reverse in plasma (12.6% at 10 min. and 55% at 120 min.). Interconversion appears to be independent of enzyme activity. In plasma, equilibrium appears to be reached at a SCH534128:SCH534129 ratio of ~1.5:1.

DM27292 – Effect of COX-2 Inhibitors and Other Compounds on the Formation of SCH629144 from SCH503034 (Boceprevir)

Study initiated February 21, 2006 at Schering-Plough Research Labs

Objective:
Identify inhibitors of SCH629144 formation from SCH503034 (boceprevir), for the purposes of identifying potential PK "boosters"

Methods:
This was a non-GLP study in which radiolabeled boceprevir was incubated in pooled human liver microsomes/S9/cytosol and monkey liver S9/cytosol in the absence and presence of various metabolic inhibitors. The formation of SCH629144 (M28) was monitored as a surrogate for aldo-keto reductase (AKR) activity.

Human Liver Microsomes (HLM), pooled human liver S9 fractions and pooled human liver cytosol were all obtained from a commercial source and each included a pool from 50 individuals of mixed gender. CYP450 activity of the HLM was confirmed by the provider using marker substrate reactions.

Pooled HLM (1 nmol P450/mL) were pre-incubated with various inhibitors of CYP3A4 and AKR, including NSAIDs, ketoconazole, ritonavir and other Schering compounds, followed by the addition of buffer, cofactor and substrate (20 µM of ^{14}C-boceprevir, 20 µCi/mg). All incubation mixtures contained 3 mM $MgCl_2$ in 100 mM potassium phosphate buffer, pH 7.4 and an NADPH-generating system. The incubation mixture was warmed for 2 min. at 37 degrees C, followed by the addition of boceprevir and termination of the reaction 30 min. later by the addition of 0.5 mL ice-cold acetonitrile with 1% acetic acid. The incubation mixture was then vortexed and centrifuged for 15 min. and the supernatants analyzed by HPLC coupled with Flow Scintillation Analysis (FSA). HLM incubations without NADPH served as negative controls.

Human liver S9 fractions and pooled cytosol (3.2 mg and 1.6 mg protein/mL, respectively) were each pre-incubated with various metabolic inhibitors for 15 min. at room temperature followed by the addition of buffer, cofactor and substrate (20 µM ^{14}C-boceprevir). All incubations followed the methods used for HLM. Reactions were initiated by addition of boceprevir, allowed to proceed for 60 min. at 37 degrees C, and then terminated with ice-cold acetonitrile. Incubations mixtures were vortexed and centrifuged and the supernatants analyzed by HPLC/FSA.

Results:
The formation of oxidative metabolites was inhibited in HLM by the potent CYP3A4 inhibitors ritonavir and ketoconazole (Table 1). Acetaminophen showed no inhibition. Although diflunisal was a potent inhibitor of AKR-mediated

formation of SCH629144, there was no inhibition of oxidative metabolites, suggesting no inhibition of CYP3A4.

Table 1 Effect of GRAS Compounds and Other Inhibitors on the Formation of Oxidative Metabolites From [14C]-SCH 503034 in Human Liver Microsomes

GRAS Compounds	Concentration (μM)	% Inhibition
BAS-100	1	91.2
	2	100
	5	100
	10	100
Ketoconazole	2	69.7
	5	92.2
Ritonavir	1	100
	2	100
	5	100
Ascorbyl Palmitate[a]	5	8.7
	50	13.6
Gallic Acid Propylester[a]	5	1.11
	50	5.20
Diflunisal (Dolobid®)	200	4.58
Naringin	100	5.09
	500	15.2
Naringenin	100	34.1
	500	77.8
Acetaminophen	100	7.70
	500	7.70
Bergamottin	10	47.7
	50	96.0
	100	100

a: GRAS compound
Vehicle control = Methanol
Average of duplicate determinations.
SCH 629144 was not detected in Human liver microsomes.

The results of the inhibition studies with NSAIDs and other potential AKR inhibitors are summarized in Table 2. The results indicate the formation of SCH629144 was inhibited most potently as follows, based on IC_{50} values: diclofenac > diflunisal > mefenamic acid > meclofenamate > oxaprozin > naproxen > nabumetone = ibuprofen. The lowest IC_{50} value was 3.43 μM for diclofenac, followed by 4.58 μM for diflunisal.

The effect of other potential inhibitors is summarized in Table 3. Diflunisal was used as a positive control. The inhibition potential of these compounds were ranked as follows: rhein (67% at 100 μM) > acetohexamide (58% at 500 μM > probenecid (45% at 100 μM) > ethacrynic acid (39.8% at 100 μM) > benzophenone (39.6% at 100 μM). None of the inhibitors was as effective as diflunisal at preventing SCH629144 formation.

Table 2 Effect of NSAIDs on SCH 629144 Formation From SCH 503034 (20 µM) using Pooled Human Liver Cytosol (1.6 mg/mL, 1h Incubation)

Generic Name	Trade Name	Conc (µM)	% of Inhibition (IC50)
Acetaminophen	Tylenol	146	0
Aspirin (Acetylsalicylic Acid)	Aspirin	200 500	18.4 43.7
Diclofenac	Voltaren, Cataflam, Arthrotec	7	57.3 (3.43 µM)
Diflunisal	Dolobid	200 500	89.4 (4.58 µM) 100
Etodolac	Lodine	100	3.74
Fenbufen	Lederfen	100	17.6
Fenoprofen	Nalfon, Progesic	80	14.2
Flurbiprofen	Ansaid	50	31.6
Ibuprofen[a]	Motrin, Advil	50 100 200	31.3 33.4 42.6 (411.8 µM)
Indoprofen	Flosint	100	13
Ketoprofen	Oruvail	10	0
Ketorolac	Toradol	4	0
Meclofenamate	Meclomen	50	76 (8.12 µM)
Mefenamic Acid[a]	Ponstel	1 10	14.6 (6.06 µM) 51.1
Meloxicam	Mobic	6	2.46
Nabumetone	Relafen, Relifex	200	42.4 (>200 µM)
Naproxen	Naprosyn, Aleve	100	44.7 (267.9 µM)
Nimesulide	NICE, Nimulid	500	38.8
Oxaprozin	Daypro	200 500	56.3 (90.7 µM) 76.1
Piroxicam	Feldene	25	0
Phenacetin	Phenacetin	10	0
Phenylbutazone	Butazolidin	200	8
Salsalate	Disalcid	100	25
Sulindac	Clinoril	30	19
Tenoxicam	Tilcotil	50	0
Tolmetin	Tolectin	125	2.14
Naringenin	-	500	86.7 (21.8 µM)
Bergamottin	-	100	9.8
Cinnamic Acid	-	50	5.9

a: Data from SN 03208[7]

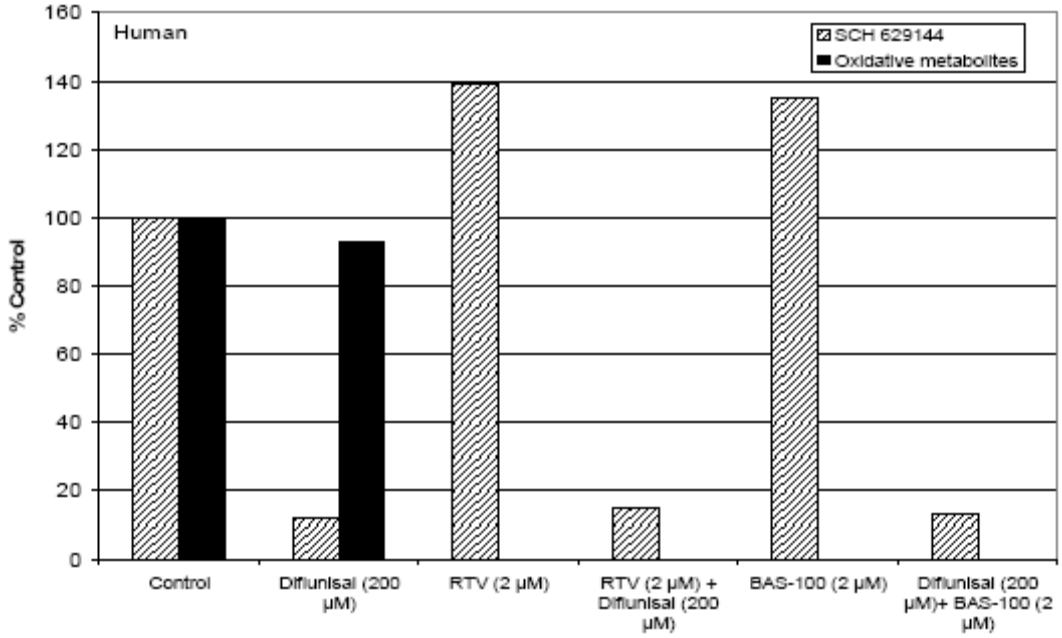
Table 3 Effect of Potential Inhibitors on the Formation of SCH 629144 Following Incubation of [14C]-SCH 503034 (20 µM) With Human Liver Cytosol (1.6 mg protein/ml) for 60 min

Name	MW	Indication	Conc (µM)	% Inhibition (IC50)
Acetohexamide	324.43	Anti-Diabetes	500	58.1
Astemizole (Hismanal)	458.6	Antihistamine	100	0
Benzophenone	182.22	-	100	39.6
Bupropion	239.74	Antidepressant	100	0.54
Butylparaben	194.23	Antifungal	100	34.1
Cimetidine[a] (Tagamet®)	252.34	Antacid	500	3.5
Chlorzoxazone	169.56	Analgesic	100	12.7
Dicoumarol	336.3	Anticoagulant	30	8.7
Diflunisal (Dolobid®)	250.2	NSAID	200	89.4 (4.58 µM)
Doxycycline	462.46	Antibiotic	6.5	0
17β-Estradiol	272.39	Hormone Therapy	100	15.9
Ethacrynic Acid (Edecrin®)	303.14	Diuretic	50, 100	24.4, 39.8
Furosemide (Lasix®)	330.75	Diuretic	60	14
Isoniazid	137.14	Antibacterial	36	0
Loperamide	513.5	Anti-Diarrheal	10	0
Lycopene	536.88	-	5	2.49
Mebendazole (Vermox®)	295.30	Anthelmintic	10	0
Niclosamide	327.12	Anthelmintic	100	10.6
Nicotinamide (Niacinamide)	122.13	Vitamin B-Complex	100	0
Nicorandil	211.18	Antianginal	100	4.3
Orphenadrine	269.38	Analgesic	100	1.13
Probenecid (Benemid®)	285.36	Uricosuric Agent	100	45.4
Quinidine	324.44	Antiarrhythmic	100	0
Rhein	284.22	Anti-Inflammatory	100	67 (37.1 µM)
Rutin	664.6	Capillary Protectant	10	0.05
Sulfaphenazole	314.4	Anti-Infective	100	0.7
Tetracycline	444.44	Antibiotic	10	0
Thymolphthalein	430.54	pH Indicator	100	0
Tolperisone	245.36	Muscle Relaxant	100	2.24

a: Human liver S9 was used instead of cytosol.

Ketoconazole, ritonavir and BAS-100 effectively inhibited production of oxidative metabolites in human liver S9 fractions (Figure 1). Diflunisal inhibited the formation of SCH629144 by 88% at a concentration of 200 µM. The combination of ritonavir with diflunisal or BAS-100 with diflunisal showed maximal inhibition of formation of all metabolites (oxidative and SCH629144). Ritonavir and BAS-100 increased the formation of SCH629144 when incubated alone with liver S9 fractions.

Figure 1. Effect of Diflunisal, Ritonavir and/or BAS-100 on the formation of SCH629144 and Oxidative Metabolites in Human Liver S9



Conclusions:

BAS-100, ketoconazole and ritonavir were potent inhibitors of oxidative metabolism of boceprevir in HLM. Diflunisal was a potent inhibitor of SCH629144 formation mediated by AKR, but did not inhibit the formation of oxidative metabolites. Among the various NSAIDs and other AKR inhibitors screened, the lowest IC_{50} values were 3.43 µM for diclofenac and 4.58 µM for diflunisal. These values compare to a Cmax value of ~2 mcg/mL (6.3 µM) for diclofenac, 75 mg and 87 µg/mL (348 µM) for diflunisal, 500 mg. Thus, diflunisal has the highest I/IC_{50} ratio of the AKR inhibitors screened. The combination of diflunisal and ritonavir showed maximal inhibition of formation of both oxidative metabolites and SCH629144 in human liver S9 fractions. Ritonavir increased the formation of SCH629144 when incubated alone with liver S9 fractions, indicating potential induction of AKR-mediated metabolism.

DM27352 – In Vitro Study to Evaluate the Ability of SCH503034 (Boceprevir) to Inhibit the Major CYP Enzymes in Human Liver Microsomes (HLM)

Study initiated on August 11, 2006 and conducted by XenoTech, LLC.

Objective:
To evaluate the ability of boceprevir to inhibit the major CYP Enzymes in HLM

Methods:
HLM from a pool of 16 mixed-gender individuals were incubated with marker substrates, at concentrations approximately equal to their Km in the absence and presence of boceprevir. The target concentration of boceprevir ranged from 0.1 to 100 µM. In addition, boceprevir was evaluated for its ability to produce time-dependent inhibition at the same range of concentrations. For time-dependency studies, boceprevir was pre-incubated with HLM and an NADPH-generating system 30 min. prior to adding the substrates to allow for generation of metabolites that could inhibit CYP activity. Known direct and metabolism-dependent inhibitors were included as positive controls. The following controls substrate reactions were assessed:

CYP1A2	Phenacetin *O*-deethylation
CYP2A6	Coumarin 7-hydroxylation
CYP2B6	Bupropion hydroxylation
CYP2C8	Amodiaquine *N*-dealkylation
CYP2C9	Diclofenac 4´-hydroxylation
CYP2C19	*S*-Mephenytoin 4´-hydroxylation
CYP2D6	Dextromethorphan *O*-demethylation
CYP2E1	Chlorzoxazone 6-hydroxylation
CYP3A4/5	Testosterone 6β-hydroxylation
CYP3A4/5	Midazolam 1´-hydroxylation

To further evaluate boceprevir as a direct inhibitor of CYP3A4/5 (using midazolam 1'-hydroxylation), HLM were incubated with the marker substrate at a range of concentrations, from Km/3 to 10xKm in the presence or absence of boceprevir to determine the Ki value. A known direct inhibitor was included as a control. Further experiments evaluated the effect without NADPH and with different levels of dilution. In addition, attempts were made to determine if a metabolite-inhibitory complex was formed using HLM from 1 individual with high CYP3A4/5 activity by performing spectrophotometric scans every minute for a total of 15 min. Trolandomycin (25 µM) served as a positive control using the same procedures.

All stock solutions and dilution solutions of boceprevir were prepared fresh each day of the experiments. In general, all incubations were conducted with potassium phosphate buffer (pH 7.4), $MgCl_2$, EDTA, an NADPH-generating system and marker substrate at the final concentration indicated. All incubations

were conducted at 37 degrees C. Concentrations of marker substrates were selected based on Km estimates obtained previously. Reactions were terminated by the addition of acetonitrile. Samples were then centrifuged and supernatants evaluated by validated LC/MS/MS methods. Spectrophotometric scans to determine if boceprevir forms an inhibitory complex were performed using a UV/Vis dual beam spectrophotometer.

IC_{50} results were determined using nonlinear regression with XLfit (v. 3.0) to fit the data to a sigmoidal-logistic IC_{50} equation. When an IC50 value fell outside of the concentration tested, the IC50 was reported to be greater than the highest concentration of boceprevir tested. All datasets (all concentrations of boceprevir at all marker concentrations) were fit to Michaelis-Menten equations for competitive, non-competitive, uncompetitive and mixed (competitive and non-) by nonlinear regression analysis. Goodness-of-fit was determined by the lowest reduced chi-square value.

Results:

In all cases the positive control inhibitor demonstrated inhibition of enzyme activity, including the metabolism-dependent inhibitors. Boceprevir caused direct inhibition of CYP3A4/5 (as assessed by midazolam 1'-hydroxylation) with an IC_{50} of 11 µM. There was also evidence of direct inhibition of CYP1A2, 2A6, 2C8, 2C19, 2D6 and 3A4/5 (as assessed by testosterone 6β-hydroxylation); however, all IC_{50} values were > 100 µM for these enzymes. There was no inhibition of CYP2B6, 2C9 or 2E1. In the time-dependency experiments, boceprevir caused no time-dependent inhibition for any of the CYP450 enzymes evaluated, except for CYP3A4/5. Boceprevir exhibited time-dependent inhibition of CYP3A4/5 using both midazolam and testosterone as marker substrates.

Boceprevir was observed to be a competitive inhibitor. A Ki of 7.7 µM was determined for inhibition of CYP3A4/5 (using midazolam hydroxylation). Further evaluation indicated that the increase in inhibition with pre-incubation did require NADPH and was not resistant to dilution. This indicates that a metabolite of boceprevir may be a more potent direct inhibitor of CYP3A4/5 than boceprevir itself. Boceprevir did not appear to form a metabolite inhibitory complex with the individual HLM sample containing high levels of CYP3A4/5.

Table 1. Summary of Results for In Vitro Inhibitory Experiments with Boceprevir in HLM

Enzyme	CYP Reaction	Direct inhibition				Time-dependent inhibition		
		Zero-minute Pre-Incubation				30-minute Pre-Incubation		
		IC_{50} (µM)	Maximum Inhibition at 100 µM (%)[a]	K_I (µM)	Type of Inhibition	IC_{50} (µM)	Maximum Inhibition at 100 µM (%)[a]	Potential for Time-Dependent Inhibition[b]
CYP1A2	Phenacetin *O*-deethylation	>100	22	ND	ND	>100	9.8	little or no
CYP2A6	Coumarin 7-hydroxylation	>100	20	ND	ND	>100	7.8	little or no
CYP2B6	Bupropion hydroxylation	>100	2.3	ND	ND	>100	6.9	little or no
CYP2C8	Amodiaquine *N*-dealkylation	>100	25	ND	ND	>100	NA	little or no
CYP2C9	Diclofenac 4´-hydroxylation	>100	3.6	ND	ND	>100	NA	little or no
CYP2C19	S-Mephenytoin 4´-hydroxylation	>100	25	ND	ND	>100	14	little or no
CYP2D6	Dextromethorphan *O*-demethylation	>100	45	ND	ND	>100	30	little or no
CYP2E1	Chlorzoxazone 6-hydroxylation	>100	NA	ND	ND	>100	NA	little or no
CYP3A4/5	Testosterone 6β-hydroxylation	>100	41	ND	ND	2.3	95	yes[c]
CYP3A4/5	Midazolam 1´-hydroxylation	11	91	7.7	competitive	0.97	99	yes[c]

Notes: Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values. IC_{50} values were calculated with XLfit.

a: Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article for which usable data were collected (results are rounded to two significant figures): Maximum inhibition (%) = 100% - Percent solvent control

b: Time-dependent inhibition was determined by comparison of IC_{50} values with and without pre-incubation, by comparison of the maximum inhibition (%) with and without pre-incubation and by visual inspection of the IC_{50} plot.

c: Upon further investigation, the increase in inhibition upon pre-incubation is dependent on NADPH and is not resistant to dilution.

ND = Not determined

NA = Not applicable. No value was obtained as the rates at the highest concentration of SCH 503034 evaluated (100 µM) were higher than the control rates.

Conclusions:

Boceprevir caused direct inhibition of CYP3A4/5 (as assessed using midazolam hydroxylation) with an IC_{50} value of 11 µM. There was no direct inhibition or very little observed (IC_{50} > 100 µM) for any other P450 enzyme, including CYP3A4/5 (as measured with testosterone hydroxylation). Boceprevir was observed to be a competitive inhibitor of CYP3A4/5 (as assessed using midazolam hydroxylation), with a Ki value of 7.7 µM. This value compares to a plasma Cmax value of ~1.9 µg/mL (3.7 µM) at the therapeutic dose of 800 mg, suggesting clinically relevant inhibition of CYP3A4/5 is likely. Time-dependent inhibition was observed with a NADPH-generating system. Boceprevir does not appear to form a metabolite inhibitory complex.

DM27866 – Evaluation of SCH503034 (Boceprevir) as a Substrate and/or Inhibitor of the MDR1 Transporter (P-glycoprotein) Using Caco-2 Bi-directional Permeability Assay

Study report February 16, 2010, performed at Schering-Research Institute, Kenilworth, NJ

Objective:
To investigate whether boceprevir is a substrate and/or inhibitor of MDR1 (P-glycoprotein, P-gp) using a Caco-2 assay

Methods:
Caco-2 cells were obtained from a commercial source and maintained in an incubated Dulbecco's Modified Eagle Medium containing fetal bovine serum (FBS), non-essential amino acids, L-glutamine and penicillin-streptomycin. Cell growth was confirmed by light microscopy. Following growth to confluence, the cells were seeded to a cell culture plate for the transport studies. Concentration of cells in suspension was adjusted with medium to maintain a density of 60,000 cells per cm^2 in a total volume of 0.5 mL on each insert of the 24-well plate. Cell membranes were grown for 21-28 days before conducting the experiments.

The cell batch used for substrate studies with boceprevir was tested using control substances, ^{3}H-digoxin, ^{3}H-propranolol and ^{14}C-mannitol. The transport buffer was Hanks Balanced Salt Solution with glucose. Cells were washed twice with the transport buffer and transepithelial electrical resistance (TEER) of each monolayer was measured before the addition of test articles. For apical (AP) to basolateral (BL) transport, 0.42 mL dosing solution was added to the AP side and 1.0 mL transport buffer was added to the BL side. For the converse, 1.02 mL dosing solution was added to the BL side and 0.4 mL transport buffer was added to the AP side. Caco-2 plates were then incubated at 37 degrees C with humidity for 2 hrs with shaking. Each determination was performed in triplicate. Samples were removed from the receiver compartment at 2 hrs and from the donor compartment at 1 and 2 hrs. At the end of the 2 hr incubation, the TEER values were again measured. The cells were then rinsed with transport buffer and Lucifer yellow was added to the AP side and re-incubated for another hour for post-experiment determination of permeability. Following the Lucifer yellow determination, TEER was again measured.

The bidirectional permeability of boceprevir was measured at 5, 10, 50, 100, 250 and 500 µM concentrations to assess efflux potential. To assess whether it is a substrate, 5 µM boceprevir was added along with three P-gp inhibitors, including cyclosporine (CsA) (10 µM), ketoconazole (50 µM), and ritonavir (50 µM), with the same concentration of inhibitor added to the receiver side. The permeability of digoxin was also measured with and without each inhibitor in parallel wells. To assess boceprevir as a potential inhibitor, multiple concentrations of boceprevir

were incubated with digoxin, using the same incubation and sampling procedures. CsA was used as a positive control. All radioactivity was measured using Liquid Scintillation Analysis (LSA).

Apparent permeability, recovery and efflux ratios were calculated as follows:

$$P_{app}\,(nm/s) = \frac{dM/dt}{S * C_0} = \frac{dC_R/dt * V_R}{S * C_0} * 10^7$$

$$\text{Efflux Ratio} = \frac{P_{app\_BL \rightarrow AP}}{P_{app\_AP \rightarrow BL}}$$

$$\text{Total Recovery } (\%) = \frac{C_{D,final}}{C_0} \times 100 + \frac{\text{Receiver Accumulated Amount}}{C_0 * V_D} \times 100$$

Where:

dCR/dt: The slope of the accumulative concentration in the receiver compartment versus time incubation ($\mu M \cdot s^{-1}$)
C0hr: Donor concentration (μM) immediately after dosing
CD, final: Donor concentration (μM) at the end of incubation
S: Membrane surface area (cm^2)
VD: Volume of donor compartment (mL)
VR: Volume of receiver compartment (mL)
Papp_BL→AP: Apparent permeability from BL to AP transport
Papp_AP→BL: Apparent permeability from AP to BL transport

The IC_{50} values for digoxin efflux inhibition by boceprevir were determined using nonlinear regression using the Hill equation.

Reviewer's Comment: Investigators did not assess the individual boceprevir diasteriomers, SCH534128 and SCH534129; therefore, the relative affinity or inhibition potential of each diasteriomers cannot be commented on.

Results:

Membrane integrity was confirmed by TEER values before and after the experiments; the permeability of mannitol was low (≤20 nm/s) and the transport of digoxin was appropriate (efflux ratio 6). The post-experiment permeability of Lucifer yellow was within acceptable range.

A concentration-dependent efflux of boceprevir was observed, with the efflux ratio decreasing to < 2 when the concentration increased to 500 μM, indicating saturable efflux. Boceprevir efflux was almost completely inhibited by all three of the P-gp inhibitors tested (efflux ratio <2), also indicating boceprevir is a P-gp substrate.

Table 1. Mean Caco-2 Bi-Directional Permeability of Boceprevir With and Without P-gp Inhibitors

Dosing Solution	Parameters	P_{app} _AP to BL (nm/s)			Recovery _AP to BL (%)			P_{app} _BL to AP (nm/s)			Recovery _BL to AP (%)			Efflux Ratio
	Analyte	Mean[a]	SD	CV	Mean[a]	SD	CV	Mean[a]	SD	CV	Mean[a]	SD	CV	
SCH 503034_5 µM	SCH 503034	10	1	12%	95	23	24%	161	21	13%	103	3	3%	15.3
SCH 503034_10 µM	SCH 503034	9	2	18%	109	1	1%	153	20	13%	111	12	11%	16.9
SCH 503034_50 µM	SCH 503034	16	2	15%	119	12	10%	147	9	6%	91	8	8%	9.2
SCH 503034_100 µM	SCH 503034	19	3	14%	96	11	11%	134	8	6%	113	8	7%	7.2
SCH 503034_250 µM	SCH 503034	43	4	9%	109	15	13%	117	6	5%	100	3	3%	2.7
SCH 503034_500 µM	SCH 503034	59	1	2%	99	3	3%	94	5	5%	98	8	8%	1.6
SCH 503034_5 µM + CsA_10 µM	SCH 503034	42	5	11%	83	5	7%	53	3	7%	100	13	13%	1.2
SCH 503034_5 µM + Ketoconazole_50 µM	SCH 503034	44	4	9%	102	12	11%	66	12	18%	98	7	7%	1.5
SCH 503034_5 µM + Ritanovir_50 µM	SCH 503034	34	4	11%	86	6	7%	55	1	2%	102	6	6%	1.6
Digoxin_5 µM	Digoxin	9	1	15%	110	20	18%	111	15	14%	85	78	92%	12.2
Digoxin_5 µM + CsA_10 µM	Digoxin	53	6	11%	109	28	26%	47	7	16%	116	7	6%	0.9
Digoxin_5 µM + Ketoconazole_50 µM	Digoxin	29	6	21%	122	24	20%	22	6	25%	90	14	16%	0.8
Digoxin_5 µM + Ritonavir_50 µM	Digoxin	38	5	12%	96	6	6%	41	1	3%	99	27	27%	1.1

a: n = 3

In the experiments to evaluate boceprevir as a potential inhibitor, the efflux ratio of digoxin alone and with CsA was within an acceptable range. The efflux ratio of digoxin decreased with increasing concentrations of boceprevir, indicating boceprevir is an inhibitor.

Table 2. Evaluation of Inhibition Potential using Digoxin as a Substrate

Parameters	Inhibitor Conc. (µM)	P_{app} _AP to BL (nm/s)			Recovery _AP to BL (%)			P_{app} _BL to AP (nm/s)			Recovery _BL to AP (%)			Efflux Ratio	REi/REa
Inhibitor		Mean[a]	SD	CV	Mean[a]	SD	CV	Mean[a]	SD	CV	Mean[a]	SD	CV		
Control	0	7.5	1	12%	96	4	5%	121	11	9%	98	2	2%	16.2	1.00
CsA	0.1	8.2	0	6%	96	9	9%	125	10	8%	98	5	6%	15.3	0.94
CsA	0.3	12	2	19%	108	4	4%	107	12	11%	101	6	6%	8.6	0.53
CsA	0.5	12	2	16%	98	4	4%	112	5	5%	104	4	4%	9.2	0.57
CsA	1	16	1	8%	97	3	3%	93	7	7%	96	7	8%	5.8	0.36
CsA	5	33	1	4%	96	5	6%	51	4	7%	101	3	3%	1.6	0.10
CsA	10	39	3	9%	109	4	4%	42	3	6%	101	5	5%	1.1	0.07
CsA	20	37	2	4%	96	4	4%	42	3	8%	104	2	2%	1.1	0.07
SCH 503034	1	6.8	0	7%	96	6	6%	114	4	4%	106	4	4%	16.7	1.03
SCH 503034	5	9.2	1	11%	96	7	7%	109	14	13%	94	5	6%	11.8	0.73
SCH 503034	10	9.3	1	9%	101	7	7%	109	7	7%	98	6	6%	11.7	0.72
SCH 503034	20	11	1	6%	106	3	2%	109	1	1%	94	6	6%	10.2	0.63
SCH 503034	50	17	1	6%	103	0	0%	85	12	15%	89	2	2%	4.9	0.30
SCH 503034	100	23	3	13%	103	11	10%	74	2	3%	98	5	5%	3.3	0.20
SCH 503034	250	32	2	5%	104	2	2%	48	3	7%	97	2	2%	1.5	0.09
SCH 503034	500	34	1	2%	100	7	7%	41	0	1%	93	2	2%	1.2	0.07

a: n = 3

The IC_{50} for both test articles was obtained by fitting the data using the Hill equation, with acceptable curve fitting results (R^2 0.9745 for boceprevir and 0.9560 for CsA). The IC_{50} was determined to be 25.0 (±7.5) µM for boceprevir

and 0.56 (± 0.14) μM for CsA.

Conclusions:

Boceprevir is a p-gp substrate and inhibitor, as assessed in Caco-2 cells. The efflux of boceprevir was concentration dependent and saturable. Maximal inhibition of digoxin efflux was 100%. The estimated IC_{50} for boceprevir was 25 μM, versus 0.56 μM for CsA. The C_{max} value for boceprevir in humans is ~1.9 μg/mL (3.7 μM) at the therapeutic dose of 800 mg. The $[I]_2/IC_{50}$ ratio for boceprevir is 246. This $[I]_2/IC_{50}$ ratio indicates that boceprevir may interact with a sensitive substrate of p-glycoprotein in the gut.

DM27368 – In Vitro Investigation of the Effect of Boceprevir on the Expression and Activity of CYP450 Enzymes in Primary Culture of Human Hepatocytes (Induction Study)

Study initiated in May 2008 at XenoTech LLC, Lenexa, KS

Objective:
To investigate the effect of boceprevir on the expression and activity of CYP450 enzymes in primary cultures of human hepatocytes to ascertain its induction potential.

Methods:
Three preparations of cultured human hepatocytes from 3 separate human donor livers were treated once daily for 3 consecutive days with DMSO, boceprevir (1, 10 or 100 µM), or one of three known inducers, including omeprazole (100 µM), phenobarbital (750 µM) or rifampin (20 µM). Following treatment, cells were harvested to prepare microsomes for the analysis substrate metabolism, including phenacetin (CYP1A2), bupropion (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), S-mephenytoin (CYP2C19) and testosterone (CYP3A4/5).

Hepatocyte isolation and culture was performed according to standard methods and in accordance with internal SOPs. The viability of each preparation was analyzed using trypan blue exclusion. Hepatocytes were seeded on collagen-coated culture dishes and incubated in a humidified chamber for 3 days, with daily removal of dead cells and replacement of media. Hepatocytes were examined by light microscope to conform normal morphology prior to use.

Cultures were treated daily for 3 consecutive days with boceprevir at one of 3 concentrations or one of the prototypical inducers, as outlined above. An additional 2 concentrations of boceprevir (40 and 70 µM) were evaluated in one of the cultures. Microsomes were prepared from the hepatocytes according to internal SOPs. The concentration of protein in microsomal samples was determined using a protein assay. Microsomal incubations of the probe substrates were carried out in duplicate at 37 degrees C for 10 or 30 min., depending on the substrate. Reactions were initiated with the NADPH-generating system and stopped by the addition of acetonitrile. Following centrifugation, supernatant fractions were analyzed by validated LC/MS/MS methods. For each enzyme assay, select samples were incubated at half and twice the normal protein concentration and for half and twice the normal incubation period to assess whether metabolite formation was proportional to protein concentration and incubation period.

Following treatment with the test articles, the hepatocytes were also harvested for gene expression analysis, if necessary. Cell lysates were shipped to Schering-Plough for RNA analysis.

Results:

The viability of isolated hepatocytes was determined to be 75-82% at the time of isolation. Cultures were confirmed by light microscopy and judged to be normal.

The prototypical inducers had effects on the activity of enzymes for which they have been characterized as inducers, consistent with what has been reported previously. CYP1A2 activity increased an average of 41-fold with omeprazole, CYP2B6 activity increased an average of 14-fold with phenobarbital (moderate inducer of CYP2B6), CYP2C8 activity increased 6-fold with phenobarbital and 7-fold with rifampin (moderate inducers of CYP2C8), CYP2C9 activity increased 2.5-fold with rifampin (moderate inducer of CYP2C9), CYP2C19 activity increased 15-fold with rifampin, and CYP3A4/5 activity, as assessed with testosterone hydroxylation, increased 5.5-fold with phenobarbital and 4.9-fold with rifampin.

Treatment with boceprevir up to 100 µM had little or no effect on CYP1A2 or CYP2B6 activity. There was a trend for an increase in CYP2C8 activity with increasing concentrations of boceprevir, but the maximum effect attained was 2-fold at 100 µM. Boceprevir caused only a 1.37-fold increase in CYP2C9 activity at 100 µM; however, this value is 27% that of the prototypical inducer rifampin. This value was also statistically significantly different from the vehicle control. There was also a trend for increased CYP2C19 activity with increasing boceprevir concentration, up to o 1.6-fold at 100 µM. Although this value reached statistical significance relative to the vehicle control, it was only 6% as effective as rifampin. Boceprevir had no induction effect on CYP3A4/5 activity, and actually caused a 43% decrease in activity at 100 µM.

Table 1. Effect of Treatment of Cultured Hepatocytes with Boceprevir or Prototypical Inducers on Microsomal CYP450 Activity (Expressed as Fold Increase Over Vehicle)

		Fold Induction[a]					
Treatment	Concentration	Phenacetin *O*-dealkylation (CYP1A2)	Bupropion Hydroxylation (CYP2B6)[b]	Amodiaquine *N*-dealkylation (CYP2C8)	Diclofenac 4′-hydroxylation (CYP2C9)	S-Mephenytoin 4′-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)[b]
Dimethyl Sulfoxide	0.1% (v/v)	1.00 ± 0.49	1.00 ± 0.50	1.00 ± 0.32	1.00 ± 0.17	1.00 ± 0.29	1.00 ± 0.45
SCH 503034	1 µM	1.27 ± 0.09	0.907 ± 0.222	0.989 ± 0.141	0.939 ± 0.150	0.821 ± 0.161	0.984 ± 0.106
SCH 503034	10 µM	1.64 ± 0.50	1.13 ± 0.29	1.74 ± 0.63	1.15 ± 0.24	1.15 ± 0.26	1.58 ± 0.77
SCH 503034	100 µM	0.939 ± 0.366	0.927 ± 0.192	1.96 ± 1.01	1.37 ± 0.07[d]	1.61 ± 0.15[d]	0.565 ± 0.153
Omeprazole	100 µM	41.0 ± 4.0[c]	8.10 ± 4.76	3.63 ± 0.56[c]	1.86 ± 0.24[c]	3.95 ± 1.06	3.06 ± 2.28
Phenobarbital	750 µM	2.98 ± 0.54	14.3 ± 11.2	5.98 ± 1.18[c]	1.87 ± 0.18[c]	4.82 ± 1.12	5.45 ± 3.02
Rifampin	10 µM	2.40 ± 0.38	8.68 ± 3.60	7.17 ± 2.03[c]	2.50 ± 0.44[c]	15.0 ± 8.1[c]	4.86 ± 2.80

a: Values are the mean ± standard deviation of three human hepatocyte preparations: H716, H719 and H724. Fold inductions are rounded to three significant figures and standard deviation is rounded to the same degree of accuracy.

b: Statistical significance found among the treatment groups according to Kruskal-Wallis One Way Analysis of Variance on ranks ($p < 0.05$) but unable to specify the groups that are significantly different from each other according to Dunnett's Method when the positive control groups (omeprazole, phenobarbital and rifampin) were included in the statistical analysis.

c: Significantly different from the vehicle control (dimethyl sulfoxide) according to Dunnett's Method ($p < 0.05$) when the positive control groups (omeprazole, phenobarbital and rifampin) were included in the statistical analysis.

d: Significantly different from the vehicle control (dimethyl sulfoxide) according to Dunnett's Method ($p < 0.05$) when the positive control groups (omeprazole, phenobarbital and rifampin) were excluded from the statistical analysis.

Table 2. Relative Effectiveness of Boceprevir over the Positive Control Inducers

in Cultured Hepatocytes

Treatment	Concentration	Relative Effectiveness[a]					
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion Hydroxylation (CYP2B6)	Amodiaquine *N*-dealkylation (CYP2C8)	Diclofenac 4′-hydroxylation (CYP2C9)	S-Mephenytoin 4′-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	0	0	0	0	0	0
SCH 503034	1 µM	0.656	-0.270	-0.800	-5.58	-1.17	-2.32
SCH 503034	10 µM	1.54	0.742	10.7	7.92	0.685	11.7
SCH 503034	100 µM	-0.119	-1.90	14.9	27.4	5.95	-16.3
Omeprazole	100 µM	100	59.6	44.4	57.3	23.2	44.6
Phenobarbital	750 µM	5.03	100	82.8	62.6	34.3	116
Rifampin	10 µM	3.53	71.6	100	100	100	100

a: Values are the mean of three determinations (human hepatocyte preparations: H716, H719 and H724).

$$\text{Calculated percent effectiveness for each individual human preparation} = \frac{(\text{activity in test article group - activity in vehicle control})}{(\text{activity in positive control - activity in vehicle control})} \times 100$$

For CYP1A2, the positive control is omeprazole and the vehicle control is DMSO
For CYP2B6, the positive control is phenobarbital and the vehicle control is DMSO
For CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5, the positive control is rifampin and the vehicle control is DMSO
Individual values are shown in Appendix 5

Conclusion:

Prototypical inducers caused anticipated increases in CYP enzyme activity. Treatment of hepatocytes with boceprevir resulted in a maximum induction of 2-fold the enzyme activity for CYP2C8 at 100 µM. All other enzymes were induced < 2-fold. Boceprevir increased CYP2C9 activity 1.37-fold at 100 µM, which was 27% that of rifampin's effect. Boceprevir is unlikely to be a clinically relevant inducer of CYP450 enzymes at the therapeutic dose of 800 mg.

03368 – In vitro binding of boceprevir to mouse, rat, rabbit, dog, monkey, and human plasma proteins using ultrafiltration.

Study initiated in July 2005 at Schering-Plough Research Institute, Kenilworth, New Jersey.

Objective:
To investigate the extent of *in vitro* protein binding of ^{14}C-boceprevir in mouse, rat, rabbit, dog, monkey, and human plasma.

Methods:
Investigators collected plasma from blood donated by four male subjects. The human blood was centrifuged (~1300g) for ~10 min at 4ºC. The supernatant (plasma) from all samples was collected and pooled across donors and stored at 4ºC prior to use within 2 days. Investigators also collected blood samples from mice, rats, rabbits, dogs, and monkeys. The blood from each species was centrifuged at ~4ºC prior to use within 2 days.

Investigators determined the protein content of the plasma samples using a bicichoninic acid (BCA)-based protein assay kit. The protein kit measured acceptable plasma concentrations from all species as shown in the table below.

Acceptance Criteria and Measured Total Protein Concentrations in Mouse, Rat, Rabbit, Dog, Monkey, and Human Plasma

Species	Acceptable Protein Concentration Range (g/dL)	Measured Protein Concentration (g/dL)
Mouse[4,5]	4.0-8.6	5.7
Rat[4]	5.6-7.1	6.8
Rabbit[5,6]	4.8-7.9	5.8
Dog[4,7]	5.0-7.8	6.3
Monkey[4]	7.3-9.8	8.5
Human[5]	6.0-8.3	7.5

A working stock solution of the highest concentration of ^{14}C-boceprevir (25 µg/mL) was developed. The first working stock solution (WS-1) was created by dissolving 20.2 mg of unlabeled boceprevir in 6.308 mL ethanol. The final boceprevir concentration was 3 mg/mL. From WS-1, the 25 µg/mL solution (WS-2) was created according to the following formula:

Target WS-2 ^{14}C-SCH 503034 Concentration (µg/mL)	Volume of WS-1 Unlabeled SCH 503034 (3 mg/mL) (µL)	Volume of ^{14}C-SCH 503034 Stock Solution (531 µg/mL) (µL)	Volume of Ethanol (µL)	Total Volume (µL)
2500	800	188	12	1000

On the day of the study, plasma from all species was prepared with 1 mM of PMSF (serine protease inhibitor) by diluting 0.2 M PMSF stock in 2-propanolol into each plasma vial. The plasma samples were incubated at 37ºC for 10 minutes to inactivate the enzymes responsible for plasma degradation. A single aliquot of plasma from each species was prepared using WS-2 to contain 25 µg ^{14}C-boceprevir/mL. Another set of plasma samples was prepared in a similar manner and with the same concentrations of ^{14}C-boceprevir, except these plasma samples were not incubated with PMSF. From the WS-2 solution, the following range of plasma concentrations was created:

Target ^{14}C-SCH 503034 (µg/mL)	Spiked Plasma/Stock Volume	Blank Plasma (mL)
25.0	40 µL of WS-2 (2.5 mg ^{14}C-SCH 503034/mL)	3.960
5.0	57 µL of original stock (0.531 mg ^{14}C-SCH 503034/mL)	5.996
0.5	600 µL of 5 µg ^{14}C-SCH 503034/mL plasma	5.4
0.05	500 µL of 0.5 µg ^{14}C-SCH 503034/mL plasma	4.5

Triplicate samples (100 µL) from each plasma sample were transferred to scintillation vials and 10 mL of scintillation fluid was added. The samples were analyzed by LSS and represented the total pre-filtered ^{14}C-boceprevir radioactivity.

Triplicate samples (1 mL) from each plasma sample were transferred to Centrifree Micropartition devices. The samples were equilibrated at ~37ºC for ~10 minutes and then centrifuged (~1500 *g*) for ~5 minutes at ~37ºC. From these samples, 100 µL of ultrafiltrate was transferred into a scintillation vial. Scintillation cocktail (10 mL) was added to each vial. The contents were mixed thoroughly, and analyzed by LSS for unbound ^{14}C-boceprevir.

Reference plasma samples for ^{14}C-warfarin and ^{14}C-chloramphenicol underwent similar preparation steps as ^{14}C-boceprevir samples. The standard concentrations for ^{14}C-warfarin were 1 and 3 µg/mL. The standard concentrations for ^{14}C-chloramphenicol were 10 and 20 µg/mL.

Data analysis:

The following equation was used to calculate the percent protein binding of ^{14}C-boceprevir and reference protein binding standards:

$$\% \text{ protein binding} = \frac{dpm_{mean}\,(\text{Prefilter sample}) - dpm_{individual}\,(\text{Ultrafiltrate})}{dpm_{mean}\,(\text{Prefilter sample})} \times 100$$

Results:

The protein binding of ^{14}C-boceprevir in rabbit, monkey, and human plasma was determined at concentrations ranging from 0.05 to 25 µg/mL with and without

1mM PMSF. ^{14}C-boceprevir was unstable in mouse, rat, and dog plasma, and the extent of plasma protein binding was only determined in the presence of 1 mM PMSF. Study results are as follows:

Table 39 Mean percent binding of ^{14}Cboceprevir to mouse, rat, rabbit, dog, monkey, and human plasma proteins

^{14}C-SCH 503034 (µg/mL)	Mouse		Rat		Rabbit		Dog		Monkey		Human	
	%Bound[a]	CV[b]	%Bound[a]	CV[b]	%Bound[a]	CV[b]	%Bound[a]	CV[b]	%Bound[a]	CV[b]	%Bound[a]	CV[b]
Plasma Without PMSF												
0.05	NT[c]		NT		73.7	1	NT		65.4	2	81.7	0
0.5	NT		NT		70.1	0	NT		63.2	1	79.5	0
5	NT		NT		64.6	1	NT		58.5	1	73.1	1
25	NT		NT		63.6	1	NT		56.3	1	68.6	0
Plasma With 1 mM PMSF												
0.05	76.1	1	60.5	1	68.7	1	87.5	1	60.9	4	74.8	1
0.5	74.9	1	59.6	1	65.3	1	86.7	1	59.0	2	73.5	2
5	71.8	0	55.4	1	59.9	0	77.2	0	56.2	3	68.0	2
25	70.5	0	54.7	1	59.1	1	65.8	0	53.4	3	70.0	3

a: Mean of 3 replicates
b: CV, coefficient of variation expressed as a percent
c: Not tested, SCH 503034 was rapidly degraded in mouse, rat, and dog plasma at 37°C in the absence of 1 mM PMSF.

In each corresponding plasma protein binding of ^{14}C-boceprevir in rabbit, monkey, and human plasma in the absence of PMSF was higher (range 2.3 to 6.9%) than in the presence of PMSF.

In all species except dog, ^{14}C-boceprevir was <80% bound. According to the FDA guidance, this drug is not considered highly bound (<80%). Dog plasma at 0.05 and 0.5 µg/mL showed >80% binding (87.5 and 86.7%, respectively).

The mean percent binding of two concentrations of ^{14}C-warfarin (97.9 and 98.6%) and ^{14}C-chloramphenicol (52.1 and 53.4%) to human plasma proteins was within the established protein binding ranges indicating that the ultrafiltration procedure performed acceptably.

Conclusion:

The extent of plasma protein binding of ^{14}C-boceprevir in all species in the presence of PMSF ranged from 53.4 to 87.5%. The concentration range of ^{14}C-boceprevir was 0.05 to 25 µg/mL. This concentration range covers the expected therapeutic concentrations of boceprevir *in vivo* (~1.9 µg/mL).

04061 – In vitro stability and diastereomer interconversion of SCH534128 and SCH534129 when incubated with rat, monkey, and human plasma.

Study initiated in February 2004 at Schering-Plough Research Institute, Kenilworth, New Jersey.

Objective:
To determine the *in vitro* stability and diastereomer interconversion of SCH534128, SCH534129, and SCH503034 in rat, monkey, and human plasma incubated at 37ºC.

Methods:
Stock solutions of SCH503034, SCH534128, and SCH534129 were formulated in DMSO at nominal concentrations of 100 µg/mL. The drug product used for creating the stock solutions for SCH503034 contained a diastereomer ratio of (b) (4) (SCH534128 to SCH534129). The drug product used for creating stock solutions of SCH534128 contained (b) (4) The drug product used for creating the stock solution of SCH534129 contained (b) (4).

Blood samples were collected from rats (n=15), monkeys (n=3), and humans (n=2). The blood samples were placed in Vacutaner® tubes containing K_3EDTA and lightly mixed by inversion. Rat and monkey samples were centrifuged for ~10 minutes at 3600 rpm in a refrigerated centrifuge at ~4ºC. Human samples were centrifuged for ~10 minutes at 3100 rpm in a centrifuge maintained at ~24ºC. Plasma from all tubes was separated and pooled by species and stored until the study day.

On the study day, the stock solutions of SCH503034, SCH534128, and SCH534129 (1 µg/mL) and plasma samples were mixed in labeled 15 mL Falcon® centrifuge tubes. The volumes of stock solution for rat, human, and monkey were 0.1 mL, 0.1 mL, and 0.040 mL, respectively. The volume of plasma from rat, humans, and monkey were 9.9 mL, 9.9 mL, and 4.0 mL, respectively.

From the tubes, plasma samples spiked with stock solution were collected at 0, 0.083, 0.17 (rat and human only), 0.25, 0.33, 0.5, 0.75, 1, 1.5 (rat only), 2, 3 (monkey and human only), 4 (monkey and human only), and 5 hours (monkey and human only) after mixing. The 0 hr samples were collected as soon as possible after the addition of plasma. The volumes of plasma collected for rat, human, and monkeys were 0.5 mL, 0.5 mL, and 0.3 mL, respectively. Spiked plasma samples were transferred to pre-chilled, labeled centrifuge tubes and flash frozen in an acetone- or hexane-dry ice bath. Samples were stored at -70ºC pending analysis.

Spiked plasma samples were analyzed for SCH534128/$^{2}H_{9}$-SCH534128 and SCH534129/$^{2}H_{9}$-SCH534129 using a non-validated LC-MS/MS method.

Results:

In rat plasma, relative concentrations (%) of SCH534128 and SCH534129 declined rapidly following incubations of 1 µg/mL SCH534128, SCH534129, or SCH503034 after incubation in plasma at 37ºC. Less than 50% of the initial (0 hr) SCH534128 concentration was found at 0.17 hr in rat plasma compared to 1-1.5 hr for SCH534129.

In monkey plasma, the relative concentrations of SCH534128 and SCH534129 following incubation at 1 µg/mL declined slowly to 39.6% and 60.7% after 3 hrs of incubation, respectively. The diastereomer interconversion was ~4% and 6% of the initial concentrations of SCH534128 and SCH534129 incubations, respectively. In contrast, the total diastereomer content remained unchanged over the 5 hour incubation interval. The diastereomer interconversion reached equilibrium with a ratio of ~1/1.8 (SCH534128/SCH534129) after 3 hours of incubation.

In human plasma, the relative concentrations of SCH534128 and SCH534129 following incubation at 1 µg/mL declined to 64.7% and 42.5% after 3 hrs of incubation, respectively. The diastereomer interconversion ranged from ~3% to 30% of the initial concentrations of SCH534128 and SCH534129 incubations, respectively. The total diastereomer content remained unchanged over the 5 hr incubation interval. The diastereomer interconversion reached equilibrium with a ratio of ~1.5/1 (SCH534128/SCH534129) after 3 hours of incubation.

The following tables display the relative concentrations (%) of SCH503034, SCH534128, and SCH503034 following incubation of 1 µg/mL in rat, monkey, and human plasma.

Table 1 Relative concentrations (%) of SCH534128, SCH534129, and SCH503034 following an incubation of 1 µg/mL SCH534128, SCH534129, and SCH503034 in rat plasma at 37ºC

Test Article[a]	Incubation Time (hr)	SCH 534128 Area Ratio[b]	SCH 534129 Area Ratio[c]	Relative Conc. of Diastereomers[d]			Diastereomer Ratio (SCH 534128/ SCH 534129)
				SCH 534128 (%)	SCH 534129 (%)	SCH 503034 (%)	
SCH 534128[e]	0	1.70	0.0314	99.9	0.100	100	1000/1
	0.083	1.11	0.0443	65.0	0.141	65.2	460/1
	0.17	0.790	0.0592	46.4	0.188	46.6	250/1
	0.25	0.425	0.0825	25.0	0.263	25.2	95/1
	0.33	0.276	0.100	16.2	0.319	16.5	51/1
	0.5	0.0793	0.0935	4.66	0.298	4.95	16/1
	0.75	0.0124	0.0822	0.729	0.262	0.991	2.8/1
	1	0.00665	0.0585	0.391	0.186	0.577	2.1/1
	1.5	0.00721	0.0511	0.423	0.163	0.586	2.6/1
	2	0.00300	0.0290	0.176	0.0923	0.268	1.9/1
SCH 534129[f]	0	0.0299	2.57	0.800	99.2	100	1/120
	0.083	0.0463	2.62	1.24	101	103	1/82
	0.17	0.0367	2.30	0.984	88.8	89.7	1/90
	0.25	0.0720	2.41	1.93	93.4	95.3	1/48
	0.33	0.0530	2.23	1.42	86.1	87.5	1/61
	0.5	0.0773	1.93	2.07	74.6	76.6	1/36
	0.75	0.0773	1.60	2.07	61.7	63.7	1/30
	1	0.0590	1.34	1.58	52.0	53.5	1/33
	1.5	0.0462	0.855	1.24	33.1	34.3	1/27
	2	0.0364	0.721	0.974	27.9	28.9	1/29
SCH 503034[g]	0	0.975	1.39	53.4	46.6	100	1.1/1
	0.083	0.654	1.34	35.8	44.8	80.7	1/1.3
	0.17	0.467	1.40	25.6	46.9	72.5	1/1.8
	0.25	0.224	1.16	12.3	38.6	50.9	1/3.1
	0.33	0.121	1.27	6.61	42.5	49.1	1/6.4
	0.5	0.0807	1.04	4.42	34.7	39.1	1/7.8
	0.75	0.0340	0.814	1.86	27.2	29.1	1/15
	1	0.0349	0.734	1.91	24.5	26.4	1/13
	1.5	0.0168	0.461	0.920	15.4	16.3	1/17
	2	0.0174	0.314	0.952	10.5	11.4	1/11

a: Test articles were incubated at nominal concentrations of 1 µg/mL rat plasma.
b: Area ratio of SCH 534128/$^{2}H_{9}$-SCH 534128 (internal standard), Schering Notebook No. 49542.
c: Area ratio of SCH 534129/$^{2}H_{9}$-SCH 534129 (internal standard), Schering Notebook No. 49542.
d: Relative composition based upon the nominal diastereomer content of test article at time zero.
e: SCH 534128 (Batch No. 081237-130-36) diastereomer content: (b) (4)
f: SCH 534129 (Batch No. 081237-130-35) diastereomer content: (b) (4)
g: SCH 503034 (Batch No. 03-503034-Y-104) diastereomer content: (b) (4)

Table 2 Relative concentrations (%) of SCH534128, SCH534129, and SCH503034 following an incubation of 1 µg/mL SCH534128, SCH534129, or SCH503034 in monkey plasma at 37ºC

Test Article[a]	Incubation Time (hr)	SCH 534128 Area Ratio[b]	SCH 534129 Area Ratio[c]	Relative Conc. of Diastereomers[d] SCH 534128 (%)	SCH 534129 (%)	SCH 503034 (%)	Diastereomer Ratio (SCH 534128/ SCH 534129)
SCH 534128[e]	0	1.94	0.0465	99.9	0.100	100	1000/1
	0.083	1.96	0.0949	101	0.204	101	500/1
	0.25	1.92	0.254	99.1	0.546	99.7	180/1
	0.33	1.67	0.319	86.0	0.684	86.7	130/1
	0.5	1.69	0.477	87.3	1.03	88.3	85/1
	0.75	1.37	0.652	70.6	1.40	72.0	50/1
	1	1.28	0.920	66.0	1.98	68.0	33/1
	2	0.978	1.59	50.4	3.42	53.8	15/1
	3	0.769	1.78	39.6	3.83	43.5	10/1
	4	0.757	1.79	39.0	3.85	42.9	10/1
	5	0.722	1.74	37.2	3.73	40.9	10/1
SCH 534129[f]	0	0.0875	2.45	0.800	99.2	100	1/120
	0.083	0.0792	2.21	0.723	89.6	90.3	1/120
	0.25	0.104	2.19	0.948	88.5	89.4	1/93
	0.33	0.123	2.22	1.12	89.8	90.9	1/80
	0.5	0.181	2.05	1.65	82.9	84.6	1/50
	0.75	0.231	1.98	2.11	80.2	82.3	1/38
	1	0.333	2.13	3.04	86.4	89.4	1/28
	2	0.553	1.63	5.06	65.9	70.9	1/13
	3	0.564	1.50	5.15	60.7	65.8	1/12
	4	0.581	1.50	5.31	60.8	66.1	1/11
	5	0.605	1.50	5.53	60.5	66.0	1/11
SCH 503034[g]	0	1.07	1.27	53.4	46.6	100	1.1/1
	0.083	1.10	1.36	54.6	49.7	104	1.1/1
	0.25	1.06	1.38	52.7	50.6	103	1.0/1
	0.33	1.04	1.42	51.8	51.9	104	1.0/1
	0.5	1.03	1.41	51.5	51.8	103	1/1.0
	0.75	0.935	1.51	46.6	55.3	102	1/1.2
	1	0.916	1.53	45.6	56.1	102	1/1.2
	2	0.776	1.71	38.7	62.6	101	1/1.6
	3	0.685	1.68	34.1	61.7	95.8	1/1.8
	4	0.687	1.81	34.3	66.3	101	1/1.9
	5	0.768	1.74	38.3	63.9	102	1/1.7

a: Test articles were incubated at nominal concentrations of 1 µg/mL monkey plasma.
b: Area ratio of SCH 534128/$^{2}H_{9}$-SCH 534128 (internal standard), Schering Notebook No. 49542.
c: Area ratio of SCH 534129/$^{2}H_{9}$-SCH 534129 (internal standard), Schering Notebook No. 49542.
d: Relative composition based upon the nominal diastereomer content of test article at time zero.
e: SCH 534128 (Batch No. 081237-130-36) diastereomer content: (b) (4)
f: SCH 534129 (Batch No. 081237-130-35) diastereomer content: (b) (4)
g: SCH 503034 (Batch No. 03-503034-Y-104) diastereomer content: (b) (4)

Table 3 Relative concentrations (%) of SCH534128, SCH534129, and SCH503034 following an incubation of 1 µg/mL SCH534128, SCH534129, or SCH503034 in human plasma at 37ºC

Test Article[a]	Incubation Time (hr)	SCH 534128 Area Ratio[b]	SCH 534129 Area Ratio[c]	Relative Conc. of Diastereomers[d]			Diastereomer Ratio (SCH 534128/ SCH 534129)
				SCH 534128 (%)	SCH 534129 (%)	SCH 503034 (%)	
SCH 534128[e]	0	1.91	0.0285	99.9	0.100	100	1000/1
	0.083	1.89	0.0546	99.1	0.192	99.2	520/1
	0.17	1.90	0.0603	99.5	0.212	99.7	470/1
	0.25	1.88	0.109	98.2	0.382	98.6	260/1
	0.33	1.81	0.144	94.7	0.505	95.2	190/1
	0.5	1.66	0.205	87.0	0.720	87.7	120/1
	0.75	1.76	0.332	92.1	1.17	93.3	79/1
	1	1.87	0.445	97.6	1.56	99.1	62/1
	1.5	1.50	0.583	78.4	2.05	80.5	38/1
	2	1.56	0.796	81.5	2.80	84.3	29/1
	3	1.24	0.940	64.7	3.30	68.0	20/1
	4	1.30	0.939	67.9	3.30	71.2	21/1
	5	1.15	1.10	60.3	3.87	64.2	16/1
SCH 534129[f]	0	0.0282	2.89	0.800	99.2	100	1/120
	0.083	0.0551	2.73	1.56	93.8	95.4	1/60
	0.17	0.0654	2.67	1.86	91.9	93.7	1/50
	0.25	0.0964	2.66	2.74	91.3	94.1	1/33
	0.33	0.133	2.67	3.77	91.8	95.5	1/24
	0.5	0.238	2.52	6.76	86.7	93.4	1/13
	0.75	0.320	2.26	9.09	77.6	86.7	1/8.5
	1	0.418	2.24	11.9	76.9	88.7	1/6.5
	1.5	0.623	1.79	17.7	61.5	79.2	1/3.5
	2	0.845	1.55	24.0	53.4	77.4	1/2.2
	3	1.04	1.24	29.5	42.5	72.0	1/1.4
	4	1.11	1.13	31.6	39.0	70.5	1/1.2
	5	1.07	1.11	30.3	38.2	68.5	1/1.3
SCH 503034[g]	0	0.929	1.22	53.4	46.6	100	1.1/1
	0.083	0.827	1.11	47.6	42.2	89.8	1.1/1
	0.17	0.952	1.25	54.7	47.7	102	1.1/1
	0.25	0.949	1.13	54.5	43.0	97.6	1.3/1
	0.33	1.01	1.20	58.0	45.8	104	1.3/1
	0.5	1.11	1.13	63.9	42.9	107	1.5/1
	0.75	0.954	1.12	54.8	42.8	97.6	1.3/1
	1	0.977	1.15	56.1	43.8	100	1.3/1
	1.5	0.990	1.05	56.9	40.1	97.0	1.4/1
	2	0.991	1.04	57.0	39.5	96.4	1.4/1
	3	1.03	1.01	59.1	38.5	97.6	1.5/1
	4	1.02	1.02	58.4	38.8	97.2	1.5/1
	5	0.959	0.952	55.1	36.2	91.4	1.5/1

Conclusion:

The rank order of plasma stability for SCH534128, SCH534129, and SHC503034 following incubation at 1 µg/mL at 37ºC was:

- Human > monkey > rat for SCH534128
- Monkey > human > rat for SCH534129
- Monkey ~ human > rat for SCH503034

Total diastereomer content remained unchanged over the 5 hour incubation period in monkey and human plasma. The diastereomer ratio reached equilibrium ~3 hours of incubation. The diastereomer ratio in monkey and human plasma was 1/1.8 and 1.5/1 (SCH534128/SCH534129), respectively.

SCH503034 was highly unstable in rat plasma.

4.4. Pharmacometrics review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Pharmacometrics Reviewer: Jeffry Florian
Pharmacometrics Team Leader: Pravin Jadhav
Clinical Pharmacology Reviewer: Ruben Ayala
Clinical Pharmacology Team Leader: Sarah Robertson

SUMMARY OF FINDINGS

Key Review Questions

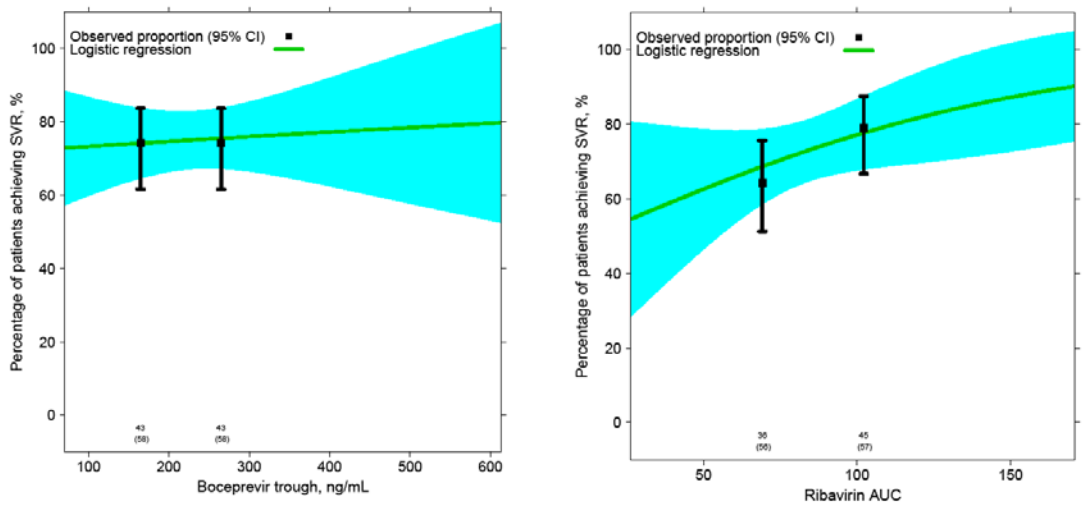
The purpose of this review is to address the following key questions.

Is there evidence of an exposure-response relationship for boceprevir or ribavirin and efficacy (SVR)?

There is no evidence of an exposure-response relationship between boceprevir C_{trough} (Figure 19) or AUC (not shown). All patients with non-zero boceprevir exposure data (i.e. exclude patients receiving only standard-of-care (SOC)) from the two Phase III trials (P05216 (SOC naive): n=67; P05101 (previous SOC failures): n=49) were combined to increase the total number of patients available for exposure-response analysis. A shallow and non-significant relationship was identified between boceprevir exposure and SVR as shown in Figure 19 (left). Similar trends in the exposure-response relationship are observed if the patients are separated based on Phase III study. These results indicate that higher exposures to boceprevir are not expected to result in greater efficacy. The current dataset does not allow us to explore the possibility that subsets of the treatment population may have an exposure-response efficacy relationship due to limited number of Phase III patients with boceprevir exposure data.

A non-significant, but trending upward relationship between ribavirin steady-state AUC (AUC_T) and SVR was observed in the same Phase III population set described above (Figure 19 (right)). These results indicate that variability in ribavirin exposure, even after dosing with multiple weight cuts so that patients over 50-120 kg receive 12-16 mg/kg, may still be an important factor in achieving efficacy even with the addition of boceprevir to treatment.

Figure 19: Percentage of Patients Achieving SVR from P05101 and P05216 Versus Boceprevir Trough Concentration (left) or Ribavirin Steady-State AUC (right).



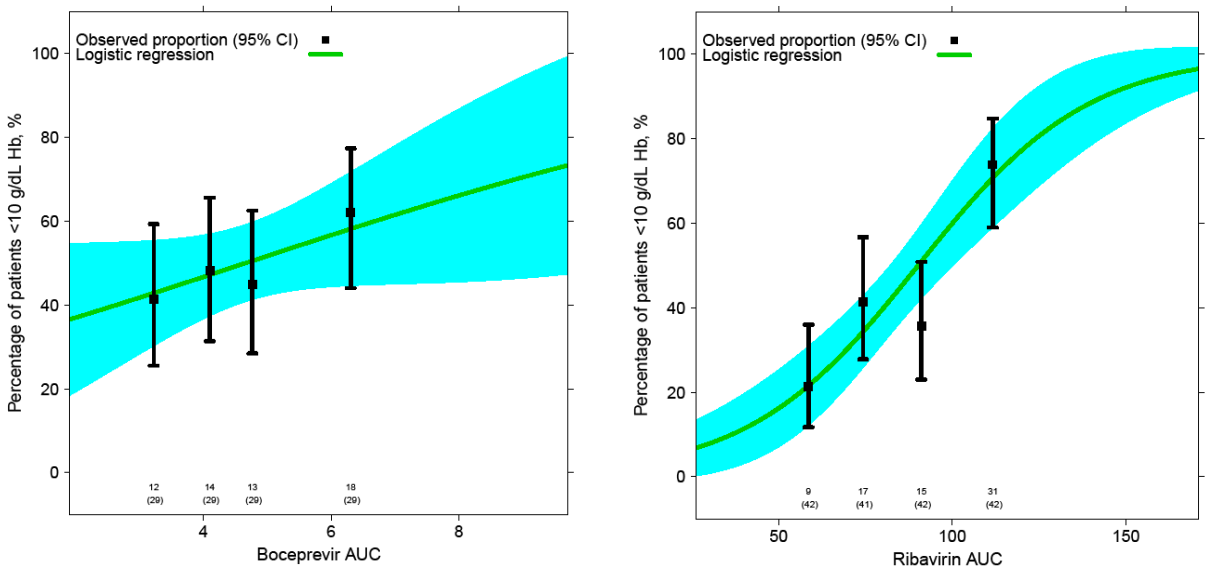
Is there evidence of exposure-safety relationships either boceprevir or ribavirin and anemia?

A non-significant upward trend of increasing incidence of anemia (lab hemoglobin measurement <10 g/dL) was observed with respect to increasing boceprevir AUC_T in the Phase III population (Figure 20 (left)). Boceprevir AUC_T was used as the PK parameter for exposure-response safety analysis as exposure over time is commonly employed as a predictor of progressive adverse events; however, similar relationships were identified between C_{trough} or C_{max} and incidence of anemia. Model predicted incidence of anemia for the median boceprevir exposure (4.3 µg·hr/mL) was 48%. Similarly, the predicted incidence of anemia at the lowest and highest exposure quartiles (3.2 and 6.3 µg·hr/mL) was 43% and 58%, respectively. Higher doses of boceprevir are anticipated to further increase incidence of anemia without an expected benefit in efficacy as shown in the previous section.

A significant (p-value<0.0001; odds ratio = 1.9 (90% CI: 1.7; 2.2) for a 15 µg·hr/mL increase in AUC_T) relationship between incidence rate of anemia and ribavirin AUC_T was observed in the Phase III population (Figure 20 (right)). This was not unexpected as ribavirin's primary toxicity is known to be anemia, with an observed incidence rate in the SOC population of ~30%. Indeed, a similar exposure-response relationship is observed if the analysis is limited to patients receiving only SOC (n=51; p-value=0.001; odds ratio = 2.3 (90% CI: 1.7; 3.1) for a 16 µg·hr/mL increase in AUC_T). Together these results show a greater contribution to the incidence of anemia from boceprevir at lower ribavirin exposures, which may be due to either the small number of patients in this analysis, or a greater impact of ribavirin exposure on the incidence of anemia masking the impact from boceprevir exposure except at lower ribavirin exposures. These results agree with the sponsor's recommendation of dose reduction of ribavirin as a strategy for managing on treatment anemia with no

accompanying dose reduction in boceprevir.

Figure 20: Percentage of Patients with Anemia from P05101 and P05216 Versus Boceprevir (left) or Ribavirin Steady-State AUC (right).



What is the appropriate boceprevir treatement duration for early and late responder (SOC naïve and previous SOC failure) patients?

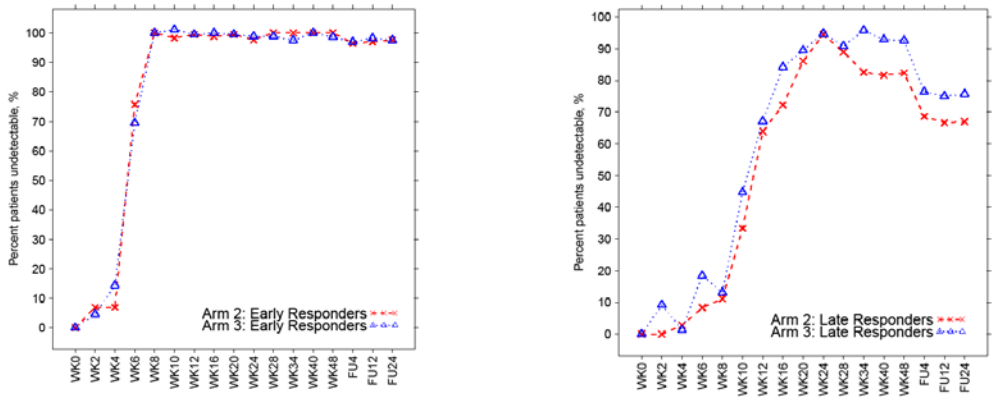
The sponsor's proposed treatment durations for SOC naïve early responders and previous SOC failures are acceptable, however, (b) (4) The alternate proposals are discussed below.

In the Response Guided Therapy (RGT) arm, SOC naive early responders (undetectable HCV RNA at weeks 8 through 24) received 28 weeks of treatment (Arm 2 early responders) and late responders (detectable HCV RNA during at least one time point between week 8 through week 20 but undetectable at week 24) received 20 weeks of additional SOC after triple therapy was stopped at week 28 (Arm 2 late responders). In the same study, patients received 44 weeks triple therapy irrespective of initial response. For comparison, patients that correspond to Arm 2 early and late responders were identified (Arm 3 early responders: early responders who received boceprevir for 44 weeks; Arm 3 late responders: late responders who received boceprevir for 44 weeks).

From this analysis, any patient that discontinued treatment prior to week 28 was removed from the analysis, as all patients received the same treatment during this period. After the end of 28 weeks of treatment, there were four groups of patients based on whether the viral load was detectable at week 8- Arm 2 early responders (N=161), Arm 2 late responders (N=68), Arm 3 early responders (N=161) and Arm 3 late responders (N=73).

For early responders, no difference in the percentage of patients with undetectable viral load was observed on treatment or during follow-up from Arm 2 or Arm 3 (SVR: 97% and 96%, respectively) (Figure 22, left). In contrast, late responders showed a numerical difference in SVR (66% for Arm 2 vs 75% for Arm 3). Further, there was a difference in the percentage of patients with detectable viral load beyond week 28. This time point also corresponds to switching late responders in Arm 2 to receive SOC only. Also, a greater percentage of late responders receiving triple therapy for the remainder of treatment in Arm 3 were undetectable at the end-of-treatment (93%) compared to patients receiving SOC (Arm 2 late responders: 82%), though this resulted in a modest increase in SVR between the two groups (Arm 2 late responders: 66% n= 45 (68); Arm 3 late responders: 75% n= 55 (73)) (Figure 22, right). This difference appears to represent virologic breakthrough while on PR after stopping boceprevir, which was not seen on triple therapy. These results indicate that SOC naive patients with detectable viral load at week 8 may benefit from receiving boceprevir in addition to SOC over the last 20 weeks of treatment. Therefore, the sponsor's proposed duration for SOC naive early responders is acceptable; (b) (4)

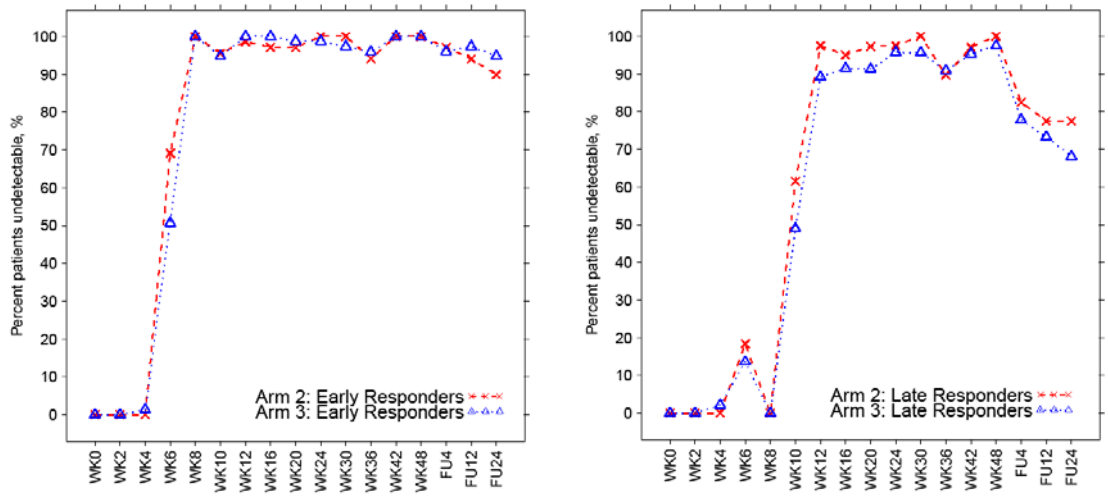
Figure 21: Percentage of SOC naive Patients with Undetectable Viral Load at Different Treatment Time Points for Early Responders (Left) or Late Responders (Right) From P05216.



A similar analysis was performed for the treatment arms in P05101 evaluating boceprevir in previous SOC failures. In this population, patients in the Arm 2 (RGT) received therapy for 36 weeks, and SOC for the remaining 12 weeks if viral load was detectable at week 8 (i.e., late responder). The early and late response categories were based on week 8 and week 12 assessments. As before, any patient that discontinued treatment prior to treatment divergence, in this case week 36, was removed from the analysis (Arm 2 early responder: n = 74; Arm 2 late responder: n=72; Arm 3 early responder: n=84; Arm 3 late responder: n=70). For early responders, no difference in the percentage of patients with undetectable viral load was observed on treatment with a slight separation in SVR between treatment groups (Arm 2 early responder: SVR 86% n=64 (74); Arm 3 early responder: SVR 88% n=74 (84)) (Figure 23, left). There

was no difference in response rate for late responders if treated with SOC or boceprevir with SOC for the remaining 12 weeks of treatment (Figure 23, right). In fact, the RGT arm (shorter boceprevir treatment) resulted in higher SVR compared to longer boceprevir treatment. Therefore, the sponsor's proposed treatment durations for previous SOC failures who are early responders and late responders are acceptable.

Figure 22: Percentage of Previous SOC failures with Undetectable Viral Load at Different Treatment Time Points for Early Responders (Left) or Late Responders (Right) From P05216.



(b) (4)

the data from SOC naive and previous failures was bridged to derive treatment duration in late responders. The rationale for bridging the data stems from the following set of observations.

- Week 4 response (lead-in) to SOC in late responders was similar to that of response in potential SOC failures (Figure 39).

- Week 4 response to SOC was similar for patients irrespective of first (naïve) or second (previous failures) round of treatment with SOC (Figure 40).

If late responders (potential SOC failures) are similar to previous SOC failure population, data from SOC failures can be leveraged to inform treatment duration in SOC naive late responders. An empirical data supports RGT (32 or 44 weeks of boceprevir) for previous relapsers and partial responders. However, there is no empirical data supporting RGT for null responders.

One option is to treat all late responders that include potential null responders, if treated with SOC, with 44 weeks of boceprevir. However, for this option the potential partial responders and relapsers, who might be benefited wit RGT will receive 44 weeks of boceprevir treatment.

Other option is to identify potential null, partial responder and relapser population based on lead in phase (week 4 response) to leverage all available data. A classification and regression tree (CART) analysis was performed on the SOC patients from Arm 1 of P05216 to determine the viral load decline at week 4 that best predicts a null responder SOC treatment outcome. A total of 363 patients were included in the SOC treatment arm, 329 of which had week 4 and week 12 data on change in viral load data available. Please note that week 12 results are used to define null responder status. The results suggest that a week 4 viral load decline ≤1.03 $\log_{10}$ is an appropriate cut point for selecting null responders. Approximately, 83 patients in the SOC arm had viral load decline ≤1.03 $\log_{10}$ at week 4. Of those 83 patients, 60 patients were eventually identified as null responders (85% sensitivity and 72% positive predictive value). In contrast, among 246 patients who had viral load decline >1.03 $\log_{10}$, only 4% were null responders.

Based on the above analyses, the following treatment regimens are recommended for SOC naive late responders.

	Week 4 response	**Treatment duration**
	Option 1[3]	
Late responders	-	PR4/BOC-PR44
	Option 2[4]	
Late responders	> 1.0 $\log_{10}$	PR4/BOC-PR32/PR 12
	≤ 1.0 $\log_{10}$	PR4/BOC-PR44

Should boceprevir treatment be extended to previous null responder patients?

Yes, boceprevir should be approved for previous null responder patients with 44 weeks of boceprevir treatment. The sponsor should evaluate shorter duration of boceprevir treatment in null responders to recommend RGT in these patients.
The sponsor proposed to leverage treatment naïve data to evaluate effect size in previous null responders. The arguments made in the previous section on similarity between week 4 response irrespective of first and second treatment cycle helped us bridge these data.

(b) (4)

As recognized in the previous section, there are 27% of these patients are not null responders. Therefore, this is slight over estimate of drug effect. Using a more stringent cut off, ≤0.5 log 10 decline, will result in >90%

[3] Option 1: Treat late responders as potential SOC failures where potential partial responder and relapser population will receive longer therapy but will cover for null responder population.
[4] Option 2: Treat late responders as potential SOC failures, however, identify potential SOC null responders using week 4 response of ≤1.0 log10 such that potential relapser and partial responder population receives appropriate treatment duration by leveraging data from previous treatment failure patients.

patients who will be null responders. Even then, the expected response rate for boceprevir treatment was 30% (Arm 2: n/N=11/37) and 28% (Arm 3: n/N=13/47) (See Table 51). By comparison, the observed SVR on SOC for ≤1.0 and ≤0.5 log10 HCV RNA decline at week 4 was 5% and 0%, respectively. Therefore, boceprevir is effective in null responder population but not amenable to RGT.

Recommendations

Based on these analyses, the Division recommends the following treatment durations for treatment naïve patients:

	Week 4 response	**Treatment duration**
Early responders	**-**	**PR4/BOC-PR24**
Option 1[5]		
Late responders	-	PR4/BOC-PR44
Option 2[6]		
Late responders	> 1.0 log10	PR4/BOC-PR32/PR 12
	≤ 1.0 log10	PR4/BOC-PR44

The Division does not recommend any changes to the sponsor's proposed treatment durations for previous treatment failures; however, boceprevir should be recommended for treatment of null responders but only with PR4/BOC-PR44 treatment duration.

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

[redacted]

[5] Option 1: Treat late responders as potential SOC failures where potential partial responder and relapser population will receive longer therapy but will cover for null responder population.
[6] Option 2: Treat late responders as potential SOC failures, however, identify potential SOC null responders using week 4 response of ≤1.0 log10 such that potential relapser and partial responder population receives appropriate treatment duration by leveraging data from previous treatment failure patients.

Pertinent regulatory background

Boceprevir is a potent, orally administered, serine protease inhibitor, specifically designed to inhibit the HCV nonstructural protein 3 (NS3) protease and, thereby, inhibit viral replication in infected host cells. The mechanism of inhibition involves formation of a stable reversible covalent bond between the ketoamide of boceprevir and the NS3 protease active site serine, which is the protease that mediates the cleavage of the HCV polyprotein to form the functional proteins essential for viral propagation. This mechanism is distinct from those of currently approved therapies; thus, boceprevir represents a novel class of HCV inhibitors.

Proposed therapy is first initiated with a 4-week treatment period with peginterferon alpha and ribavirin after which time boceprevir is added for a duration depending on the patient's response to therapy. Based on the results of the pivotal trials, the recommended dosing regimen is boceprevir 800 mg orally (PO) three times per day (TID) using response-guided therapy (RGT) based on response at Treatment Week (TW) 8. Previously untreated patients receive a

total treatment duration of 28 (RGT) or 48 weeks while previous SOC failures receive 36 (RGT) or 48 weeks. For patients assigned to the longer duration of therapy, the remainder of treatment was 20 weeks for previously untreated patients and 12 weeks for previous SOC failures with peginterferon alpha plus ribavirin alone. The duration of boceprevir therapy is limited to 24 or 32 weeks for the previously untreated and previous treatment-failure patients, respectively. The primary efficacy endpoint of the boceprevir studies is SVR (undetectable HCV-RNA 24 weeks after completion of therapy).

These completed Phase 2/3 studies evaluated the efficacy and safety of boceprevir using the recommended dose (800 mg TID) of boceprevir added to PR standard of care. For safety, data from the two SOC naive trials, P03523 and P05216, were pooled by combining data from the two standard-of-care (PR) arms and then combining data from all arms including boceprevir therapy (BOC/PR). For efficacy, data from the PR control arms were pooled, and data from the one identical treatment arm in both studies, the BOC/PR48 arm (48-week treatment duration with a 4-week PR lead-in), were pooled.

FDA was consulted during the transition from Phase 2 to Phase 3 in regard to issues involving dose, durations, and optimization of treatment regimens. Feedback was obtained at discussions held on May 30, 2006, and in November 2007. FDA concurred that data from P03659 together with available data from P03523 were sufficient to warrant start of Phase 3 studies. For the Phase 3 program, agreements were reached that 1) two well-controlled studies were sufficient to support licensure; 2) a lead-in phase was acceptable for these studies; 3) a 48-week boceprevir treatment arm, as well as a short-term arm with response-guided parameters were appropriate; 4) futility criteria were needed for SOC failures; and 5) long-term follow-up should be conducted for at least 3 years. The final Phase 3 protocols were submitted in February 2008 and fulfilled these general requirements.

Results of Sponsor's Analysis

Introduction

The applicant evaluated exposure-response efficacy and safety relationships for boceprevir and ribavirin in two separate reports: study-report-phase-1-2-pk-pd.pdf and study-report-phase-3-pk-pd.pdf. The initial report (Phase I/II) focused on dose selection while the second report (Phase III) investigated relationships between probability of SVR at 24 weeks or key adverse events (i.e. anemia based on laboratory hemoglobin measurement < 10 g/dL) based on boceprevir and ribavirin exposures.

Phase I/II Dose Response Analysis

Report study-report-phase-1-2-pk-pd.pdf: Pharmacokinetics-Pharmacodynamics of Boceprevir Using Phase 1 and 2 Studies to Explore Phase 3 Dose

Data

The data included in the population PK-PD model development was obtained from five Phase 1 studies (P03527, P03648, P03516, and P04487/P04531) and two Phase 2 studies (P03523 and P03659) conducted in subjects infected with HCV. Of these studies, three (P03527, P03648, and P03523) did not have PK data with corresponding viral load. A summary of the Phase I studies used in developing the population PK model for Phase II analysis is shown in Table 40.

Table 40: Phase 1 Studies Used for the Construction of the Population-Pharmacokinetic Model Used in Study P03659

Study	Type of Subjects	Number of Subjects
P04487	Hepatitis C Virus	16
P04488	Healthy	34
P04624	Healthy	12
P03516	Hepatitis C Virus	64
P03527	Hepatitis C Virus	23
P03648	Hepatitis C Virus	29

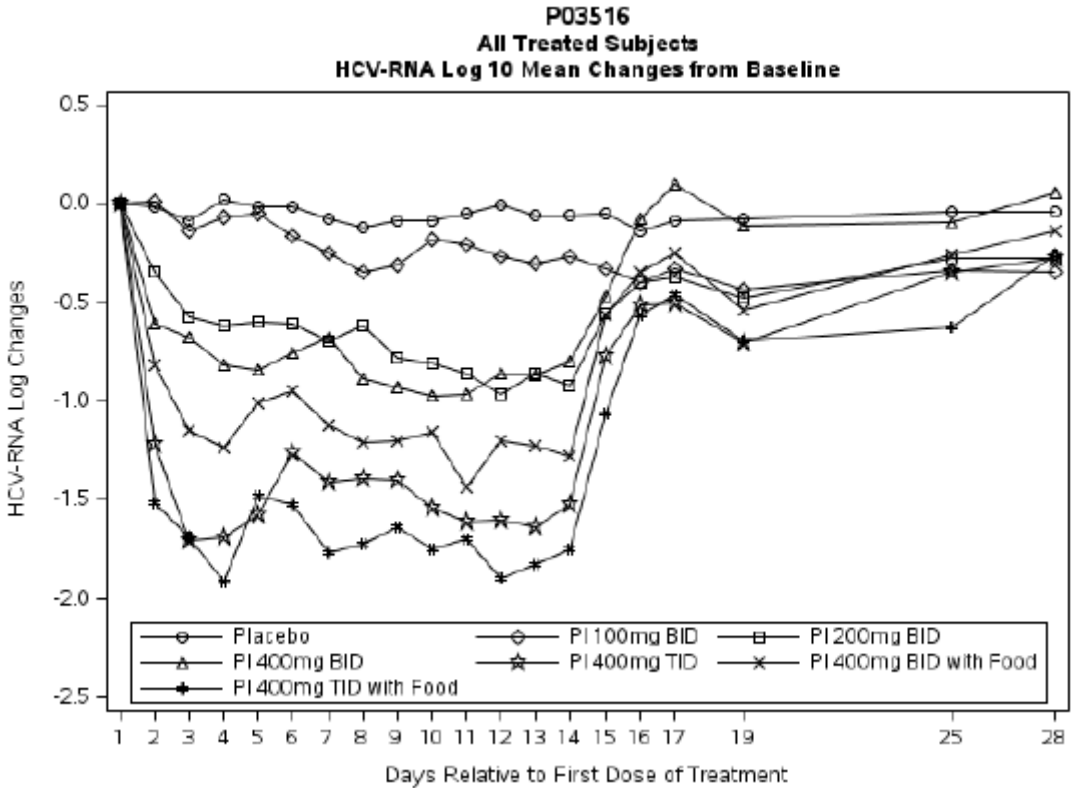
Sponsor's study-report-phase-1-2-pk-pd.pdf, page 10

Results

Relationships Between Viral Load Change and Pharmcokinetics or Dose From P03516

Study P03516 was a randomized, third-party blind, placebo-controlled, multiple-dose study in HCV genotype 1 interferon-nonresponders. The PK-related objective in this study was to determine the correlation between the dosing regimen of boceprevir monotherapy and the change in viral load (HCV-RNA) for various boceprevir doses and schedules. Six groups (n=7-12 per group) received 14 days of boceprevir Monotherapy. The results showed that the mean maximal viral load drops from baseline following boceprevir administration for 14 days in each of these six groups were -0.43, -0.96, -0.98, -1.69, -1.44, and -1.91, respectively Figure 23 and Figure 24), and the highest reduction in viral load was observed with the group administered boceprevir at 400 mg TID with food. These results indicate that dosing at the most frequent interval (TID), at the highest dose (400 mg), with food (and thus increased exposure) result in the greatest antiviral activity.

Figure 23: Mean log10 HCV-RNA Viral Load Change Over Time from P03516. Patients Received HCV Treatment From Day 1 Through Day 14.



Sponsor's study-report-phase-1-2-pk-pd.pdf, page 11

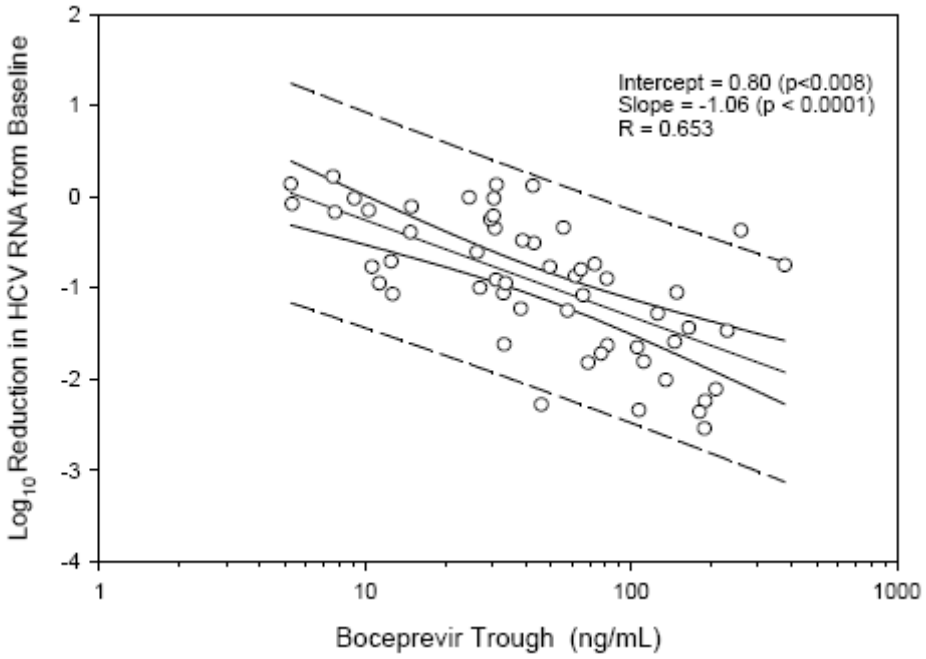
Table 41: Mean (SD) Maximal Viral Load Drop From Baseline and Mean (CV%) AUC(τ) Following Boceprevir Administration for 14 Days

	BOC 100 mg BID (n=12)	BOC 200 mg BID (n=12)	BOC 400 mg BID (n=11)	BOC 400 mg TID (n=10)	BOC 400 mg BID With Food (n=12)	BOC 400 mg TID With Food (n=7)
Maximal Viral Load Drop (Δlog10)	-0.43 (0.40)	-0.96 (0.54)	-0.98 (0.57)	-1.69 (0.62)	-1.44 (0.79)	-1.91 (0.76)
AUC(τ) (ng·hr/mL)	700 (33)	1390 (28)	1640 (32)	1990 (16)	3620 (35)	2990 (33)

Sponsor's study-report-phase-1-2-pk-pd.pdf, page 11

The relationship between the reduction in HCV-RNA levels (log-transformed values) and C_{trough}, C_{max}, and AUC_{τ} of boceprevir on dosing Day 14 were also examined. This analysis excluded data in the fed state from seven subjects because dosing in a fasted state had the most data at different dose levels. Regression analyses were performed between log10 changes in viral load from baseline and log10 PK parameters of boceprevir. The data indicate that maximal HCV-RNA drop correlated best (larger correlation coefficient value, R=0.653) with trough concentrations of boceprevir (Figure 24); a less robust relationship was noted for C_{max} (R=0.466) and AUC (R=0.511). The PK/PD correlation is consistent with the assumption that the maintenance of high C_{trough} levels of boceprevir is associated with high efficacy.

Figure 24: Log10 Boceprevir C_{trough} Versus Predicted Mean ± 90% CI Log10 Changes in Viral Load (Day 14) from P03516



Sponsor's study-report-phase-1-2-pk-pd.pdf, page 13

Reviewer's Comments: The sponsor performed a preliminary exposure-response analysis based on data from P03516 and observed a dose-dependent change in HCV-RNA viral load for treatment with boceprevir as a monotherapy. In addition, the sponsor developed a linear relationship between changes in viral load at day 15 on monotherapy versus boceprevir PK parameters and found the best correlation with boceprevir C_{trough}. However, resistant to direct-acting antivirals rapidly develops during monotherapy treatment, and this analysis should have been performed using data from earlier on treatment (Day 4-5).

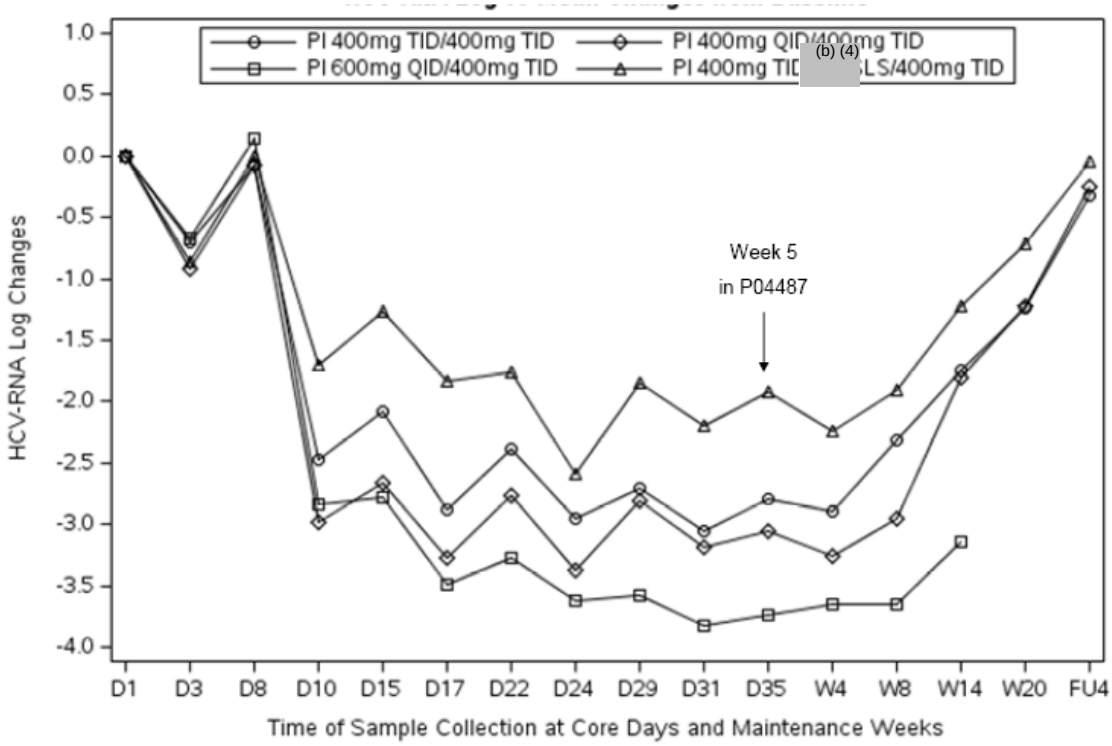
Correlation between Viral Load and Boceprevir PK Following Combination Therapy in P04487/P04531

Study P04487 was a randomized, controlled, open-label, multiple-dose, parallel group, exploratory study of boceprevir in HCV genotype 1 subjects. Study P04531 was an open-label, multiple-dose study evaluating the long-term safety, effectiveness, and antiviral activity of boceprevir in those subjects who completed the core treatment protocol (P04487) with boceprevir. The PK-related objectives in these two studies were to examine the relationship between the dosing frequency of boceprevir in combination with peginterferon alfa-2b and the change in viral load (HCV-RNA). All subjects received peginterferon alfa-2b starting at Day 1, and started on the treatment arm dose of boceprevir (400 mg TID – original formulation, 400 mg QID – original formulation, 600 mg QID – original

formulation, 400 mg TID – current formulation) starting on Day 8. Subjects received 400 mg TID (original formulation) and peginterferon alfa-2b (PEG2B) for 20 weeks in P04531.

The mean log10 changes from baseline in HCV-RNA during both the exploratory and maintenance protocols from P04487/P04531 showed the greatest maximal mean HCV-RNA declines were observed for boceprevir at either 400 or 600 mg QID (4.05 and 4.18 [Δlog10 HCV-RNA], respectively) (Figure 25). The median maximum change in HCV-RNA was lower for both TID dosing arms (400 mg TID – original formulation: 3.30; 400 mg TID – current formulation: 2.66).

Figure 25: HCV-RNA Log10 Mean Change from Baseline Over Time for Four Boceprevir Treatment Arms from P04487/P04531

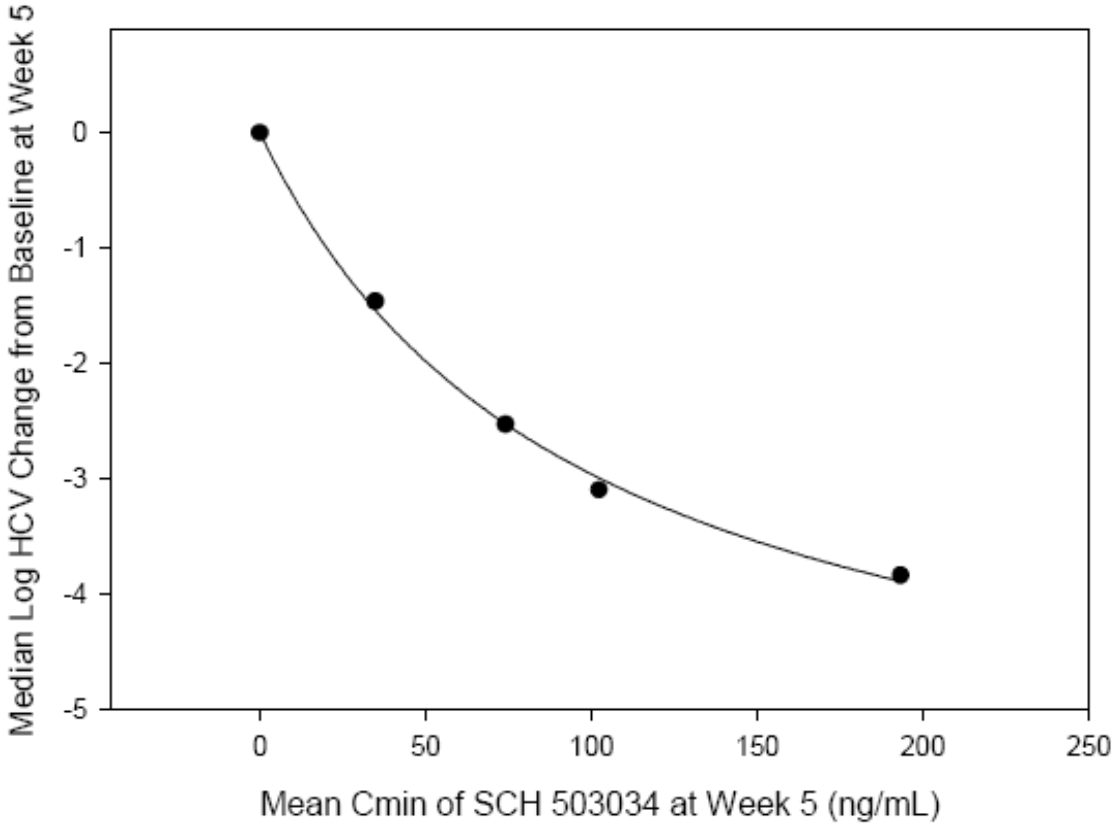


Sponsor's study-report-phase-1-2-pk-pd.pdf, page 16

C_{trough} was chosen as the PK parameter to further examine PK/PD relationship between boceprevir and antiviral activity in combination therapy in HCV genotype 1 PEG2b nonresponder subjects given the somewhat stronger association with maximal HCV-RNA than other PK parameters in prior analyses. The relationships between mean of boceprevir C_{trough} at Week 5 for each C_{trough} quartile and its corresponding early responsiveness to combination treatment as measured by median log10 HCV-RNA change at Week 5 is presented in Figure 26. There was a consistent moderate positive correlation between boceprevir C_{trough} and reduction in viral load. The lines represent curve fit by a simple E_{max} (maximum log10 HCV decline from baseline) model. The model estimated E_{max} value (Week 5) (in this case, maximum log HCV-RNA decline from baseline) was

-5.86 (±0.316) and effective concentration (EC_{50}) was 97.8 (±11.3) ng/mL (Figure 26), which is similar to the in vitro IC_{50} (~100 ng/mL).

Figure 26: Relationship Between Boceprevir C_{trough} at Week 5 and Early Responsiveness to Combination Treatment With Boceprevir and Peginterferon alfa-2b (log HCVRNA change from baseline at Week 5



Sponsor's study-report-phase-1-2-pk-pd.pdf, page 18

<u>Reviewer's Comments</u>: The sponsor performed a preliminary exposure-response analysis based on data from P04487/P04531 and observed greatest decreases in HCV-RNA viral load with QID boceprevir dosing compared to TID (no ribavirin was administered with this regimen). This suggests that more frequent QID dosing may have result in more rapid viral decline and improved efficacy; however, this dosing schedule was not evaluated further by the sponsor.

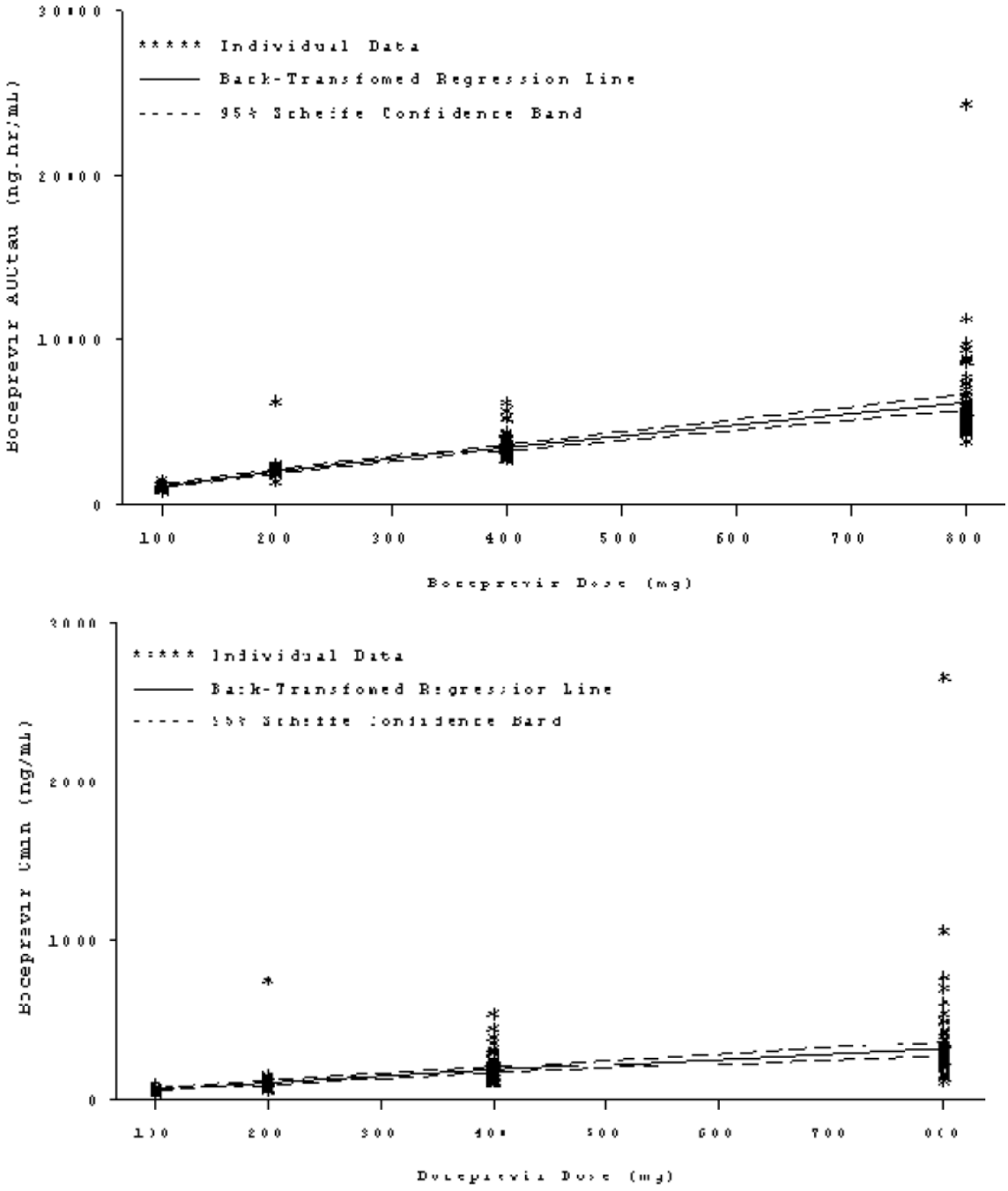
The appropriateness of the TID regimen was justified based on an E_{max} exposure-response relationship developed from change in viral load data at week 5 and boceprevir trough concentrations from P04487/P04531. The model predicts a similar decrease in viral load between C_{trough} of 100-200 ng/mL, and the sponsor selected a dose and dosing frequency to target that range. This analysis should also have included counts of patients that developed resistance while on treatment and the corresponding exposure interval they were within.

Relationship between Population PK (AUC, C_{max}, and C_{trough}) to Boceprevir Dose

The Phase 2 dose-ranging study of boceprevir (P03659) was a randomized, blinded, safety and efficacy study of four dose levels of boceprevir in HCV genotype 1 nonresponder subjects. Subjects in Arms 1 to 6, were treated with a single dose of PEG2b (1.5 µg/kg SC) for 1 week. This was followed by PEG2b (1.5 µg/kg SC QW) plus double-blinded treatment with either boceprevir (100, 200, or 400 mg TID) or placebo plus either ribavirin (800-1400 mg/day) or placebo, for an additional 24 or 48 weeks. Sparse PK concentration data from subjects in this study were combined with intensive PK concentration data from six Phase 1 studies (P04487, P04488, P04624, P03516, P03527, and P03648) for population PK analysis.

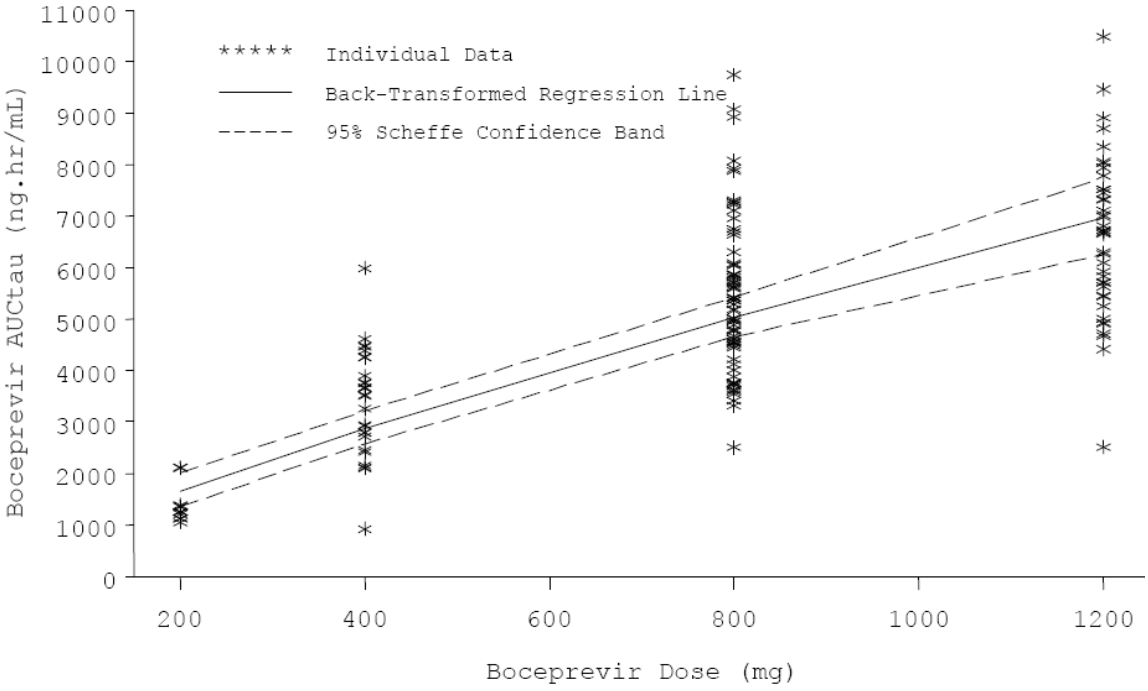
Predicted parameters from PPK model applied to P03659 data demonstrated a less than dose-proportional increase in AUC and C_{trough} (Figure 27) (similar relationships for C_{max} not shown) of boceprevir from the 100 mg TID to 800 mg TID dose groups. Also, dose-proportional assessment using power-law model on Phase 1 data showed that boceprevir AUC, C_{max}, and C_{trough} were less than dose-proportional and fairly overlapped from 800 mg and 1200 mg. Therefore, dose escalation past 800 mg TID will not substantially increase trough concentrations and associated efficacy since C_{trough} has good association with viral load drop.

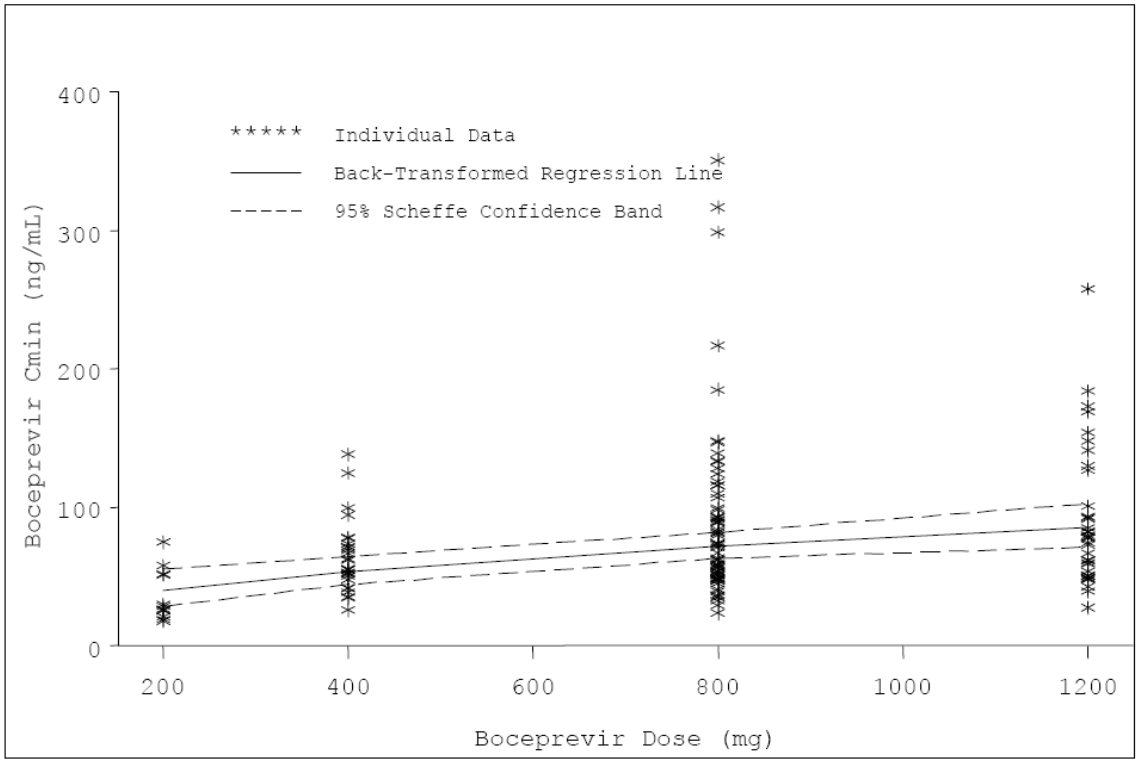
Figure 27: Dose Proportionality Assessment for AUC and C_{trough} Following Administration of Boceprevir TID to Fed HCV Genotype-1 Subjects from P03659



Sponsor's study-report-phase-1-2-pk-pd.pdf, page 21

Figure 28: Dose Proportionality Assessment for AUC Following Administration of Boceprevir TID to Fed Healthy Subjects (Combined Phase I Studies)





Sponsor's study-report-phase-1-2-pk-pd.pdf, page 23

<u>Reviewer's Comments</u>: The sponsor's early Phase population PK analysis indicates a less-than dose proportional increase in exposure with boceprevir doses above 800 mg TID. These results demonstrate that increasing boceprevir doses would have diminishing increases in exposure, but do not demonstrate that a higher dose would have resulted in unacceptable increases in toxicity or

non-significant increases in efficacy. Modeling and simulation might have helped at this stage of drug development by combining data from all Phase I/II trials and assessing exposure-response efficacy and safety relationships.

Phase III Dose Response Analysis

Report study-report-phase-3-pk-pd.pdf: Pharmacokinetics-Pharmacodynamics of Boceprevir Using Phase 3 Data

Data Sets

The Phase 3 P05101 and P05216 studies each included three arms: (1) standard-of-care (SOC) control of 1.5 µg/kg/week of PEGINTRON (pegylated interferon) plus 600-1400 mg/day (weight-based) of REBETOL (ribavirin) for 48 weeks; (2) 4-week SOC lead-in followed by the addition of boceprevir 800 mg TID for 44 weeks, and (3) response-guided therapy, like Arm 2 except that patients with undetectable virus at week 8, and again at certain points later in the studies, were able to stop all treatment at 36 weeks in P05101 and at 28 weeks in P05216 (patients who did not meet these criteria continued SOC treatment for a total treatment duration of 48 weeks). Study P05101 patients had failed previous therapy, while study P05216 patients were SOC naive.

A population pharmacokinetic (PPK) analysis pooled measurements from seven Phase 1-3 studies was used for generating individual predictions of steady-state Cmin, Cmax, and AUC of each included subject, including a subset of the P05101 and P05216 patients. Similarly, individual predictions were generated for ribavirin plasma concentrations measured in Studies P05101 and P05216. Table 42 shows the number of patients available for analysis by study and type of data.

Table 42: Combined PK and Efficacy/Safety Data Available from Phase III Patients

		PD Data			PK Individual Predictions			
Study	N	All Arms	Control		BOC	BOC+Ctrl.	RBV	Both
P05101	403	258	52		49	101	60	57
P05216	1097	653	217		67	284	107	103
Total	1500	911	269		116	385	167	160

Sponsor's study-report-phase-3-pk-pd.pdf, page 9

Methods

Exposure-Response Relationships

Exposure-response relationships were explored visually in exploratory plots and

were tested using multivariate logistic regression approaches. The multivariate logistic regression analyses were conducted using a 2-step approach; that is, individual pharmacokinetic parameter values were first determined and then a statistical analysis of the potential relationship between PK and a variety of efficacy/safety response parameters was performed. Boceprevir PK parameters were available for 49 patients in P05101 and 67 patients in P05216 and included C_{trough}, C_{max}, and AUC_{τ}. The antiviral efficacy responses being assessed in the multivariate logistic regression analyses included: SVR (undetectable viral load at week 24 or missing data from week 24 but undetectable at week 24), Early Viral Response (EVR) at Weeks 8, 12, 24 and End of Treatment (EOT) (undetectable viral load at these time points). One additional safety response, anemia, was also examined, defined as an on treatment lab measurement of hemoglobin <10 g/dL.

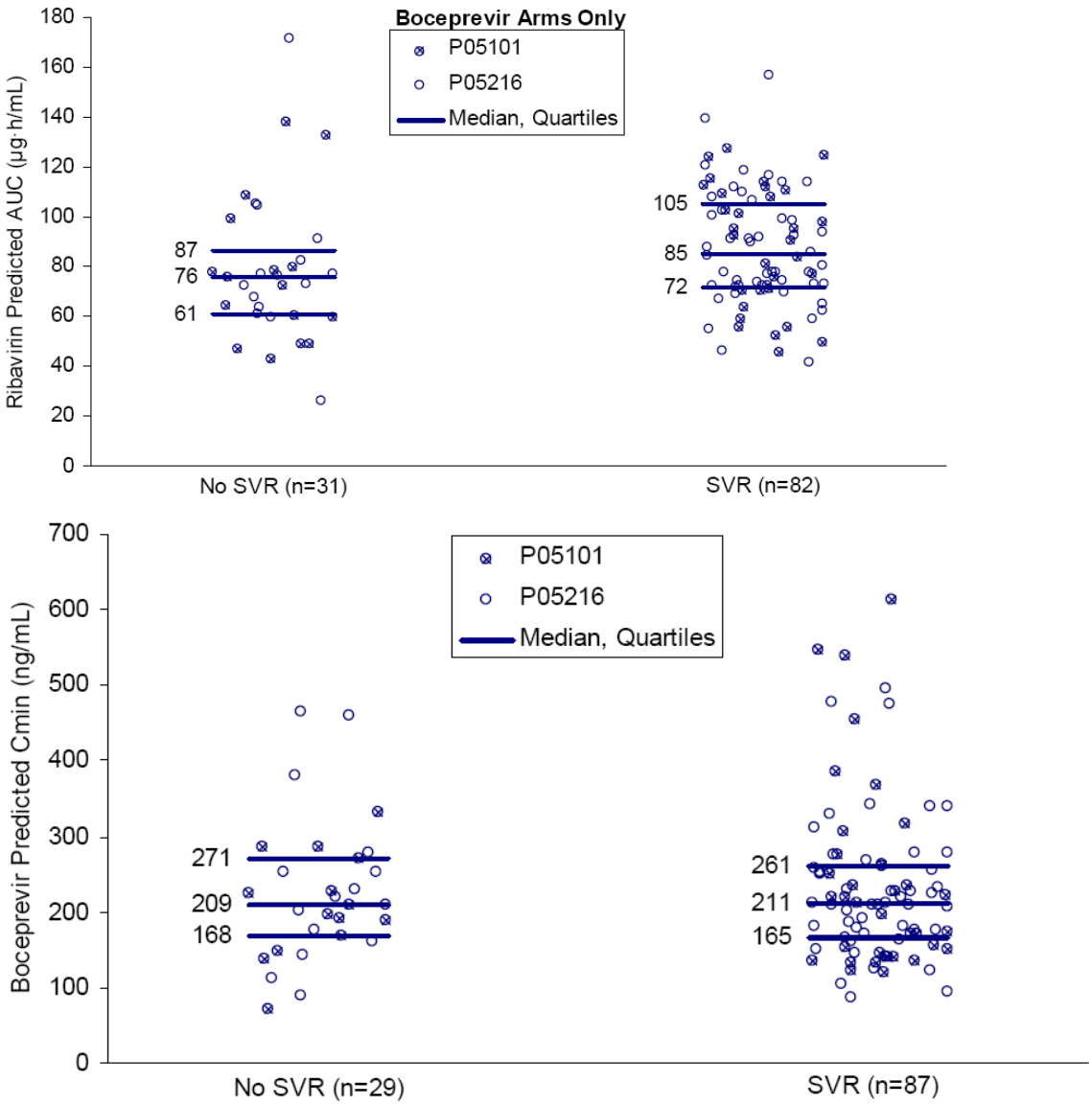
The potential associations between PK parameters and efficacy/safety response measures were assessed through logistic regression models. Some of these models also included other factors known to influence efficacy outcome: ribavirin PK (AUC), previous response, baseline HCVRNA, race, fibrosis, change from baseline in HCV-RNA at Week 4 and IL28 genotype.

Exposure-response Results

Exploratory Exposure-response Analysis: SVR

Evaluation of the potential exposure-response relationships in the PK/PD dataset were conducted using exploratory graphical approaches and were formally tested with a multivariate logistic regression approach. Figure 29 illustrates the range of individual ribavirin and boceprevir PK values obtained in Phase 3 patients achieving or not achieving SVR. Somewhat higher ribavirin exposures are noted in patients with SVR versus without, which may suggest an association of ribavirin exposures with SVR achievement. No clear differences in boceprevir exposures between patient achieving SVR or not were noted, suggesting that boceprevir response may have little association with viral response in the Phase 3 studies.

Figure 29: Ribavirin (top) and Boceprevir (bottom) Exposure Measures for Patients With and Without SVR



Sponsor's study-report-phase-3-pk-pd.pdf, page 11-12

Exposure-response Analysis: Boceprevir PK and Viral Response for Protocol P05101

For SVR, EVR at Week 24 and EOT, the following covariates were included in the logistic regression: previous response (Some Negative/Never Negative), baseline HCV-RNA (≤800,000/>800,000 IU/mL), fibrosis (0/1/2 or 3/4), change from baseline in log10 HCV-RNA at Week 4 (log10 IU/mL), ribavirin $AUC_{0\text{-}24}$ (µg·h/mL) and boceprevir PK parameters. The factor IL28 genotype (CC, CT or TT) caused quasicomplete separation in the model for these endpoints and therefore was excluded. For EVR at Weeks 8 and 12, IL28 genotype did not cause convergence issue and was included in the model. For each endpoint, the estimated odds ratios associated with one unit increase in boceprevir PK

parameter are presented in Table 43 along with corresponding 95% CI and p-value.

Marginally significant associations ($p<0.05$) were identified between EVR at Week 8 and all boceprevir PK AUC and Cmax, indicating some association of exposure with response in early therapy. However, none of the viral responses after Week 8, including the primary endpoint of SVR, appear to be correlated with the examined boceprevir exposures. For ribavirin AUC_{0-24}, other than marginally significant association with EVR at Week 12, was not found to be significantly correlated with the various viral responses under examination.

Table 43: Boceprevir PK Parameter as a Predictor of Antiviral Resposne in P05101

	n‡	N‡	Odds Ratio (95% CI)†	p-Value†
Sustained viral response (SVR)				
AUC at Steady State (µg·hr/mL)	29	41	0.973 (0.575, 1.645)	0.918
Cmin (ng/mL)	29	41	1.000 (0.992, 1.008)	0.992
Cmax (ng/mL)	29	41	1.000 (0.998, 1.002)	0.947
Early viral response (EVR) at Week 8				
AUC at Steady State (µg·hr/mL)	24	41	2.285 (0.851, 6.134)	0.047
Cmin (ng/mL)	24	41	1.011 (0.996, 1.027)	0.066
Cmax (ng/mL)	24	41	1.004 (0.999, 1.008)	0.034
Early viral response (EVR) at Week 12				
AUC at Steady State (µg·hr/mL)	30	41	1.061 (0.569, 1.978)	0.850
Cmin (ng/mL)	30	41	1.002 (0.992, 1.011)	0.688
Cmax (ng/mL)	30	41	1.000 (0.997, 1.002)	0.900
Early viral response (EVR) at Week 24				
AUC at Steady State (µg·hr/mL)	32	41	1.112 (0.592, 2.088)	0.737
Cmin (ng/mL)	32	41	1.002 (0.992, 1.011)	0.708
Cmax (ng/mL)	32	41	1.000 (0.998, 1.003)	0.807
Early viral response (EVR) at End of Treatment				
AUC at Steady State (µg·hr/mL)	32	41	1.112 (0.592, 2.088)	0.737
Cmin (ng/mL)	32	41	1.002 (0.992, 1.011)	0.708
Cmax (ng/mL)	32	41	1.000 (0.998, 1.003)	0.807

Sponsor's study-report-phase-3-pk-pd.pdf, page 15

Reviewer's Comments: The sponsor's logistic regression analysis does not take into account the different boceprevir treatment arms used during the study, nor does it differentiate between patients that are eligible for early treatment completion versus those patients characterized as late responders (i.e. treated for the entire 48 week duration). It is observed that the impact of boceprevir on SVR rate was less pronounced in patients who responded well during the 4 week lead-in phase (≥ 2 log decline in viral load) (81% SVR for BOC+SOC; 36% SVR for SOC) compared patients without a substantial lead-in phase antiviral

response (47% SVR for BOC+SOC; 8% SVR for SOC). The analysis should have separated these populations prior to the logistic regression analysis rather than including it as a model covariate. In addition, the sponsor should have investigated these same populations in relation to ribavirin exposure prior to adding boceprevir PK parameters in the model.

Potential relationships between boceprevir and/or ribavirin exposures may have been masked due to the small number of subjects with boceprevir exposure available from P05101 (n= 49 with non-zero boceprevir exposure measurements). The reviewer will explore exposure-response relationships using the entire Phase III population with boceprevir and ribavirin exposure data available. In addition, the review will investigate utility of lab measures such as on treatment change in hemoglobin as a possible surrogate for boceprevir and ribavirin exposure.

Exposure-response Analysis: Boceprevir PK and Viral Response for Protocol P05216

Covariates race (Blacks/Non-blacks), fibrosis (0/1/2/ or 3/4), IL28 genotype (CC, CT or TT), change from baseline in log10 HCV-RNA (log10 IU/mL), ribavirin. AUC_{0-24} (µg·hr/mL) and boceprevir PK parameter were included in the logistic regression for SVR, EVR at Weeks 8 and 24. Baseline HCV-RNA (≤400,000/>400,000 IU/mL) caused quasi-complete separation for all endpoints therefore was excluded from all models. Race caused quasi-complete separation for EVR at Week 12 and EOT, so it was excluded in model for these two endpoints. The estimated odds ratio, 95% CI and p-value were reported in Table 44.

Similar to findings with protocol P05101, none of the boceprevir PK parameters were found to be significantly correlated to viral response, including the early response at Week 8. For ribavirin AUC_{0-24}, other than marginally significant association with EVR at End of Treatment, was not found to be significantly correlated with the various viral responses under examination.

Table 44: Boceprevir PK Parameter as a Predictor of Antiviral Resposne in P05216

	n‡	N‡	Odds Ratio (95% CI)†	p-Value†
Sustained viral response (SVR)				
AUC at Steady State (µg·hr/mL)	49	60	1.159 (0.649, 2.069)	0.615
Cmin (ng/mL)	49	60	1.002 (0.993, 1.011)	0.666
Cmax (ng/mL)	49	60	1.001 (0.998, 1.003)	0.574
Early viral response (EVR) at Week 8				
AUC at Steady State (µg·hr/mL)	43	60	0.747 (0.445, 1.254)	0.267
Cmin (ng/mL)	43	60	0.996 (0.989, 1.004)	0.363
Cmax (ng/mL)	43	60	0.999 (0.997, 1.001)	0.212
Early viral response (EVR) at Week 12				
AUC at Steady State (µg·hr/mL)	53	60	1.062 (0.533, 2.116)	0.864
Cmin (ng/mL)	53	60	1.002 (0.992, 1.013)	0.680
Cmax (ng/mL)	53	60	1.000 (0.997, 1.002)	0.873
Early viral response (EVR) at Week 24				
AUC at Steady State (µg·hr/mL)	51	60	0.672 (0.391, 1.153)	0.148
Cmin (ng/mL)	51	60	0.994 (0.986, 1.002)	0.137
Cmax (ng/mL)	51	60	0.999 (0.997, 1.001)	0.190
Early viral response (EVR) at End of Treatment				
AUC at Steady State (µg·hr/mL)	53	60	1.171 (0.583, 2.352)	0.653
Cmin (ng/mL)	53	60	1.003 (0.993, 1.014)	0.543
Cmax (ng/mL)	53	60	1.000 (0.997, 1.003)	0.910

Sponsor's study-report-phase-3-pk-pd.pdf, page 16

Reviewer's Comments: As for P05101, the sponsor's logistic regression analysis does not take into account the different boceprevir treatment arms used during the study, nor does it differentiate between patients that are eligible for early treatment completion versus those patients characterized as late responders (i.e. treated for the entire 48 week duration). For P05216, It is observed that the impact of boceprevir on SVR rate was les pronounced in patients who responded well during the 4 week lead-in phase (≥ 2 log decline in viral load) (85% SVR for BOC+SOC; 69% SVR for SOC) compared patients without a substantial lead-in phase antiviral response (52% SVR for BOC+SOC; 15% SVR for SOC). The analysis should have separated early and late responders as the impact of boceprevir (or ribavirin) may be masked by the greater contribution from the interferon-response. The reviewer's analysis further investigates the impact of treatment duration from response-guided therapy on treatment outcome.

Exposure-response Analysis: Boceprevir and Ribavirin Exposure versus Anemia

Similar to the section on exposure-response for viral response, this section

examines the potential for exposure-response relationships with occurrence of anemia through a combination exploratory graphical and multivariate logistic regression approaches. Increasing ribavirin AUC_{0-24} was found to be significantly associated with increased incidence rate of anemia. Regardless of which boceprevir PK parameter was modeled, the estimated odds ratio associated with one unit increase of ribavirin AUC_{0-24} was 1.048, with corresponding 95% CI (1.029, 1.068) and p-value <.0001. When translated into probability, at the median value of steady state boceprevir AUC of 3.6 µg·hr/mL, the predicted probability of anemia incidence (95% CI) are 25.2% (16.9%, 35.8%), 38.5% (30.1%, 47.7%) and 68.8% (56.5%, 78.9%) at 20%, 50% and 80% percentile of observed ribavirin AUC0-24 in these two Phase III studies. On the other hand, none of the boceprevir PK parameters was found to be correlated with anemia incidence rate.

Table 45: Boceprevir PK Parameters as a Predictor of Anemia (P05101 and P05216 Combined)

	n‡	N‡	Odds Ratio (95% CI)†	p-Value†
Anemia Status				
AUC at Steady State (ug.h/mL)	71	160	1.070 (0.930, 1.232)	0.344
Cmin (ng/mL)	71	160	1.001 (0.998, 1.004)	0.412
Cmax (ng/mL)	71	160	1.000 (1.000, 1.001)	0.374

Sponsor's study-report-phase-3-pk-pd.pdf, page 16

Reviewer's Comments: The sponsor combined data from P05101 and P05216 for evaluating exposure-response safety relationships between boceprevir and/or ribavirin exposure and anemia. None of the PK parameters were found to be correlated with anemia event rate; however, patients on boceprevir had a mean decrease of 1 g/dL in hemoglobin lab measurements compared to patients receiving only SOC. The identification of a possible exposure response relationship between boceprevir exposure and anemia was hindered by the small number of subjects with non-zero boceprevir exposures available for the analysis (n=116). The reviewer will investigate exposure-response relationships between boceprevir and ribavirin exposure variables and provide comments on any observable trends.

Reviewer's Analysis

Introduction

The aim of this review to examine exposure-response efficacy and safety relationships for boceprevir and ribavirin, evaluate alternative surrogates for boceprevir or ribavirin exposure to compensate for the small population subset with exposure measures available, and explore the validity of response-guided therapy in early and later responders based on results from P05101 and P05216.

Objectives

Analysis objectives are:

1. Evaluate exposure-response efficacy relationships between boceprevir or ribavirin and sustained virologic response 24 weeks after completion of treatment (SVR24)
2. Evaluate exposure-response safety relationships between boceprevir or ribavirin and anemia based on treatment lab measurement of hemoglobin (Hb) <10 g/dL
3. Determine if response-guided therapy (RGT) resulted in similarly efficacy results for patients receiving a shortened duration of therapy
4. Evaluate change in Hb as a surrogate for boceprevir and/or ribavirin exposure and evaluate relationships between SVR and change in Hb for patients classified as early (undetectable viral load at week 8) and late (detectable viral load at week 8) viral responders

Methods

Data Sets

Data sets used are summarized below.

Table 46: Analysis Data Sets

Study Number	Name	Link to EDR
P03523	(b) (4) t	\\cdsesub1\evsprod\NDA202258\0002\m5\datasets\p03523aims
P05101	(b) (4)	\\cdsesub1\evsprod\NDA202258\0002\m5\datasets\p05101aims \\cdsesub1\evsprod\NDA202258\0001\m5\datasets\p05101\analysis\datasets
P05216	(b) (4)	\\cdsesub1\evsprod\NDA202258\0002\m5\datasets\p05216aims \\cdsesub1\evsprod\NDA202258\0001\m5\datasets\p05216\analysis\datasets
popPK/PD	20100910p05101exposurebypoppkid.csv, 20100910p05216exposurebypoppkid.csv	\\cdsesub1\evsprod\NDA202258\0001\m5\datasets\phase-3-pk-pd\analysis\datasets

Software

Analysis workflow was organized and maintained using the Statistical Computing Environment Waban. Diagnostic graphs, model comparison, and statistical analysis were performed in R (version 10.1).

Models

Logistic Regression: Efficacy and Safety Exposure-Response Relationships

Logistic regression models for patients achieving SVR and the primary on treatment adverse event (anemia based on lab Hb < 10 g/dL) were performed using the applicant's Phase III trial data. Three boceprevir exposure variables (C_{trough}, C_{max}, and AUC_{τ}) and one ribavirin exposure variable (AUC_{0-24}) were used for developing logistic regression plots. This analysis was limited to those patients with boceprevir and ribavirin exposure information available as summarized in Table 47 below.

Table 47: Combined PK and Efficacy/Safety Data Available from Phase III Patients

		PD Data			PK Individual Predictions			
Study	N	All Arms	Control		BOC	BOC+Ctrl.	RBV	Both
P05101	403	258	52		49	101	60	57
P05216	1097	653	217		67	284	107	103
Total	1500	911	269		116	385	167	160

In addition to above logistic regression analysis, minimum on treatment hemoglobin measurement was evaluated with respect to percentage of patients achieving SVR. This independent variable was selected as it was correlated with ribavirin exposure, which had a trend of increasing SVR with increasing exposures, but was non-significant due to the small treatment sample size. Evaluating minimum on treatment hemoglobin as a surrogate for ribavirin exposure allows the entire efficacy population to be included in the exposure-response efficacy analysis and allows investigation of the potential impact of ribavirin exposure on patients based on lead-in phase (week 4) or treatment decision (week 8) viral load response.

Response-Guided Therapy (RGT) Treatment Duration

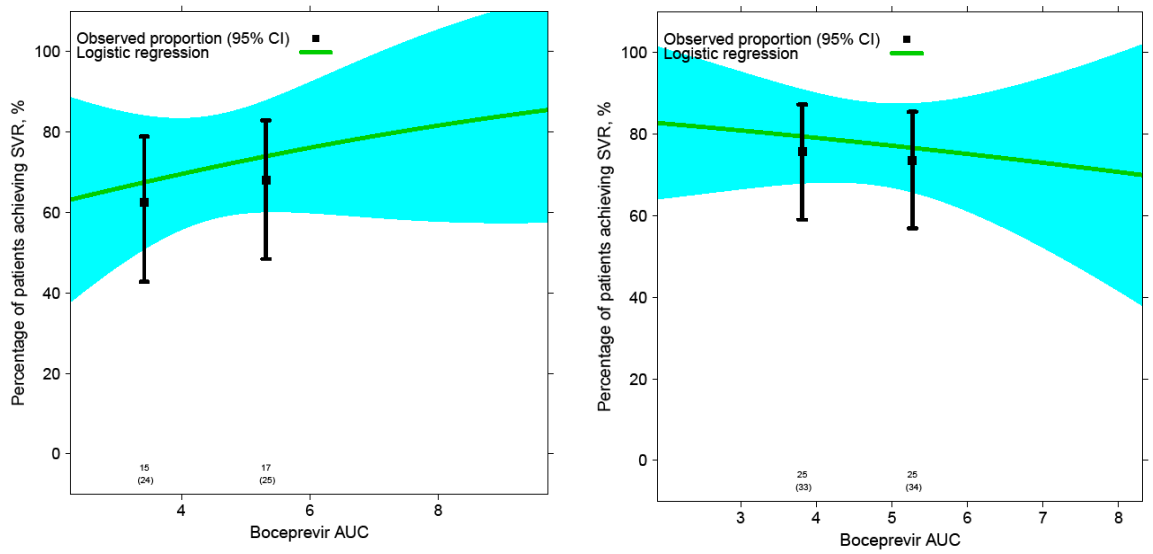
The impact of RGT for SOC naive (P05216) and SOC failure (P05101) was explored using sponsor's provided efficacy data sets ((b) (4)). Exploration of treatment outcome was limited to those patients receiving the correct treatment as outlined in the protocol, and a more detailed description of the methods used for identifying those patients who received incorrect treatment duration in the RGT treatment arms is included in Dr. Zeng's analysis. Briefly, for P05216, 161 and 68 early and late responders, respectively, in Arm 2 received the correct treatment based on viral load measurements between week 8 and 24 and received treatment through week 28 of the study. Similarly, 161 and 73 patients classified as early and late responders, respectively, from Arm 3 received treatment through week 28.

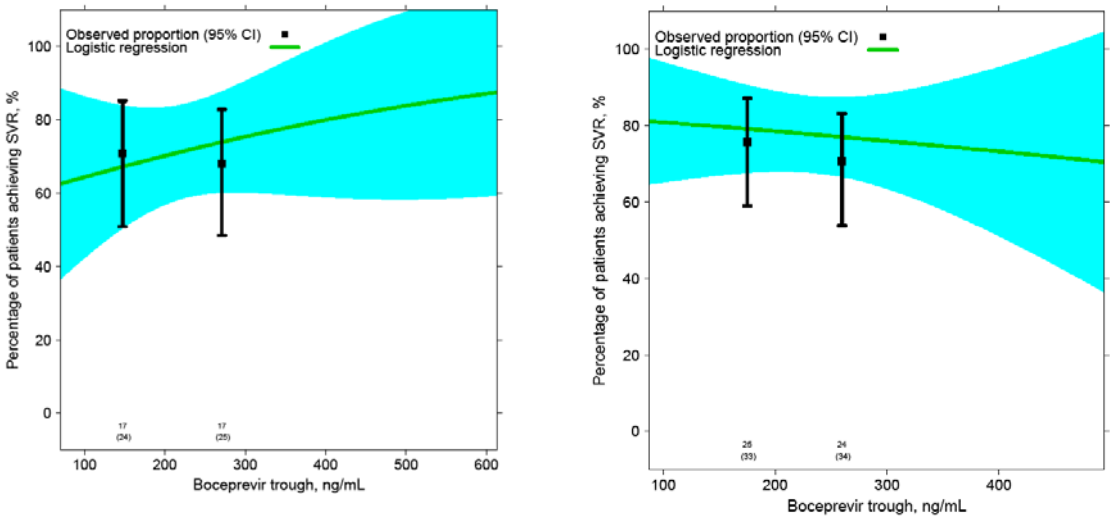
Results

Exposure-Response for Efficacy: SVR

Logistic regression models were evaluated for boceprevir AUC_T (top) and C_{trough} (bottom) for P05101 (left) and P05216 (right) with no significant relationships identified (Figure 30). Modeling results indicate a shallow but increasing trend between boceprevir exposure and SVR from P05101 that may indicate an exposure-response relationship for boceprevir in previous SOC failures. However, an decreasing, shallow trend was observed between boceprevir exposure and SVR for P05216. It is difficult to interpret the results of this analysis divided by study due to the small number of subjects included in the analysis. One method of addressing this limitation is combining both study populations as was presented in Figure 30. Alternatively, the exposure-response analysis can be performed with patients who received only SOC, treating observed boceprevir concentration from these patients as zero.

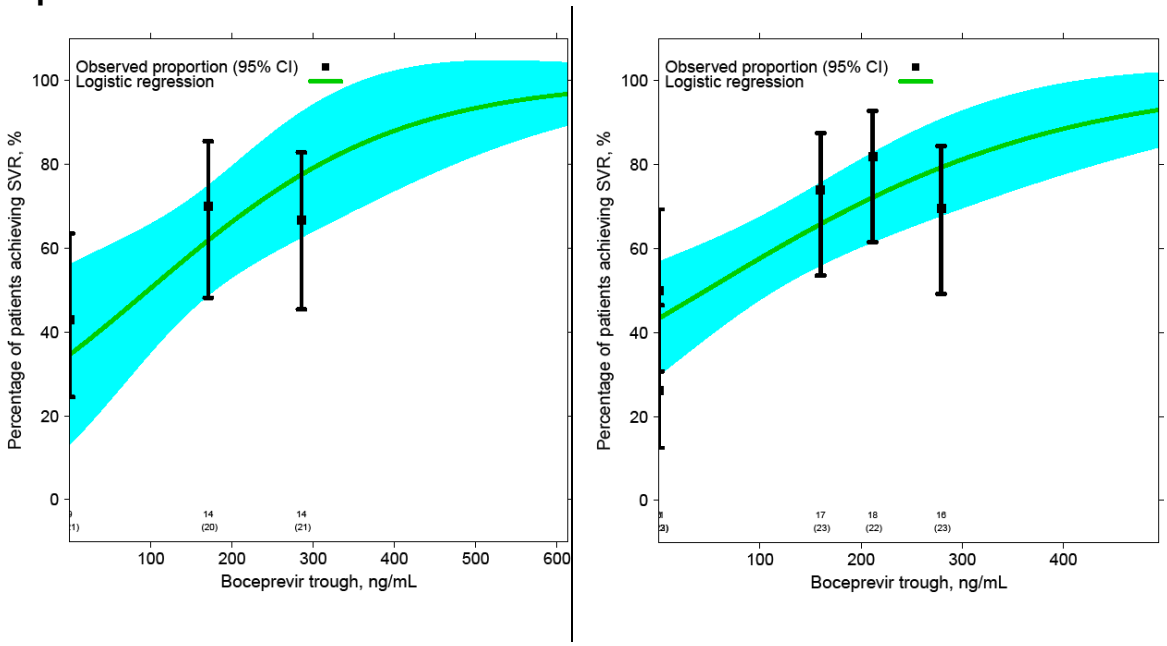
Figure 30: Percentage of Patients Achieving SVR from P05101 (left) or P05216 (right) Versus Boceprevir Trough Concentration (top) or Steady-State AUC (bottom).

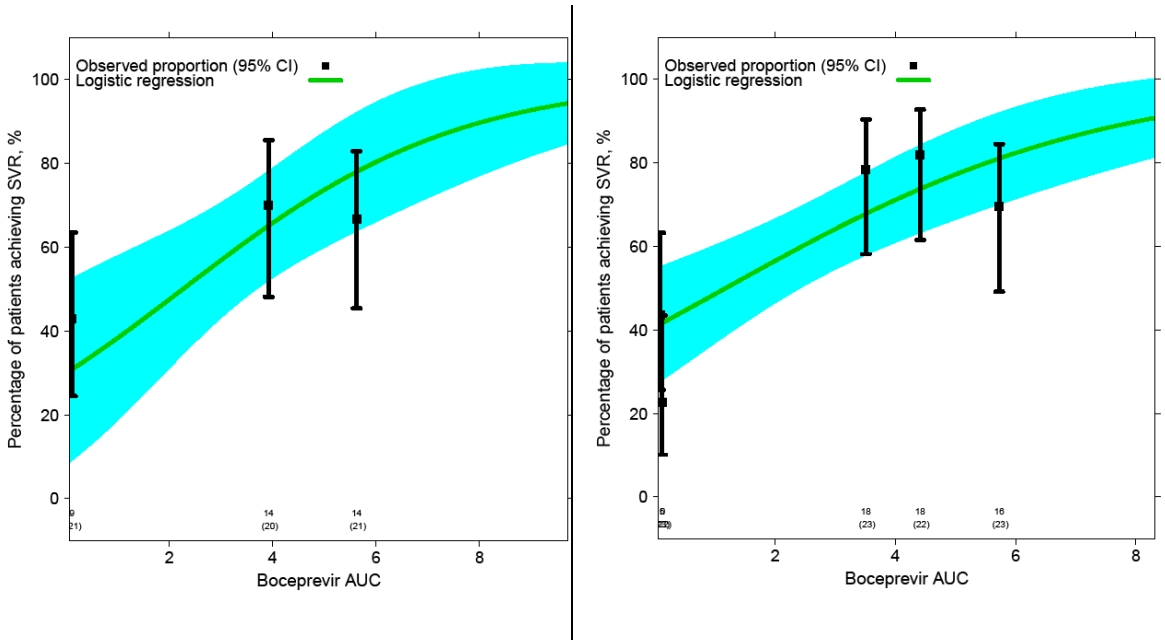




Including patients receiving SOC as patients with boceprevir concentrations of zero results in significant exposure response relationships between SVR and boceprevir C_{trough} and AUC_{τ} for both P05101 and P05216. However, the significant of these relationships is driven by the increase in sample size, and the interpolated relationship between a boceprevir C_{trough} of 0 ng/mL and the lowest observed C_{trough} (87 ng/mL) should be interpreted with caution.

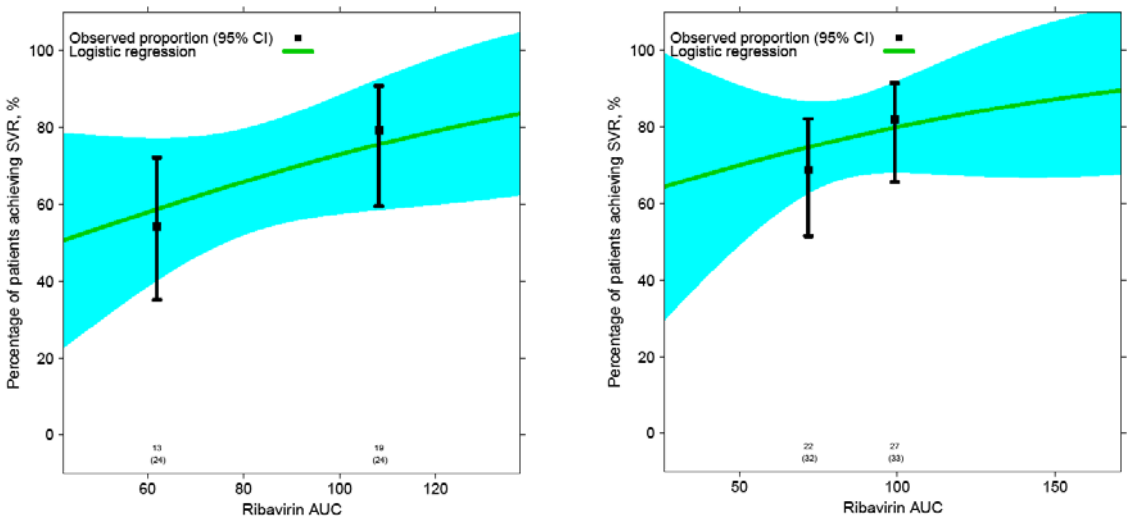
Figure 31: Percentage of Patients Achieving SVR from P05101 (left) or P05216 (right) Versus Boceprevir Trough Concentration (top) or Steady-State AUC (bottom). Analysis Includes Patients on SOC with Boceprevir Exposures of Zero.

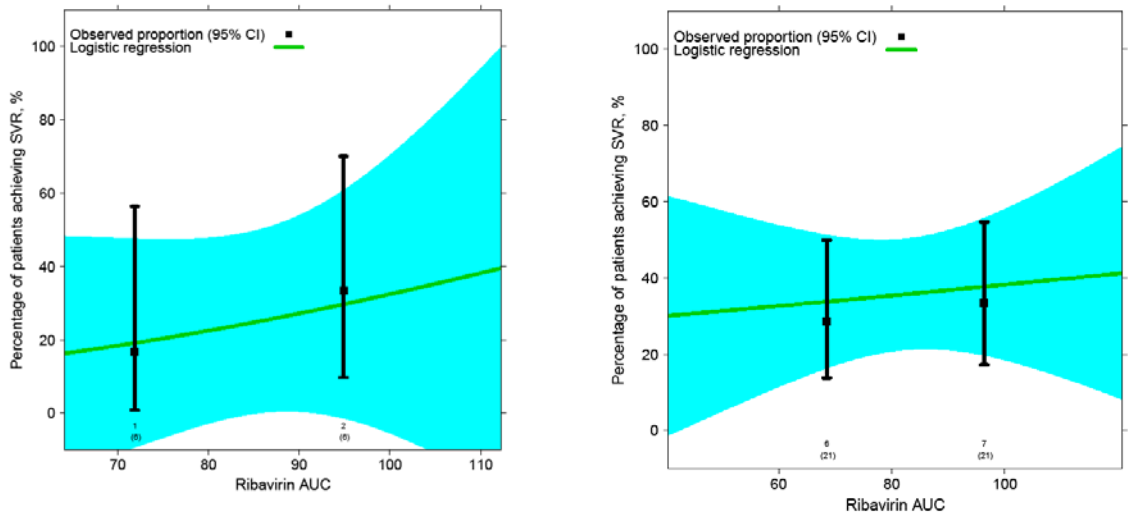




Logistic regression models were also evaluated for ribavirin AUC_T with (top) and without (bottom) boceprevir for P05101 (left) and P05216 (right). All analyses showed non-significant relationships between ribavirin AUC_T and SVR; however, steeper relationships were identified between ribavirin exposure and SVR when administered with boceprevir beyond the upward in response rate anticipated from treatment with boceprevir.

Figure 32: Percentage of Patients Achieving SVR from P05101 (left) or P05216 (right) Versus Ribavirin Steady State AUC Administered with (top) or Without Boceprevir (bottom).





Exposure-Response for Safety: Anemia

A non-significant trend of increasing anemia was observed with respect to increasing boceprevir AUC_T in the Phase III population (Figure 33 (left)). Similarly, a significant relationship between incidence rate of anemia and ribavirin AUC_T was observed in the Phase III population (Figure 33 (right)). This was not unexpected as ribavirin's primary toxicity is known to be anemia, with an observed incidence rate in the SOC population of ~30%. Indeed, a similar exposure-response relationship is observed if the analysis is limited to patients receiving only SOC (n=51; p-value=0.001; odds ratio = 2.3 (90% CI: 1.7; 3.1) for a 16 µg·hr/mL increase in AUC_T) (Figure 34). Together these results show a greater contribution to the incidence of anemia from boceprevir at lower ribavirin exposures, which may be due to either the small number of patients in this analysis, or a greater impact of ribavirin exposure on the incidence of anemia masking the impact from boceprevir exposure except at lower ribavirin exposures.

Figure 33: Percentage of Patients with Anemia from P05101 and P05216 Versus Boceprevir (left) or Ribavirin Steady-State AUC (right).

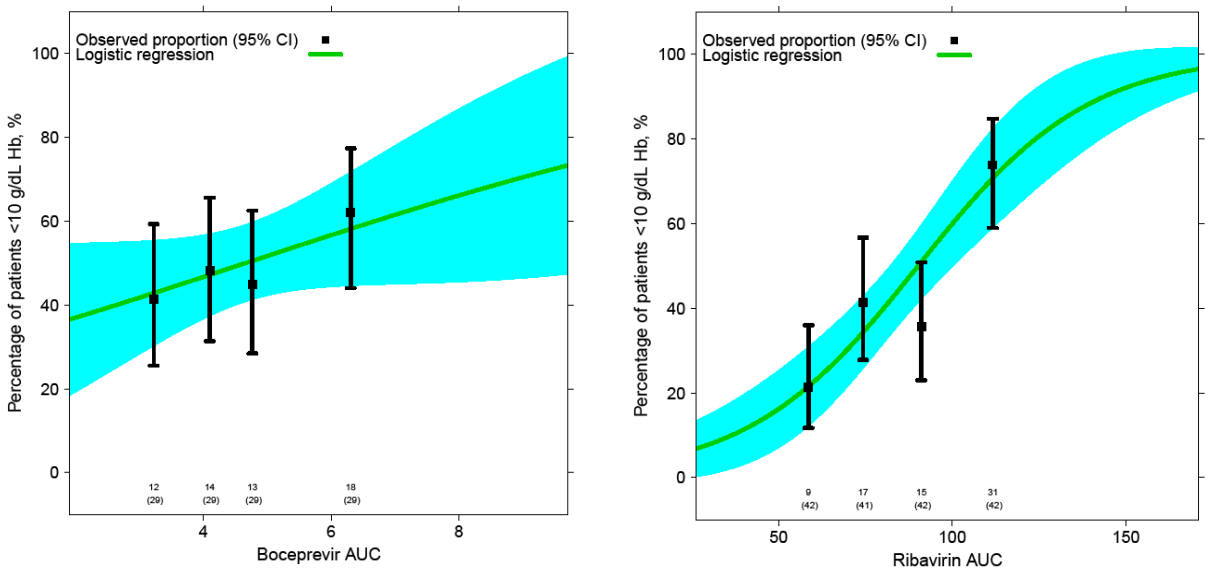
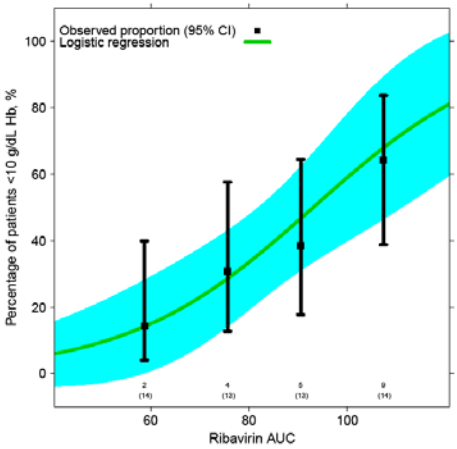


Figure 34: Percentage of Patients with Anemia from P05101 and P05216 Versus Ribavirin Steady-State AUC (right). Analysis Was Limited to Patients Receiving SOC



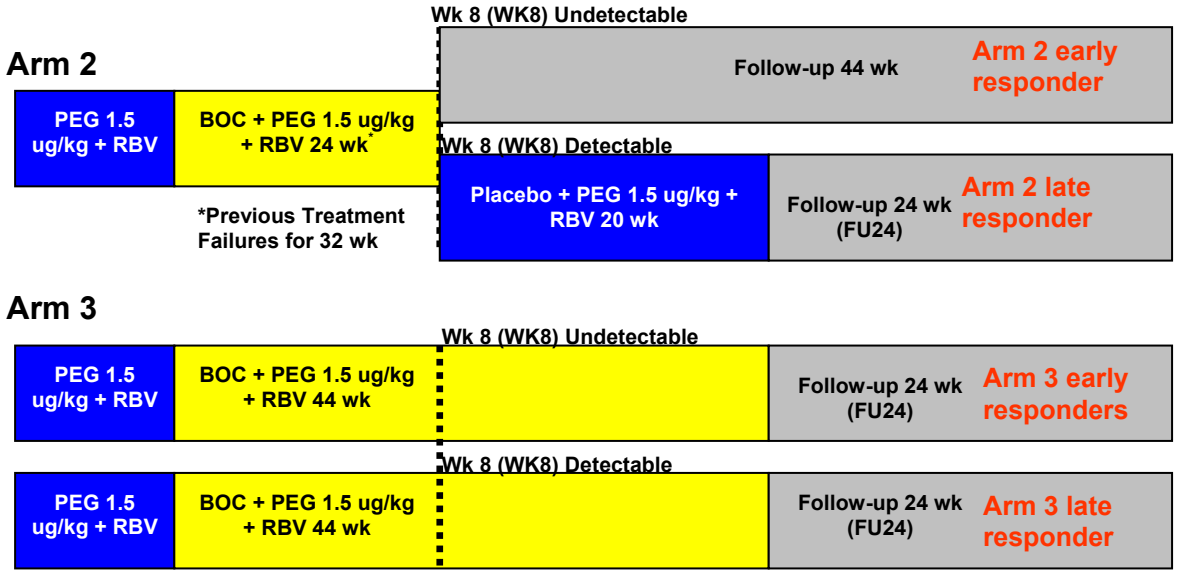
Impact of RGT on Treatment Outcomes: SOC naive and Previous SOC failures

During Phase III development, the sponsor pursued two different boceprevir treatment arms: i) a response-guided therapy (RGT) arm; and ii) a 48-week active treatment arm with boceprevir and SOC (triple therapy). In the RGT treatment arm, patients would finish treatment at week 28 for SOC naive patients or week 36 for previous SOC failures if viral load was undetectable at week 8 (early reponders). Otherwise, patients received SOC treatment for the remaining during of treatment (20 weeks for SOC naive and 12 weeks for previous SOC failures). The RGT arm (Arm 2) can be divided into Arm 2 early responders and Arm 2 late responders.

In the same study, a 48-week active treatment arm was included where patients

received 48 weeks of treatment regardless of initial viral response. Similarly, this treatment arm can be divided into Arm 3 early responders and Arm 3 late responders. This study design allowed us to compare two different treatments with respect to early viral response. Therefore, the impact of shorter therapy durations (Arm 2 early responders versus Arm 3 early responders) and the impact of triple versus SOC treatment over the last 12 or 20 weeks of treatment in later responders (Arm 2 late responders versus Arm 3 late responders) was studied. A schematic of the treatment arms, and the grouping described above is shown in Figure 35.

Figure 35: Schematic of Active Boceprevir Treatment Arms from Phase III With Subsequent Divisions to Permit Comparison of Treatments for Patients With Undetectable and Detectable Viral Load at Week 8.



Comparison of Sustained Virologic Response (SVR) for SOC naive Patients

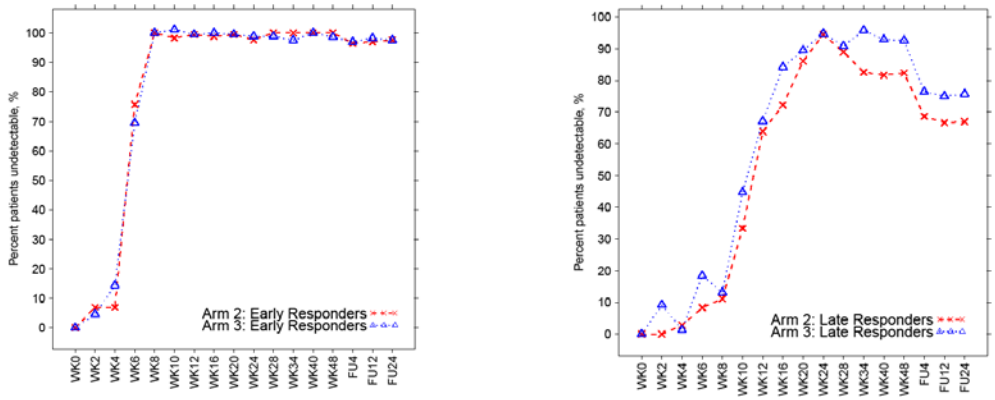
Overall response rates for early and late responders from P05216 are shown below. The overall response between early responders was similar (>95%) irrespective of treatment duration. There was a 9% numerical difference in response rate for late responders administered SOC for the last 20 weeks of treatment (Arm 2) compared to boceprevir with SOC for the last 20 weeks of treatment (Arm 3).

Table 48: SVR for Early and Late Responders from P05216 (SOC naive)

Study and Treatment Group	Arm 2: RGT (PR4/BOC-PR24/PR20) SVR n/N (%)	Arm 3: BOC44 (PR4/BOC-PR44) SVR n/N (%)
P05216 Early Responders	156/161 (97)	155/161 (96)
P05216 Late Responders	45/68 (66)	55/73 (75)

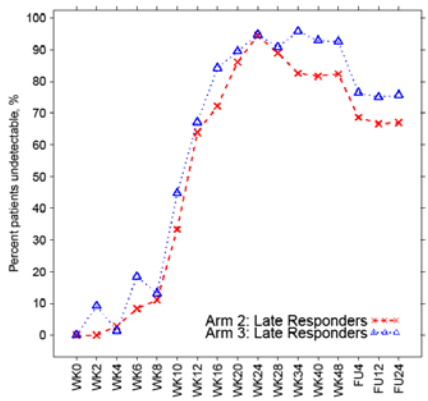
The above numeric difference was further explored by investigating the percent of patients with undetectable viral load for early and late responders for Arm 2 and 3 from P05216. For early responders, no difference in the percentage of patients with undetectable viral load was observed on treatment or during follow-up from Arm 2 or Arm 3 (SVR: 97% and 96%, respectively) (Figure 36, left). In contrast, late responders showed a separation in the percentage of patients with detectable viral load beyond week 28. This time point also corresponds to switching late responders in Arm 2 to receive SOC only.

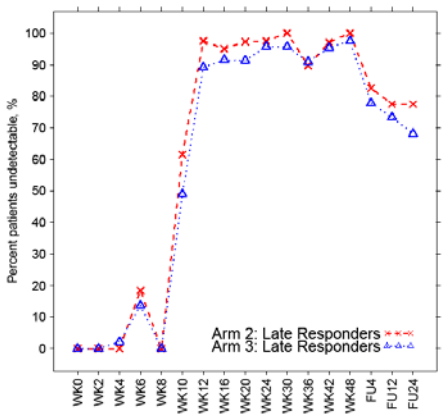
Figure 36: Percentage of SOC naïve Patients with Undetectable Viral Load at Different Treatment Time Points for Early Responders (Left) or Late Responders (Right) From P05216.



For previous SOC failure late responders from P05101 (Figure 37, right), it was observed that no separation between the percent of patients with undetectable viral load occur once boceprevir treatment is stopped at week 36. These two results demonstrate the treatment with boceprevir through week 28 in late responders is insufficient, and that a longer duration of triple therapy (i.e. 32 or 44 weeks) is necessary in late responders. However, as 32 weeks of triple therapy was not formally evaluated in SOC naive patients. The data from previous SOC failures and SOC naïve was bridged to fill this gap.

Figure 37: Percentage of Late Responders with Undetectable Viral Load at Different Treatment Time Points for SOC naive (Left) or SOC failure (Right) Patients.





Bridging Observations between SOC naïve and SOC Failure Patients

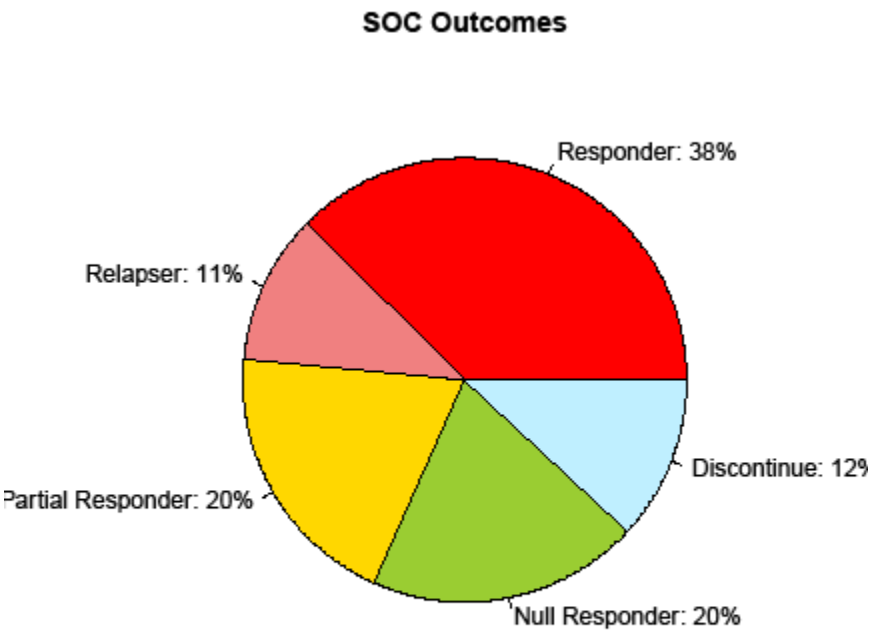
A comparison between the SOC naïve and SOC failure patients was based on two observations:

1. Week 4 response to SOC is similar between SOC naïve and SOC failure patients
2. SOC naïve late responders are predominantly those patients who would have failed SOC treatment

The first observation is obtained by evaluating the overall treatment outcomes and week 4 lead-in viral load change from the SOC arm in SOC naïve patients. A total of 363 patients were administered SOC in this study with overall results shown in Figure 38. Of this entire treatment arm, 38% achieved SVR, 11% were relapsers, 20% were partial responders, 20% were null responders, and 12% discontinued treatment. Definitions for relapsers, partial responders, and null responders are based on definitions from the September 2010 draft FDA Guidance for Industry (Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment) and are summarized below:

- **Null Responder:** less than 2 $\log_{10}$ reduction in HCV RNA at week 12 of a SOC regimen
- **Partial Responder:** greater than or equal to 2 $\log_{10}$ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at the end of treatment with a SOC
- **Relapser:** HCV RNA undetectable at the end of treatment with SOC, but HCV RNA detectable within 24 weeks of treatment follow-up.

Figure 38: Treatment Outcomes with SOC (Arm 1) in SOC naive Subjects (P05216)



As all boceprevir treatment arms included a 4-week lead-in with SOC, it is possible to make a comparison between the SOC treatment arm, all SOC failure patients based on their week 4 lead-in, and early and later responders in the SOC naive boceprevir treatment arms based on week 4 viral load change. The following figures provide the relationship between week 4 viral load change and treatment outcome for the SOC naive (P05216) population who received SOC (Figure 39, left) and the relationship between week 4 viral load change and previous SOC response in the treatment failure patients (P05101) (Figure 39, right). Similarly, 25th, 50th, and 75th percentile viral log decline for the groups of patients shown in Figure 39 are listed in Table 49. SOC naive patients with large viral load decreases (median=3.4 log decrease) at week 4 are more likely to be SVR responders and those with smaller week 4 viral load changes (median=0.7 log decrease) are more likely to be null responders to SOC (<2 log decline at week 12). More importantly, both the qualitative shape of the week 4 response for SOC naive patients whose treatment results in relapse or partial response and the qualitative shape of the week 4 response for patients who have previously failed SOC treatment are similar. This is further supported by investigating the actual distributions of response which demonstrates good agreement between the 25th, 50th, and 75th percentile for patients who go on to fail or have previously failed SOC as relapsers (median=2.1 or 2.2 log decreases) or partial responders (median=1.6 or 1.2 log decreases) (Table 49). Hence, the week 4 viral load decline is a good predictor of SOC outcome in SOC naive patients and a similar SOC week 4 response is maintained if patients classified as relapsers or partial responders are retreated with SOC.

Figure 39: Relationship between SOC Treatment Outcome and Week 4 HCV RNA Change from P05216 (SOC naive Subjects) and Previous SOC Outcome and Week 4 HCV RNA Change from P05101 (Treatment-Experienced Subjects)

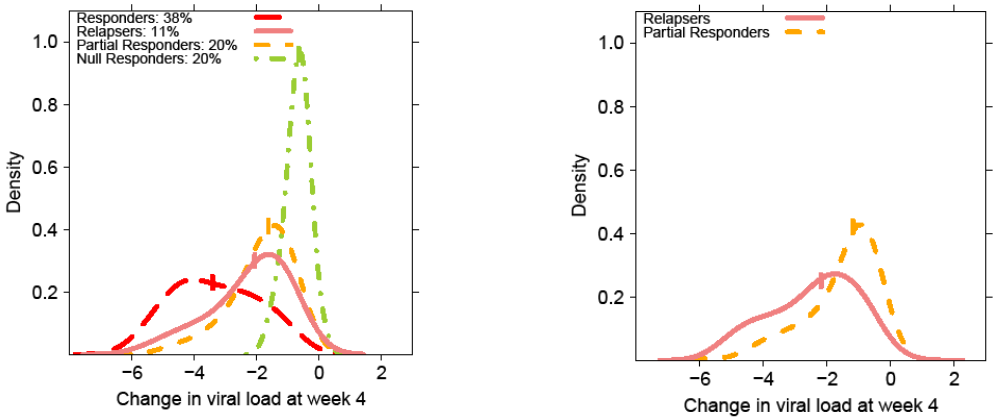


Table 49: Week 4 Viral Load Decline Based on SOC Outcome from P05216 or Previous SOC Treatment Outcome for P05101

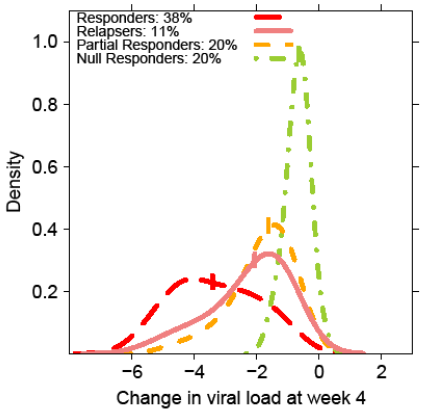
SOC Response Category		Week 4 Viral Load Decline Percentile		
		25th	50th	75th
P05216, SOC naive	Null Responder	-0.9	-0.7	-0.5
	Partial Responder	-2.3	-1.6	-1.1
	Relapser	-2.9	-2.1	-1.2
	Responder	-4.4	-3.4	-2.3
P05101, SOC failure	Partial Responder	-2.1	-1.2	-0.7
	Relapser	-3.4	-2.2	-1.4

Week 4 Response in SOC naive Late Responders

An additional analysis of the boceprevir RGT arm in P05216 based on week 4 response identified those subjects with >2.0 log10 decrease at week 4 as comprising >75% of the early responder population who received 4 weeks of SOC followed by 24 weeks triple therapy, as shown in the Figure 40. In contrast, late responders in Arm 2 receiving the full 48 week treatment duration (4 weeks SOC, followed by 24 weeks triple therapy, then 20 weeks PR) were those subjects with smaller changes in HCV RNA at week 4 (Figure 40). For example, 50% (34/68) of subjects receiving 48 weeks of therapy in Arm 2 from P05216 had ≤1.0 $\log_{10}$ decrease at week 4; and 91% (62/68) of subjects receiving 48 weeks of therapy in Arm 2 from P05216 had ≤2.0 log10 decrease at week 4. Therefore, the late responder treatment arms from P05216 are predominantly comprised of subjects that would have failed SOC treatment.

Figure 40: Relationship between SOC Treatment Outcome (Arm 1, left) or Response Guided Treatment Arm Assignment (Arm 2, right) and Week 4 HCV RNA Change from P05216 (SOC

naive Subjects)



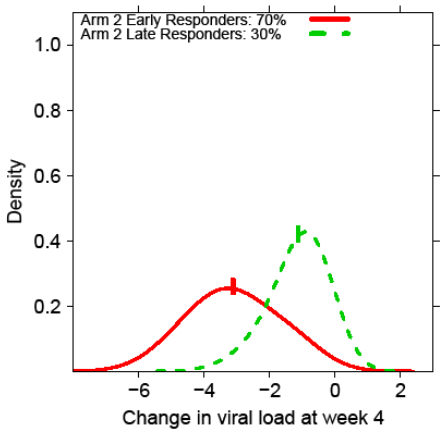


Table 50: Week 4 Viral Load Decline Based on SOC Outcome from P05216 or Response Guided Treatment Arm Assignment from P05216

SOC Response Category		Week 4 Viral Load Decline Percentile		
		25th	50th	75th
P05216, SOC naive, Arm 1, SOC	Null Responder	-0.9	-0.7	-0.5
	Partial Responder	-2.3	-1.6	-1.1
	Relapser	-2.9	-2.1	-1.2
	Responder	-4.4	-3.4	-2.3
P05216, SOC naive, Arm 2, RGT	Early Responder	-4.0	-2.8	-1.8
	Late Responder	-1.9	-1.3	-0.9

Late Responder Comparison between SOC failure and SOC naive Patients

The previous two analyses demonstrate that SOC treatment does not influence future SOC response and that those patients in the late responder arms are those patients that would predominantly fail SOC treatment and become the next set of 'SOC failure' patients. Therefore, SOC naïve late responders should be treated similar to that of previous SOC failure patients by leveraging all data. However, the study for SOC failure patients did not include null responders, and it is currently unresolved whether null responders are amenable to RGT. Based on these analyses, one of the two following treatment options are recommended for SOC naive late responders:

- Option 1[7]: PR4/BOC-PR44 in all SOC naive late responders
- Option 2[8]:

[7] Option 1: Treat late responders as potential SOC failures where potential partial responder and relapser population will receive longer therapy but will cover for null responder population.

- PR4/BOC-PR32/PR12 in late responders with viral load decline >1.0 at week 4
- PR4/BOC-PR44 in late responders with viral load decline ≤1.0 at week 4

The selection of a 1.0 viral load decline as the cut point for boceprevir treatment duration is justified below as this cut point accounts for a majority of potential null responders from the SOC naive population (i.e. those patients who may still benefit from a full 44 weeks of boceprevir treatment duration) and is supported by the SOC failure study (P05101) that demonstrated no difference in SVR for late responders administered 32 weeks or 44 weeks of triple therapy in a patient population that *excluded null responders.*

Classification and Regression Tree Analysis to Determine Week 4 Viral Load Decline Associated with Null Response to SOC

As the SOC failure Phase III trial did not include null responders, it is currently unknown what SVR would be expected in this patient population. While the approval boceprevir for the treatment of null responders is still under discussion, the analyses shown above (Figure 38 and Figure 39) demonstrate that a portion of the SOC naive patients administered SOC will result in classification as null responders. Combined with the observation that patients who are relapsers, partial responders, and null responders will primarily be in the late responder treatment arms and that treatment until 36 weeks was sufficient in previous SOC failures who were relapsers or partial responders, an analysis was performed to identify what, if any, week 4 change in viral load was most appropriate for selecting potential null responder patients following week 4 lead-in with SOC. It is these patients, in particular, that may be more appropriate candidates for boceprevir treatment for 44 weeks in addition to SOC.

A classification and regression tree (CART) analysis was performed on the SOC patients from Arm 1 of P05216 to determine the viral load decline at week 4 that best predicts a null responder SOC treatment outcome. A total of 363 patients were included in the SOC treatment arm, 329 of which had week 4 and week 12 data on change in viral load data available. Please note that week 12 results are used to define null responder status. The results suggest that a week 4 viral load decline ≤1.03 log10 is an appropriate cut point for selecting null responders. Approximately, 83 patients in the SOC arm had viral load decline ≤1.03 log10 at week 4. Of those 83 patients, 60 patients were eventually identified as null responders (85% sensitivity and 72% positive predictive value). In contrast, among 246 patients who had viral load decline >1.03 log10, only 4% were null responders.

[8] Option 2: Treat late responders as potential SOC failures, however, identify potential SOC null responders using week 4 response of ≤1.0 log10 such that potential relapser and partial responder population receives appropriate treatment duration by leveraging data from previous treatment failure patients.

These results demonstrate that while a 1.0 log10 decline at week 4 includes a portion of patients that are not null responders, selection of this value as a representative cut point for the null responder population will ensure that >85% of the SOC naive null responders will be included in this population.

Calculation of Anticipated SVR Rate in Null Responders Based On P05216 and P05101

As discussed previously, it is anticipated that null responders will make up some portion of the SOC naive population. Based on this observation, the sponsor has proposed the use of a ≤1.0 log10 HCV RNA decline as appropriate for identifying null responders. While this cut point is supported by the sponsor's and reviewer's CART analysis, it is important to acknowledge that the SVR rates reported for SOC naive patients with ≤1.0 log10 HCV RNA decline at week 4 includes a portion of subjects who are not null responders as discussed above. As such, the reported SVR rates for this "poorly interferon-responsive" population (28% and 38%) exceed the anticipated SVR rate in a true null responder population. To obtain a more accurate estimate of the true SVR rate in null responders' two analyses were performed.

First, as it is recognized that <1 log10 HCV RNA decline at week 4 includes patients that are not null responders, the SVR rates for patients <0.5 log10 HCV RNA decline at week 4 were investigated. Based on the SOC treatment outcomes for patients with this characteristic from P05216 (n=25, includes discontinuations), 22 patients were null responders (88%), 1 was a partial responder, and 2 discontinued treatment. For this population, the overall response rate in the boceprevir treatment arms was 30% (Arm 2: n/N=11/37) and 28% (Arm 3: n/N=13/47), which may better approximate the expected SVR rate in a null responder population (Table 51). By comparison, the observed SVR on SOC for ≤1.0 and ≤0.5 log10 HCV RNA decline at week 4 was 5% and 0%, respectively.

Table 51: Observed Percentage of SOC Patients That Were Null Responders and Overall SVR Rates in Boceprevir Treatment Arms for Patients Based on Week 4 Viral Load Decline from P05216

	Null responders in TN SOC Arm, n/N (%)	Observed SVR Rate in BOC TN Arms, %
≤1.0 log10 HCV RNA decline week 4	57/83 (69%)	28-38%
≤0.5 log10 HCV RNA decline week 4	22/25 (88%)	28-30%

A second analysis back-calculated the anticipated SVR rate for null responders using the distribution of week 4 HCV RNA declines from the SOC treatment arm in P05216 (n=83). Of these subjects, 3 were responders, 1 was a relapser, 15

were partial responders, 57 were null responders, and 7 discontinued. Response rates for the relapser and partial responder patients when treated with boceprevir are available from P05101 and ranged between 69-75% for relapsers and 40-52% for partial responders. Assuming that all responders to SOC treated with boceprevir would still be responders, and that a similar percentage of patients would discontinue triple therapy treatment due to adverse events, a back-calculated SVR rate for null responders would range between 20-35% in order to obtain an overall SVR rate in this subpopulation of 28-38%. As such, we anticipate that the lower bound of SVR in a null responder population is at least 20%, and that this represents an improvement in treatment response compared to historic SVR rates in this population of 5%.

Table 52: Predicted SVR Rate in Null Responders to Achieve Observed SVR Rate in Patients with ≤1.0 log10 HCV RNA Decline at Week 4 from P05216

	Proportion of patients with ≤1.0 log10 decline[1], %	Expected SVR Rate, %	Overall SVR, %
Responder	4%	100%[2]	4%
Relapser	1%	75%[3]	1%
Partial Responder	18%	52%[3]	9%
Null Responder	69%	*20-35%*[4]	14-24%
Discontinuation	8%	0%[2]	0%
	100%		28-38%[5]

[1]Observed distribution of SOC treatment outcomes from P05216
[2]Assumed SVR rate for patients who are responders or discontinue treatment
[3]Observed SVR rates for previous relapsers and previous partial responders from P05101
[4]Calculated SVR rate for null responders based on observed population distribution, SVR rates for subgroups, and overall SVR rates
[5]Observed SVR rates in boceprevir treated arms from P05216 for patients with ≤1.0 $\log_{10}$ decrease in viral load at week 4

Appropriateness of RGT in Blacks versus Non-Blacks

Similar to what has been presented in previous analyses with early and late responders, the same groups were further divided based on race (blacks versus non-blacks, or Cohort 1 versus Cohort 2) (Table 53). A larger numeric difference was observed for blacks who were late responders receiving SOC for the last 20 weeks of treatment compared to triple therapy (numeric difference of 29%). Similarly, a numeric difference, albeit slightly smaller, was observed in non-black late responders (numeric difference of 6%). These differences have been addressed in the previous section.

Table 53: Early and Late Responder Comparison Between Arm 2 and Arm 3 For Blacks and Non-Blacks from P05216

Virologic Response	Arm 2 (RGT) SVR n/N %	Arm 3 BOC/PR48 SVR n/N (%)
Cohort 1 (non-Blacks)		

Early Responders	143/146 (98)	137/142 (97)
Late Responders	38/56 (68)	48/65 (74)
Cohort 2 (Blacks)		
Early Responders	13/15 (87)	18/19 (95)
Late Responders	7/12 (59)	7/8 (88)

Also similar to previous analyses, no difference was observed between non-black early responders while a numeric difference of 8% in SVR was observed between early responders who were blacks and on Arm 2 versus Arm 3. However, it is important to consider three points when evaluating this difference.
First, the overall distribution of week 4 viral load decline for blacks who were classified as early responders is different than the distribution of week 4 viral load decline for non-blacks. For Arm 2 and 3, the median (25^{th} and 75^{th} percentile) week 4 change in viral load for non-blacks was -3.2 and -3.4 (Arm 2: -3.9 and -2.2; Arm 3: -4.1 and -2.1), respectively, compared to a median (25^{th} and 75^{th} percentile) week 4 change in viral load for blacks of -2.5 and -2.2 (Arm 2: -3.6 and -2.2; Arm 3: -3.2 and -1.7), respectively. Clearly, the black patients have a lower week 4 viral load decrease compared to non-blacks and comparing the response rates across the entire early responder treatment group will be influenced by already understood racial differences in interferon response.
Second, it should be noted that small numbers are being compared in the black early responder analysis, and that the numeric difference observed is driven by the additional failure of one patient at a response that may already be saturated (i.e. SVR rate in all groups is bounded by complete success which is not achievable).

Finally, the week 4 responses of the black early responder patients who failed treatment were -3.3 and -2.4 for treatment Arm 2 and -3.2 for treatment Arm 3. Both arms had a patient that failed treatment with a week 4 viral load change similar to the median change observed in non-blacks. However, the patient that accounts for the numeric difference between the treatment groups had a worse week 4 viral load decline and would be expected to be less likely to achieve SVR. Also, one of the black early responders that failed treatment in Arm 2 was a cirrhotic compared to zero such patients Arm 3.

Taken together, these analyses and observations demonstrate that the difference in SVR between black early responders in the boceprevir treatment arms is not a reflection of response-guided therapy being inappropriate for blacks. Blacks, by virtue of decreased responsiveness to interferon therapy, are simply more likely to be patients with lower initial week 4 viral load decline, and blacks that are also early responders will have similar treatment outcomes to non-black early responders whose week 4 response is towards the lower end of the distribution.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
RGT_undetectableplotTE.R	Plots percent of SOC failure patients with	Boceprevir_NDA202258_JAF\ER Analyses

	undetectable viral load for the three treatment arms from trial P05101	
RGT_undetectableplotTN.R	Plots percent of treatment naive patients with undetectable viral load for the three treatment arms from trial P05216	Boceprevir_NDA202258_JAF\ER Analyses
TN_RGT_vs_BOC44_Analysis.R	Subgroup analysis and early/late responder comparison for boceprevir Phase III trials	Boceprevir_NDA202258_JAF\ER Analyses

APPENDIX

Impact of Boceprevir and Ribavirin Exposure on Minimum on Treatment Hb

Due to the limited number of patients with exposure measurements available from the Phase III trial, the reviewer explored the use of minimum on treatment hemoglobin as a surrogate for ribavirin and possibly boceprevir exposure. Previous investigations by Sulkowski *et al.* (Gastroenterology, 2010, EASL 2009) indicated that decline in Hb were associated with an increase rate of SVR in genotype 1 patients receiving SOC. Also, the primary toxicity associated with ribavirin use is an increase incidence of anemia that shown an exposure-response relationship with increasing ribavirin exposure. Based on these two observations, the reviewer explored linear regression relationships between minimum on treatment Hb and ribavirin and/or boceprevir exposure from the Phase III population.

A significant relationship was identified for ribavirin, predicting a baseline Hb measurement of 12.7 g/dL, decreasing -0.5 g/dL for every 15 µg·hr/mL increase in ribavirin exposure (Figure 41). In contrast, while a trend between increasing boceprevir exposure and lower minimum on treatment Hb was observed, this relationship was not significant and was not included during a subsequent multivariate analysis. Also, a similar exposure response relationship between minimum on treatment Hb and ribavirin exposure was observed if the analysis was limited to patients receiving only SOC (Figure 42). Take together, these results indicate that minimum on treatment Hb is primarily driven by ribavirin exposure and not boceprevir, and that minimum on treatment Hb may serve as a surrogate for ribavirin exposure.

Figure 41: Linear Regression of Minimum on Treatment Hb Versus Boceprevir (left) and Ribavirin (right) AUC_T (right) from Phase III Patients.

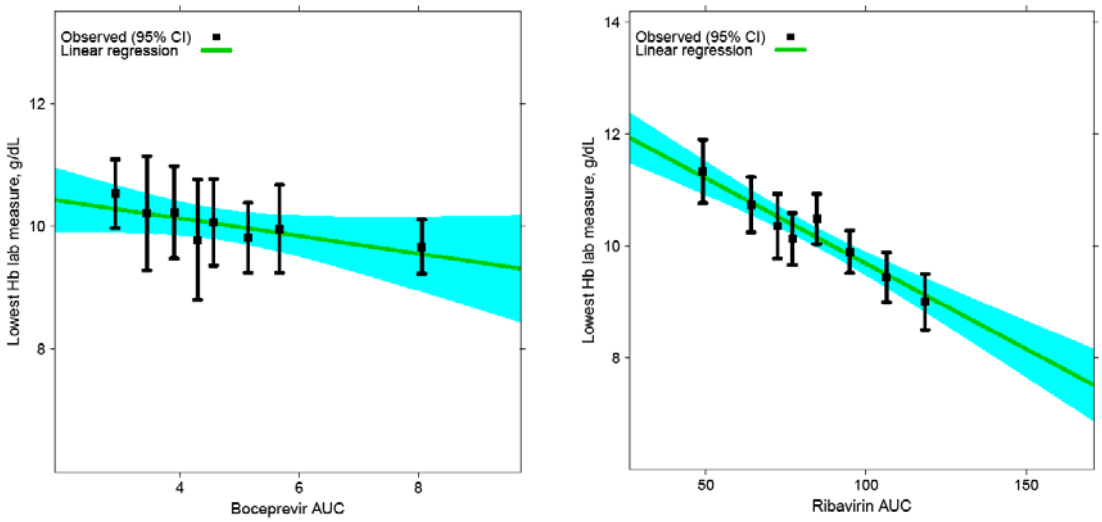
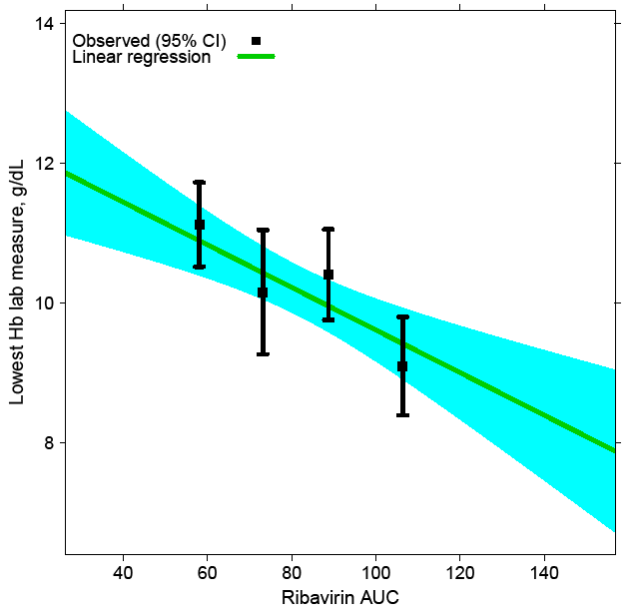


Figure 42: Linear Regression of Minimum on Treatment Hb Versus Ribavirin AUC_T from Phase III Patients. Analysis Was Limited to Patients Receiving SOC

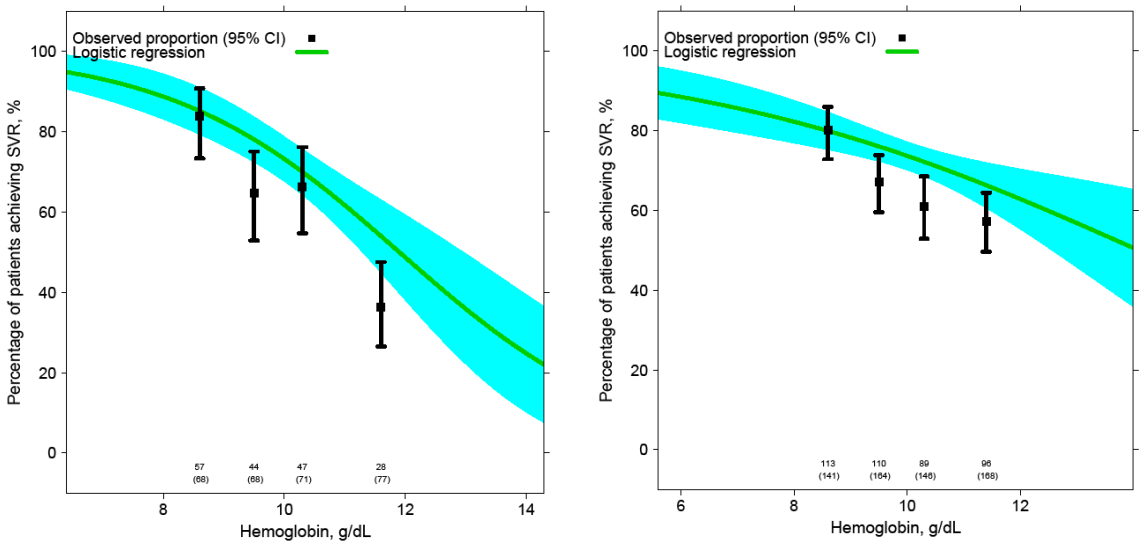


'Exposure'-Response Efficacy Relationship: SVR and Minimum on Treatment Hb

A logistic regression analysis between minimum on treatment Hb and SVR was evaluated for both Phase III trials (P05101 and P05216). Significant relationships between SVR and minimum hemoglobin were observed for both trials (Figure 43), and this observation is consistent with the sponsor's analysis. However, model fits were not in good agreement with the observed data, suggesting that multiple populations with different response characteristics may have been

combined in the analysis.

Figure 43: Percentage of Patients Achieving SVR Versus Minimum on Treatment Hb from P05101 (left) and P05216 (right).



The analysis was repeated for both P05216 (Figure 44) and P05101 (Figure 45) but the population was separated into those patients with undetectable versus detectable viral load at week 8. A significant exposure-response relationship was identified for patients with detectable viral load at week 8 for P05216 (p-value=0.007); however, the relationship was not significant for patients with undetectable viral load at week 8 (p-value=0.44) though the quartile with the lowest on treatment hemoglobin did have the highest response. This analysis suggests that in late responders, the ribavirin exposure may be a key factor in attaining SVR, and, subsequently, that ribavirin dose reduction will have a greater impact in patients who are late responders compared to early responders. In contrast to the analysis in P05216 patients, significant exposure response relationships were identified for patients with undetectable (p-value=0.005) and detectable (p-value<0.0001) viral load in P05101 (Figure 45). However, the overall trends were similar for both patient groups, including the quartile with the lowest on treatment hemoglobin having the highest observed SVR for patients with undetectable viral load at week 8, but otherwise no trend being observable in this group.

Figure 44: Percentage of Patients Achieving SVR Versus Minimum on Treatment Hb from P05216 for Patients with Undetectable (left) and Detectable (right) Viral Load at Week 8.

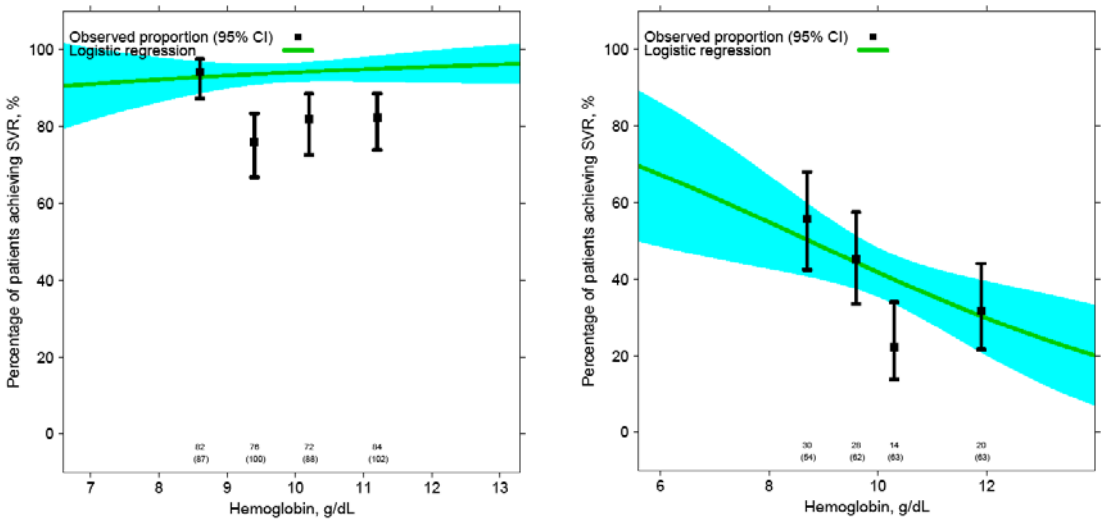
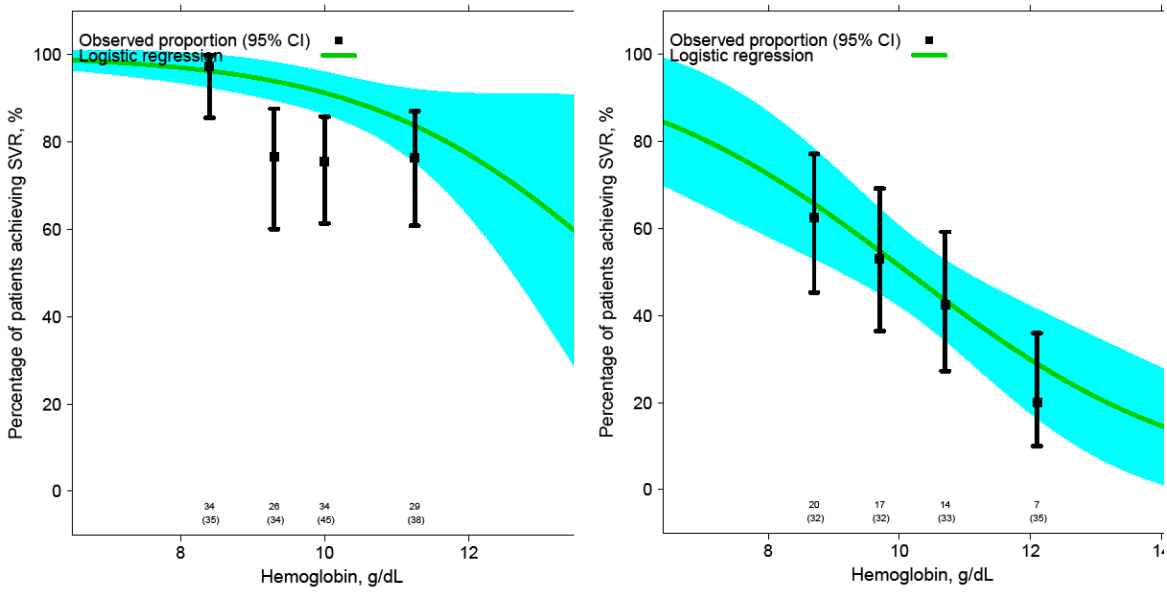


Figure 45: Percentage of Patients Achieving SVR Versus Minimum on Treatment Hb from P05101 for Patients with Undetectable (left) and Detectable (right) Viral Load at Week 8.



4.3.3 Population PK Model

Office of Clinical Pharmacology: Pharmacometric Review: Boceprevir

Pharmacometrics Reviewer: Jeffry Florian
Pharmacometrics Team Leader: Pravin Jadhav
Clinical Pharmacology Reviewer: Ruben Ayala
Clinical Pharmacology Team Leader: Sarah Robertson

Summary of Findings

Key Review Questions

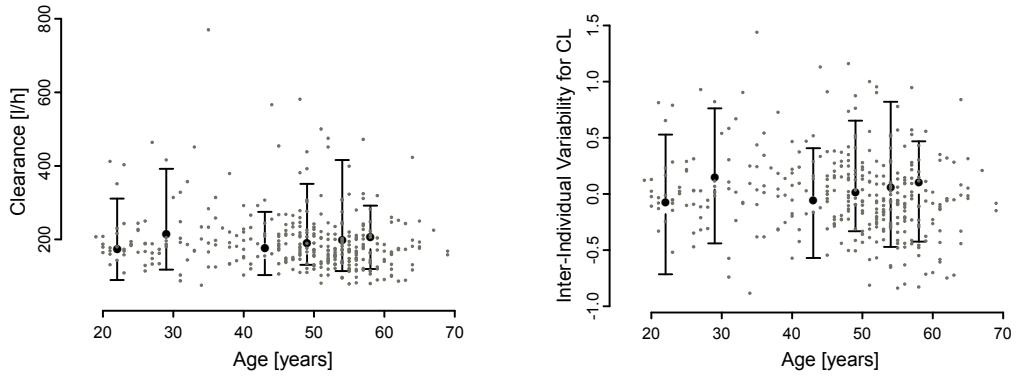
The purpose of this review is to address the following key questions.

Are the labeling statements derived from the population pharmacokinetics (PK) analysis of boceprevir acceptable?

The labeling statements from the population PK analysis are acceptable. The sponsor claims that the PK exposures are similar across age, gender and race groups.

The population PK concentration data consisted of 3111 values in 358 subjects. The median age was 50, ranging between 19 and 69 years. The results of the sponsor's analysis indicate that distributions of AUC, Cmin, Cmax, and CL/F estimates over the age range of 19 to 69 (3 subjects >65) years were reasonably similar. Figure 46 shows CL and inter-individual variability for CL expressed as median (5^{th} – 95^{th} percentile) for each of the 6 quantiles of age values. The quantiles are plotted at the median of their respective age values.

Figure 46: Clearance and Eta Plot versus Age.



Among the 358 subjects included in the analysis, 121 were females, 54 Black, 18 Asian and 277 Caucasian. The distributions of the different exposure parameters were consistent for male and female and across race groups as shown in Figure 55 of this report.

Did the weight based dosing provide consistent ribavirin concentrations across the different weight categories and is it consistent with concentrations achieved after currently labeled ribavirin doses?

In the Phase 3 RESPOND-2 (P05101) and SPRINT-2 (P05216) studies, weight-based dosing of 600-1400 mg/day (BID) was used for ribavirin: 600 mg for body weight ≤50 kg, 800 mg for >50-65 kg, 1000 mg for >65-80 kg, 1200 mg for >80-105 kg, and 1400 mg for >105 kg. Figure 50 summarizes the observed ribavirin $AUC_{0\text{-}24h}$ levels per dosing group. Overlapping exposure values were observed across the weight based dosing categories. However, as few data were available for the lowest dosing group, and to confirm this finding, the final sponsor's population PK model was used to simulate concentration levels for the 5 dosing levels. The simulated concentration levels and AUCs were compared and proved to be consistent across the different weight categories, as shown in Figure 50 of this report.

Table 54. Summary of Ribavirin $AUC_{0\text{-}24h}$ levels per Weight-Based Dosing Category.

Weight Category	Subjects N	Weight (kg) Mean	$AUC_{0\text{-}24}$ (ng.h/ml) Mean	$AUC_{0\text{-}24h}$ (ng.h/ml) Range (min – max)
≤50	3	46	73	(62 – 94)
51 - 65	59	60	87	(43 - 147)
66 - 80	160	74	85	(43 - 177)
81 - 105	279	91	83	(43 - 303)
>105	70	113	79	(28 - 117)

In the current study, concentrations averaged 2810 ng/mL at the 4-week visit and 3290 ng/mL (17% higher) at the 8-week visit. For daily doses of ≥1200 mg only, concentrations average 2750 ng/mL at the 4-week visit and 3190 ng/mL at the 8-week visit, whereas for daily doses of <1200 mg only, concentrations average higher levels of 2920 ng/mL at the 4-week visit and 3410 ng/mL at the 8-week visit. Around 70 percent of the concentration levels in this analysis were within 1000 to 3500 ng/ml, Jin 2009[1] reported 82% of the concentration data values lying within the same range. For both studies the blood-sampling schedule was not specified relative to the last ribavirin dose, and elapsed time between the last dose of ribavirin and blood sampling varied from <1 to 24 hours. Concentrations in this analysis were modestly higher than the approximately 2600 ng/mL average in Wade 2006[2], based on 800-1200 mg/day dosing with sampling at weeks 8-48, which may reflect differences in the patient population or study

conditions in this study relative to those used to build the published model. In this analysis, modestly higher concentrations than the Rebetol label were reported. The label reports: “Following oral dosing with 600 mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL.” Since high-fat meals increase bioavailability, one possible explanation is higher-fat meals in the new studies. Another possibility is differences in the population disease severities in the studies here vs. the literature studies and the label study (N=12, presumably healthy volunteers).

The current label for Rebetol lists only 4 body weight dosing categories: i) 800 mg for body weight ≤65 kg; ii) 1000 mg for >65-80 kg; iii) 1200 mg for >80-105 kg; iv) and 1400 mg for >105 kg. In this study, 600 mg were administered to patients with body weight <50 kg. The median model predicted AUCs for these patients, when given the label prescribed dose (800 mg), would be 123 (90% prediction interval: 59 - 251) ng.h/ml. These levels are within the range of the observed exposures for the other dosing groups. As such, it is appropriate to administer patients <50 kg 800 mg of Rebetol, and the Rebetol label does not require any changes to reflect the dosing evaluated in the boceprevir Phase III trials.

Recommendations

The office of clinical pharmacology Division of Pharmacometrics has reviewed this population PK report and found it acceptable.
No boceprevir dose changes are recommended based on age, race, gender or other patient characteristics.

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

Pertinent regulatory background

Boceprevir is an orally administered, novel serine protease inhibitor, specifically

designed to inhibit the hepatitis C virus (HCV) NS3/4A (nonstructural protein 3) protease and, thereby, inhibit viral replication in infected host cells. Plasma concentration-time data from seven Phase 1-3 studies were pooled for the population pharmacokinetic analysis. These included 3 studies in healthy subjects (P04624, P04488 and P04489) and a clinical trial conducted in HCV genotype-1 subjects who failed previous interferon treatment (e.g. classified as non-responders). In addition, one Phase 2 study (P03659) and two Phase 3 studies (P05216 and P05101) provided PK data.

Ribavirin PK data were obtained from studies P05101 and P05216, only one or two ribavirin samples per patient, at approximately 4 and 8 weeks of treatment, were available for a subset of the patients in these two studies.

Results of Sponsor's Analysis

Population Boceprevir PK Analysis

Clinical Data

Plasma concentration-time data from seven Phase 1-3 studies were pooled for the sponsor's analysis (Table 55). Only arms using the new formulation TID with food were included. Since no studies used intravenous administration, absolute bioavailability could not be estimated.

Table 55. Studies Included in Sponsor's Analysis.

Study	Phase	Population	Title	Doses Analyzed	Type of PK data
P04487	1	Tx-experienced genotype 1	A Multi-Dose Study to Evaluate QID Dosing Regimen of SCH 503034 in Combination With Peg-Intron on Safety, Pharmacokinetics and Pharmacodynamics in HCV Genotype 1 Patients	400	dense
P04488	1	healthy	Influence of Race/Ethnic Origin on the Pharmacokinetics of SCH 503034	200, 400, 800	dense
P04489	1	healthy	A Thorough QT/QTc Study to Evaluate Cardiac Safety for the HCV Protease Inhibitor SCH 503034 in Healthy Volunteers	800, 1200	dense, crossover
P04624	1	healthy	A Study to Assess the Pharmacokinetics, Safety, and Tolerability of SCH 503034 Administered in Combination With Ritonavir or Diflunisal	400	dense
P03659	2	Nonresponder genotype 1	PegIntron/REBETOL vs PegIntron/SCH 503034 With and Without Ribavirin in Chronic Hepatitis C HCV-1 Peginterferon alfa/Ribavirin Nonresponders: A SCH 503034 Dose-Finding Phase 2 Study	800	sparse
P05101 (RES-POND-2)	3	Tx-experienced genotype 1	A Phase 3 Safety and Efficacy Study of Boceprevir in Subjects With Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin	800	sparse
P05216 (SPRINT -2)	3	Tx-naïve genotype 1	A Phase 3, Safety and Efficacy Study of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C Genotype 1	800	sparse

From Sponsor's study-report-pop-pk.pdf page 9.

Methodology
Population PK analysis of boceprevir was performed using non-linear mixed-effect modeling in NONMEM's first-order conditional estimation method with interaction (FOCEI). The analysis used the following strategy: base model development, random effect model development, inclusion of covariates, final model development, assessment of model adequacy (goodness of fit), and validation of the final model.
During model building, the goodness of fit of models to the data was evaluated using the following criteria: change in the objective function, visual inspection of scatter plots, precision of the parameter estimates obtained from NONMEM covariance step output, and decreases in both inter-individual variability and residual variability.

The significance of potential covariates (age, race, gender, healthy vs. patients, AST, ALT, CrCl, weight and BMI) was tested with a sequential forward selection algorithm using likelihood ratio tests (based on ΔOFV). The test for inclusion of an individual covariate was performed at a pre-specified significance level of $\alpha = 0.01$. The covariate with the smallest p-value (greatest significance) less than α was included in the model for the next forward step. Parameters for the covariates were included in the model until no additional covariate parameter resulted in a p-value less than that specified. The full model resulting from the forward selection algorithm was subjected to a backward elimination algorithm, using likelihood ratio tests (based on ΔOFV) to assess the significance of the covariate parameters in the model when eliminated one at a time. The test for elimination of an individual covariate parameter given the others in the model was performed at a pre-specified significance level of $\alpha = 0.001$. The covariate parameter with the greatest p-value (least significance) greater than α was eliminated from the model for the current backward elimination step. The final model was obtained from the last stage of the backward elimination algorithm, in which all of the remaining covariate parameters, when excluded one at a time, resulted in significant likelihood ratio tests (i.e., $p<0.001$). At all stages of model development (base, full, and final), diagnostic plots were examined to assess model adequacy, possible lack of fit or violation of assumptions.

The performance of the final model was evaluated by simulating data using the final model (fixed and random effects) and conducting a predictive check. Simulations were performed using the subjects' characteristics as well as the dosing and sampling history from the original dataset. From these simulations, concentration-time data were summarized using median and low and high percentiles. The concordance between individual observations and simulated values as well as the distribution of observed and simulated data were evaluated by visual predictive checks (VPCs).

Results
Boceprevir PK was described using a two-compartment model defined in terms of apparent systemic clearance (CL/F), apparent volume of distribution (Vd/F), apparent inter-compartmental clearance (Q/F), apparent peripheral volume (Vp), first-order rate of absorption (ka), and absorption lag time (tlag). The base model

used separate residual errors for dense and sparse data because the latter had much higher standard deviation; this improved the objective function value and fit. The model included inter-individual variability on CL/F and Vd/F, but inter-individual variability on the ka, Q, and Vp could not be estimated reliably or was not significant. Covariance between CL/F and Vd/F was included because it significantly improved the fit. A multiplicative residual error was used (additive error for log-transformed) concentrations, which were used rather than the untransformed concentrations to stabilize the estimation). Inter-compartmental clearance Q was allowed to differ between sparse-data studies and dense data studies, and also to differ for Study P04489, because this significantly improved the objective function and avoided an implausibly large estimate of the peripheral volume Vp. Continuous covariates such as, age, BMI, CrCL, AST, ALT and body weight as well as binary covariates such as gender, Race (Black *vs.* Non Black, Asian *vs.* Non Asian), healthy *vs.* patients were tested on CL/F, Vd/F and ka. The full model assessed the significance of the covariate parameters. The covariate search found three significant covariates: health status on Vd/F and gender on CL/F and ka. Table 56 shows a summary of the resulting parameters and relative standard errors (%SE) for all parameters.

Table 56. Parameter Estimates for Base and Final Models.

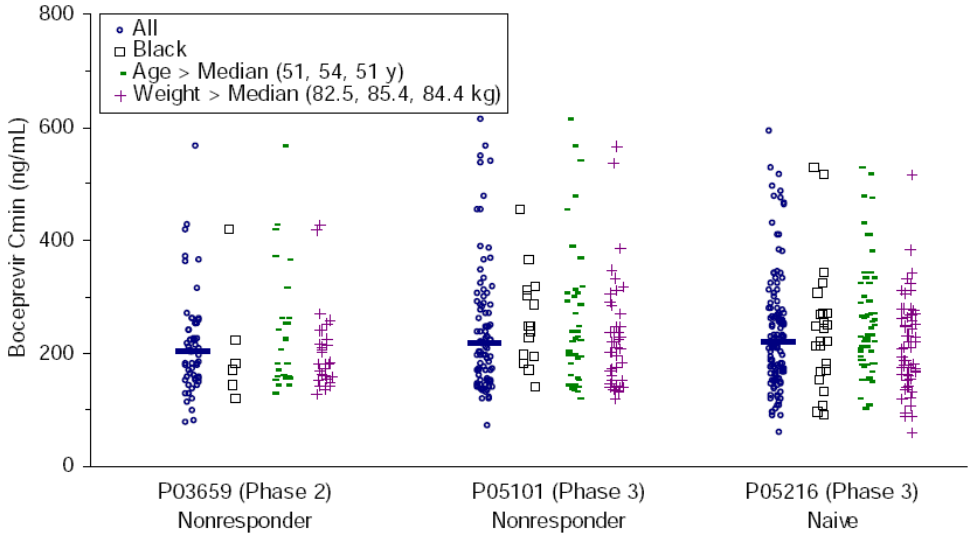
	Base Model				Full = Final Model			
OFV	1401.2				1359.4			
Change from Base	0				-41.8			
Parameter	Estimate	%SE	95% CI*		Estimate	%SE	95% CI*	
CL/F (L/h)	178	3.3%	167	190	191	3.5%	178	205
CL multiplier for females					0.814	5.5%	0.731	0.907
Vc/F (L)	126	13%	97.5	163	94.0	14%	71.8	123
Vc multiplier for patients					2.09	17%	1.49	2.93
ka (1/h)	0.526	2.0%	0.505	0.547	0.495	2.6%	0.471	0.521
ka multiplier for females					1.16	3.6%	1.08	1.25
Q/F (L/h)	21.9	16%	16.1	29.8	20.7	14%	15.6	27.5
Q/F for sparse data (L/h)	102	24%	63.9	163	84.2	17%	60.8	117
Q/F for Study P04489 (L/h)	2.99	22%	1.95	4.59	3.18	14%	2.44	4.15
Vp/F (L)	676	47%	270	1690	779	28%	451	1345
tlag (h)	0.893	1.5%	0.867	0.920	0.896	1.9%	0.864	0.929
CL/F ω^2	0.189	18%	0.133	0.268	0.174	18%	0.121	0.250
CL/F ω · 100% (%CV)	*43.5%*				*41.7%*			
Vc/F ω^2	1.84	25%	1.13	3.00	1.56	23%	0.995	2.45
Vc ω · 100% (%CV)	*136%*				*125%*			
CL/F-Vc/F ω Covariance	0.402	27%	0.237	0.681	0.331	28%	0.192	0.570
CL/F-Vc/F ω Correlation	68.2%				*63.5%*			
ka ω^2	0 Fixed				0 Fixed			
Q/F ω^2	0 Fixed				0 Fixed			
Vp/F ω^2	0 Fixed				0 Fixed			
Resid. error σ—dense	0.600	3.5%	0.560	0.643	0.597	3.5%	0.557	0.639
Resid. error σ—sparse	0.838	4.4%	0.769	0.913	0.835	4.3%	0.768	0.908

* Confidence interval is calculated as estimate·exp(±1.96 %SE/100%).

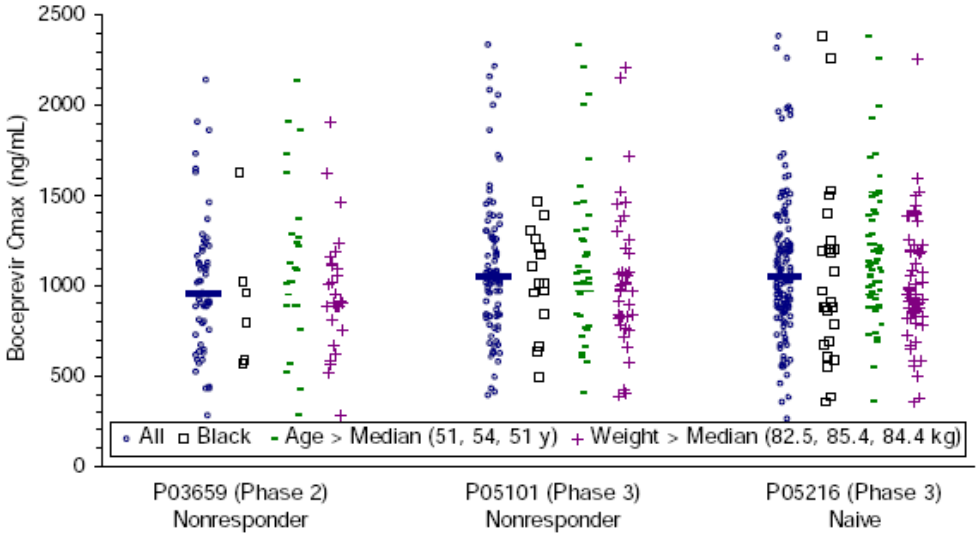
From Sponsor's study-report-pop-pk.pdf page 19.

Figure 69 shows that individual predictions of steady-state C_{min}, C_{max}, and AUC_{τ} are similar across the sparse-data patient studies, and that Black race, age, and weight do not appear correlated with concentrations.

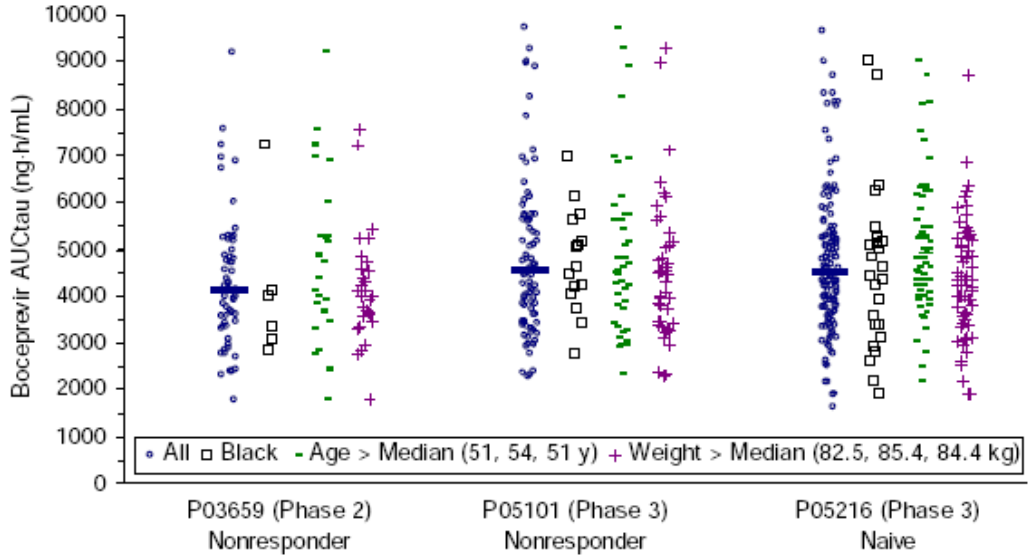
Figure 47: Individual Predictions in Sparse-data Patient Studies with Selected Demographics.



(a) Cmin



(b) Cmax

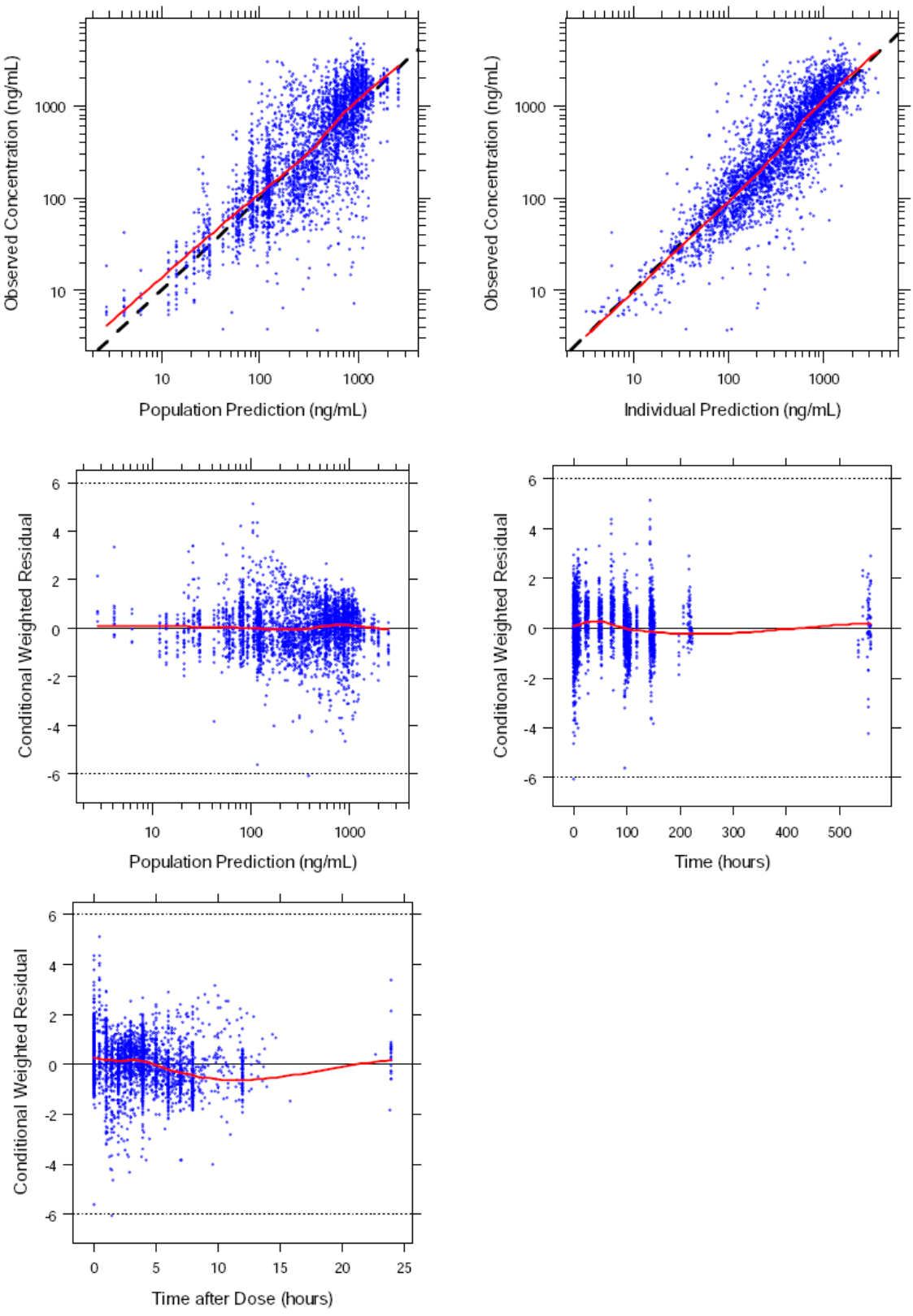


(c) AUC_{tau}

From Sponsor's study-report-pop-pk.pdf page 20 and 21.

Diagnostic plots presented in Figure 70 were reviewed to ensure the adequacy of the fit. Overall, individual predicted concentrations of boceprevir values were well fitted with the final population PK model. High and low concentration values well distributed around the line of identity and weighted residuals were homogeneously distributed around zero.

Figure 48: Basic Diagnostic Plots with Smooth (LOESS) Trends



From Sponsor's study-report-pop-pk.pdf page 26.

***Reviewer's comments**: Many aspects of the basic model were solely data*

driven and did not have proper justification i.e. the use of different intercompartmental clearance (Q) and residual error for dense and sparse data. This could have been circumvented by developing the model using data from dense sampling studies first, then fixing the parameters (Q, Vp) in sparse sampling studies to their previously estimated values. The reviewer's analysis will emphasize model development using this approach in addition to identifying clinically relevant patient covariates, as this would be useful in performing further exposure response analysis.

Population Ribavirin PK Analysis

Clinical Data

The analysis included 291subjects: 99 from study P05101 and 192 from P05216, with 529 total concentrations: 176 from P05101 and 353 from P05216. Because only one or two ribavirin samples per patient, at approximately 4 and 8 weeks of treatment, were available for a subset of the patients in these two studies, a full ribavirin population PK model could not be built with this data. Instead, the data was tested for consistency with existing models.

Methodology

The first-order conditional estimation with interaction (FOCE-I) method of NONMEM VI Level 1.0 was used for the parameters estimation. The data was tested for consistency with existing models; a three-compartment, sequential zero-order and first-order absorption population PK model of ribavirin has been published (Wade 2006), as well as a two-compartment first-order absorption model (Jin 2009) and earlier models of ribavirin clearance (Jen 2000). The sequential zero-order and first-order absorption of Wade[1] model was simplified to first-order absorption. The wade model was then tested in three ways:

1. With fixed parameters (without estimation), simply to compare objective functions evaluated on the Phase 3 data.

2. Re-estimating only clearance and its variability as well as the overall residual error (used as the base case model).

3. Re-estimating the above and also central volume and absorption rate, with variability.

Subsequently, the sponsor reviewed population PK differences between the available data and that of the Wade and Jin models. The sponsor provided individual exposures for future exploratory pharmacokinetic-pharmacodynamic (PK-PD) analyses.

Results

The concentrations were plotted vs. time after dose; seven values with time after dose > 24 hours are not shown) and vs. dose (Figure 71). The observed range of concentrations was reasonably consistent across all doses, supporting the

weight-based dosing scheme used in these studies to provide consistent exposures, although there a slight trend towards decreases with dose at both the 4-week and 8-week visits.

Figure 49: Ribavirin Concentration vs. Time after Dose (dose jittered for readability).

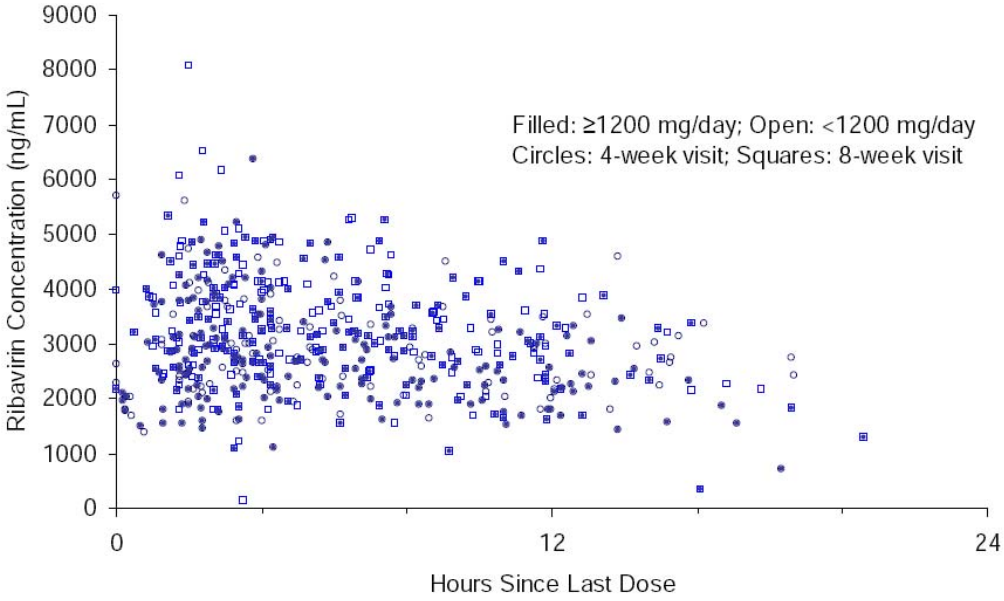
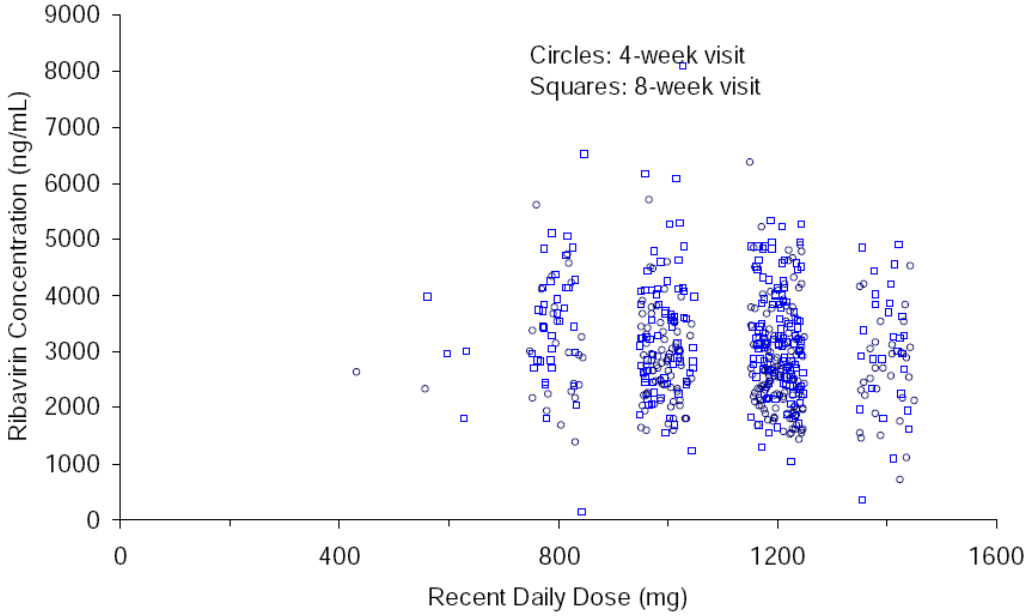


Figure 50: Ribavirin Concentration vs. Dose (dose jittered for readability)



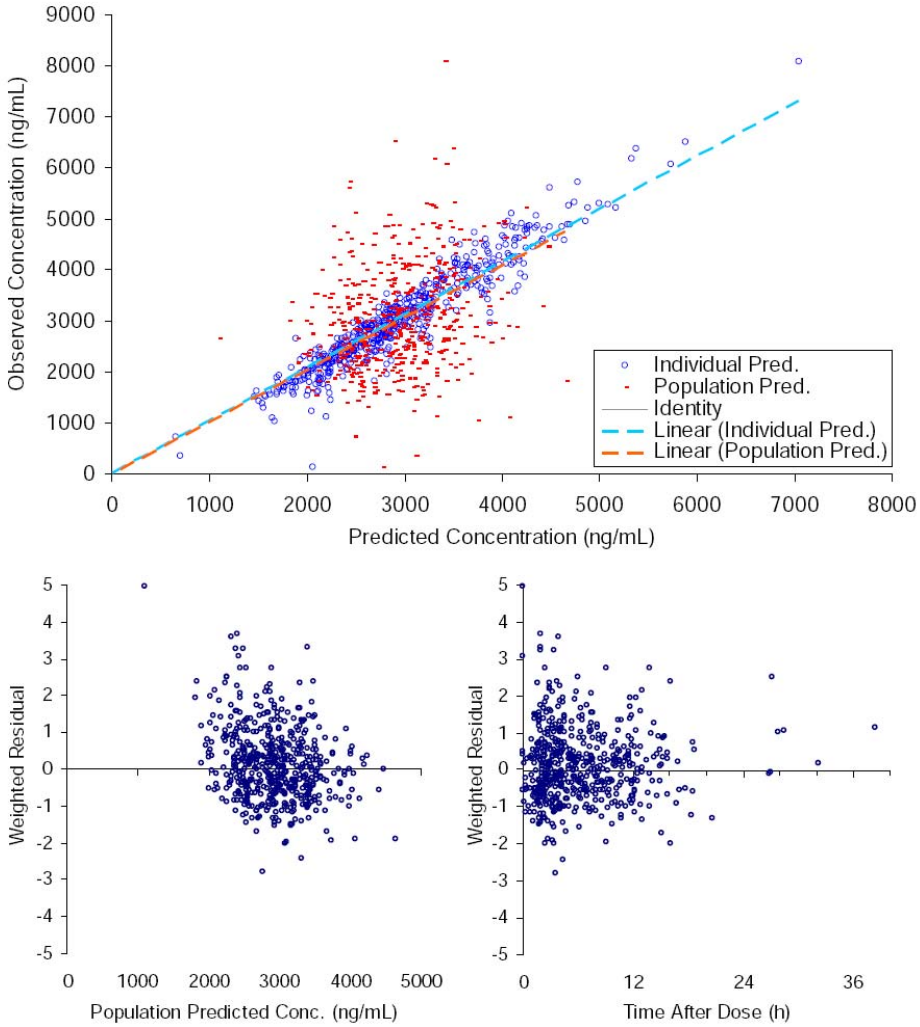
Modestly higher steady-state concentrations than in both Wade 2006 and Jin 2009, were reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL (37%)." Since high-fat meals increase bioavailability, one possible explanation is higher-fat meals in the new studies. Another possibility is differences in the population disease severities in the studies here vs. the literature studies and the label study (N=12, presumably

healthy volunteers).

Concentrations are 17% higher at the 8-week visit than the 4-week visit. This is well captured in the model, which actually predicts about 21% higher concentrations at 8 weeks, and another 8% higher concentrations at steady state. The slowness of the approach to steady state could be important clinically. Since these features appeared to be well captured in the Wade model (with re-estimated clearance), the individual post-hoc estimates of PK parameters from this model, including clearance and corresponding steady-state AUC for each patient, appear adequate for subsequent use in exploratory PK-PD modeling of the Phase 3 data.

Figure 73 show diagnostic plots for Wade Model 2 (clearance re-estimated). This was the most appropriate model given the data limitations. In general, individual predicted concentrations of ribavirin values were well fitted with the final population PK model. Concentration values well distributed around the line of identity and weighted residuals were homogeneously distributed around zero.

Figure 51: Ribavirin Diagnostic Plots



Reviewer comments: Since very sparse sampling was available to fully develop the population PK model, the reviewer agrees with the sponsor's approach i.e. fitting previously reported model to the data, fixing the parameters to their previously reported values. As very few data points are available in the low weight category (≤50kg), the reviewer suggests using the final model to simulate data for each weight group and compare the results with the available data. This will provide one more levels of assurance for the consistency of concentration distribution across different weight groups.

Reviewer's Analysis
This section describes the reviewer's evaluation of the sponsor's basic and final PK model and the covariate analysis for boceprevir and ribavirin. The review is focused on the evaluation of the label statements that age, race, gender had no apparent effect on boceprevir exposure. Additionally, the review aimed to assess the importance of the selected population PK covariates, i.e. health status and gender on bocreprevir exposure. Moreover, the weight based dosing was evaluated to assess if it provides consistent ribavirin concentrations across the different weight categories.

Introduction
The sponsor used their population PK model to make claims in the label regarding the covariate effects on the pharmacokinetics of boceprevir. It is the aim of this review to examine whether the label claims and proposed ribavirin doses are justified using the population PK analyses.

Objectives
The purpose of this review is to address the following key questions:

1. Are the labeling statements derived from the population pharmacokinetics of boceprevir acceptable?

2. Did the weight based dosing provide consistent ribavirin concentrations across the different weight categories?

Methods

Data Sets

Data Sets Boceprevir

Data from healthy subject studies (

Table **57**), intense PK sampling, was used to asses the importance of the different covariates on the exposure parameters (dose normalized AUC_{tau} (ng.h/ml), C_{max} (ng/ml) and C_{min} (ng/ml) calculated using non-compartmental PK analysis.

Table 57. Healthy Subjects Non-Compartmental PK Data.

Study	Phase	Subjects With PK Parameters N	Total Subjects/ Trial N	PK sampling	Dose (mg/TID)
P04488	I	33	36	dense	200, 400,800
P04489	I	35	36	dense	800, 1200
P04624	I	12	12	dense	400
Total		80	84		

The PK data from 4 patients clinical trials (
Table 58) involving 277 patients (age: 23–69 yrs; weight: 47–124 kg; Males: 182) were available and used for the review of boceprevir population PK modeling and covariate selection. Baseline characteristics are summarized in Table 59.

Table 58. Patients Trials Data Used in the Reviewer Population PK Analysis.

Study	Phase	Subjects N	Total Patients/ Trial N	Obs. N	PK sampling	Dose (mg/TID)
P04487	I	6	30	191*	dense	400
P03659	II	58	357	292	sparse	800
P05101	III	87	404	409	sparse	800
P05216	III	126	1099	533	sparse	800
Total		277	1890	1425		

*Full PK profile at three different occasions (Day1, Day9/10, Day23/24)

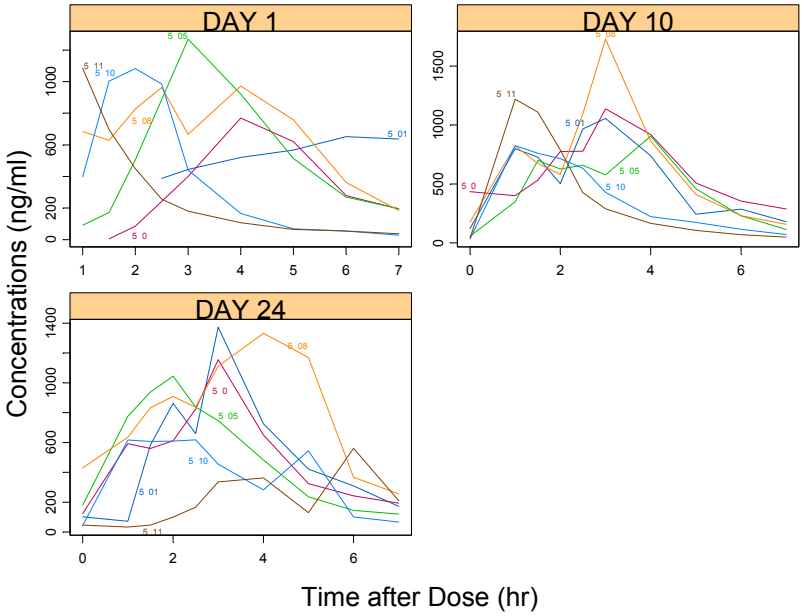
Table 59. Demographic Summary of Population PK Data.

Study	Phase	Subjects N	Age (years) Median (Range)	Weight (Kg.) Median (Range)	AST(U/l) Median (Range)	ALT(U/l) Median (Range)	Male N	Black N
P04487	I	6	52 (47 - 59)	83 (45 - 127)	47 (37 - 123)	75 (42 - 176)	4	6
P03659	II	58	51 (23 - 65)	82 (49- 97)	26 (15 - 143)	26 (9 - 214)	37	0
P05101	III	87	54 (27 - 69)	85 (53 - 12)	28 (13 - 214)	25 (8 - 189)	56	15
P05216	III	126	51 (25 - 67)	84 (47 - 124)	26 (11 - 207)	25 (7 - 315)	85	26

Total	277	52 (23-69)	84 (45 - 127)	27 (11-214)	25 (7 - 315)	182	47

Concentration versus time after dosing profiles, for HCV Genotype 1 patients in study P04487, where intense sampling was performed are described in Figure 52.

Figure 52: Boceprevir Concentrations versus Time after Dose



Data Sets Ribavirin

The review data was the same as the sponsor's data described in section 3.2.1.

Software

Estimation and simulation were performed NONMEM VI on the Pharmacometrics Group Linux cluster using the front end manager Perl Speaks NONMEM (PsN). S-PLUS 8.0 (TIBCO Software Inc., Palo Alto, CA) was used to generate all plots and manage datasets. The statistical software R (www.r-project.org) was used in combination with the population PK tool library in order to generate diagnostic and pertinent covariate plots. A statistical computing environment (WABAN) was used for organizing and submitting models and simulations for the reviewer's analysis.

Model

Model for Boceprevir

The review emphasized on patient's data and patients covariates. The observations were log-transformed and a two-compartment structural model with a first-order rate of absorption (ka), and absorption lag time (tlag) was evaluated in NONMEM. The reviewer considered refining the sponsor final model by fitting

the basic model to healthy subject's dense data, estimating the PK parameters. Then, the same model was fitted to the patient's data fixing the peripheral parameters to their previously estimated values. This circumvented, the unjustified additional parameter estimated in the sponsor's final model i.e.; the separate inter-compartmental clearance Q allowed for sparse-data studies and dense data studies, and also for study P04489, and the separate residual error estimated for dense and sparse data.

Moreover, inter-individual variability on primary model parameters (CL/F, Vd/F) were included as log-normal distributions with mean 0 and variance σ^2. Further, the residual variability was modeled using the log-transformed error model and the same residual error for sparse and dense data was used. The same inter-compartmental clearance for the different trials was used. Age, weight, BMI, CrCl, AST, ALT, race, dose, and gender effect were tested on Cl/F, Vd/F and Ka.

Model for Ribavirin

Based on the results, the sponsor's population PK model for ribavirin did not require further refinement.

Results

The pharmacokinetic models and concentration data for boveprevir and ribavirin were evaluated to determine if the label claims based on the population PK models were justified. For boceprevir the main emphasis of the evaluation was placed on discerning whether the covariate relationships were identified correctly, were clinically meaningful, and if they were described accurately in the label.

Boceprevir Population Pharmcokinetic Model

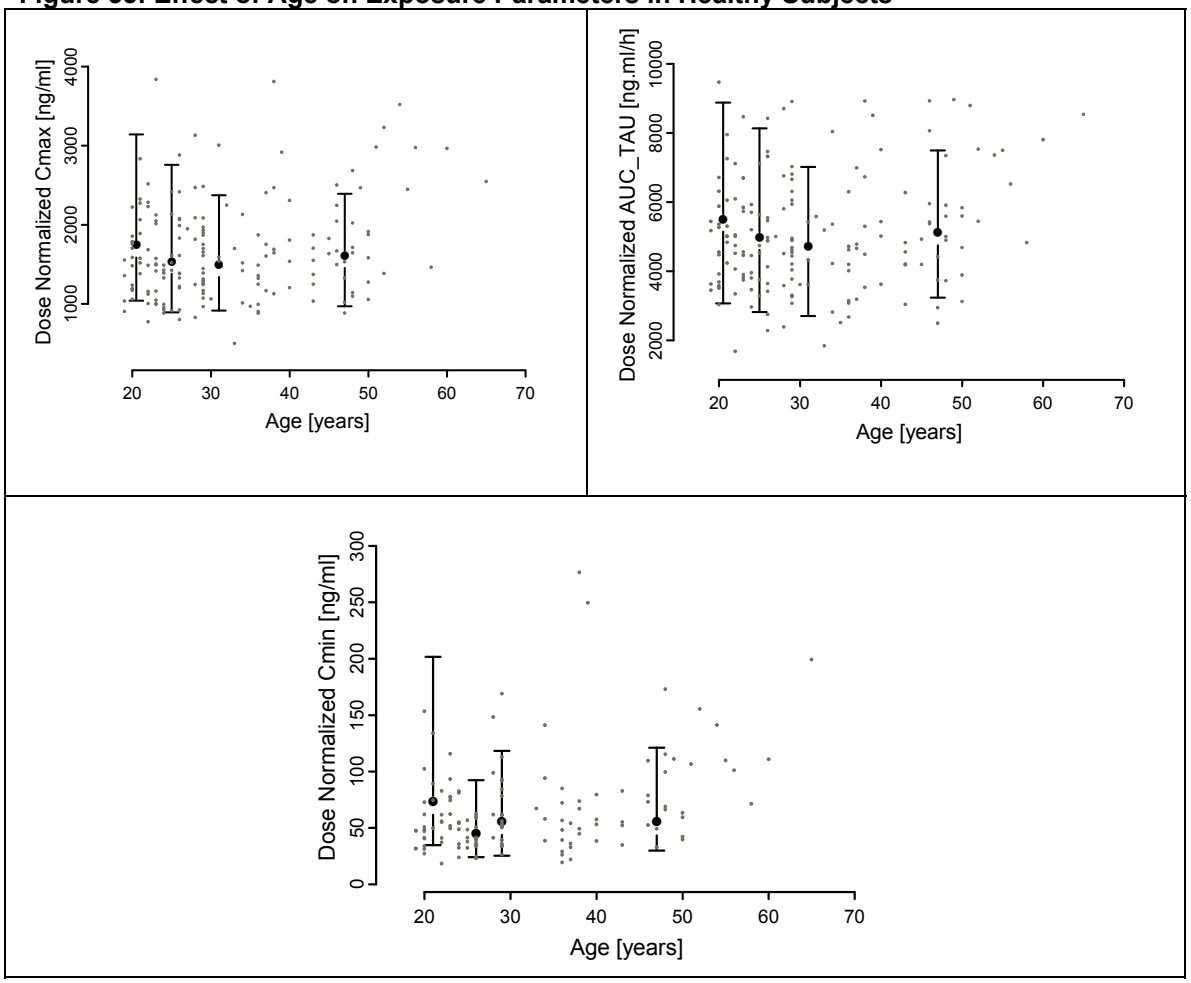
Non-compartmental Covariates Assessment

The label states that age, weight, gender and race are not related to any pharmacokinetic differences in boceprevir exposure. This claim was investigated using non compartment analysis data in healthy subjects. Median C_{min}, C_{max} and AUC_T (90%CI) were plotted against covariate quantile values, the quantiles are plotted at the median of their respective covariate values. Then, the consistency of the exposure parameters across the different demographic quantiles was tested.

Effect of Age on Exposure Parameters

Boceprevir is primarily eliminated via the liver, undergoing metabolism through the aldoketo-reductase (AKR)-mediated pathway to ketone-reduced metabolites that are inactive against HCV. The age effect on exposure could only occur if age mainly affects the subject's hepatic functions. The median (range) age in healthy subjects was 29 (19 -65) years. Within this age range the PK exposure parameters were consistent Figure 75.

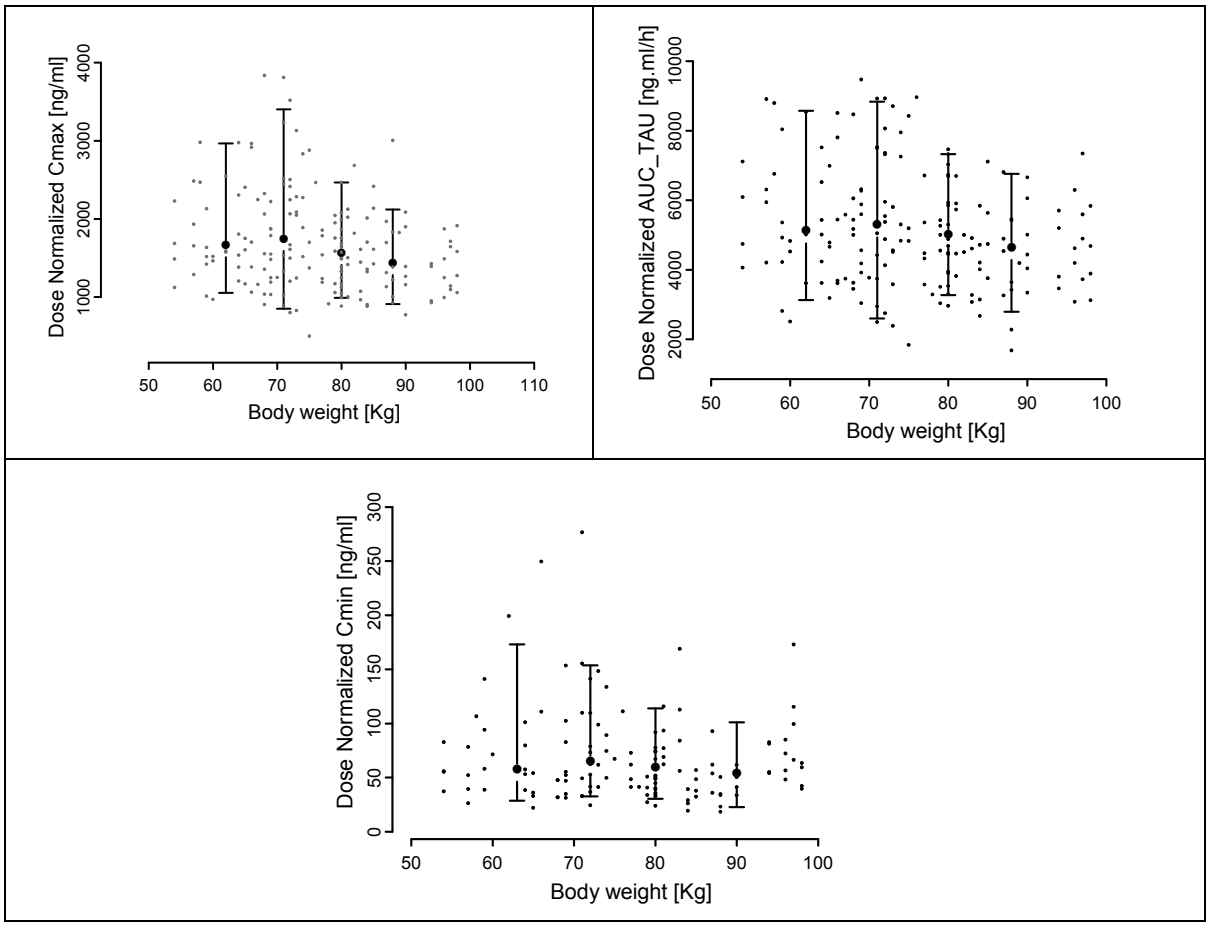
Figure 53: Effect of Age on Exposure Parameters in Healthy Subjects



Effect of Body Weight on Exposure Parameters

Healthy subjects' median body weight was 75.4 Kg (54.3 – 98.1). The effect of Body weight on the PK exposure was assessed and no relationship was identified, see Figure 76 below.

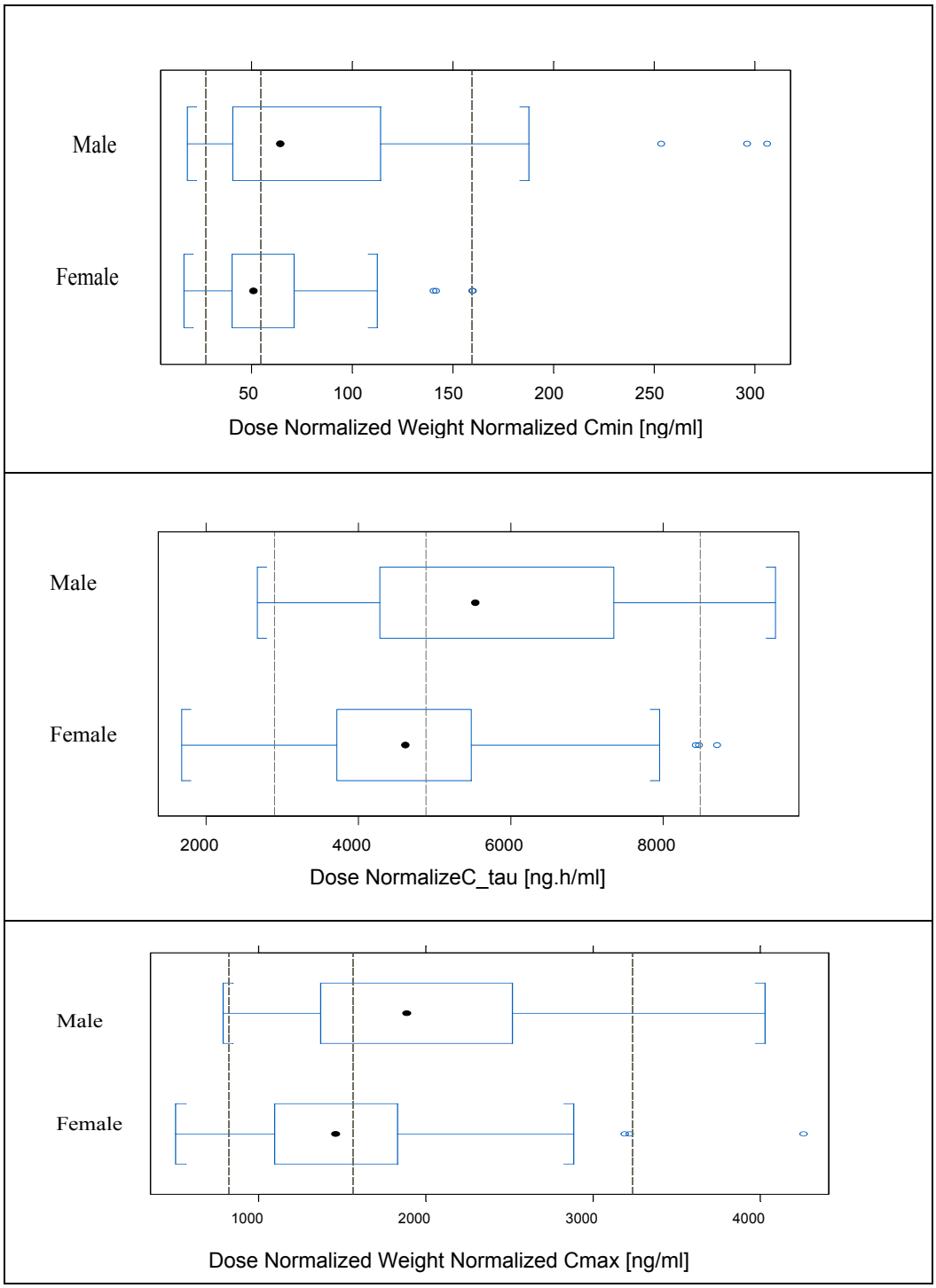
Figure 54: Effect of Body Weight on Exposure Parameters in Healthy Subjects.

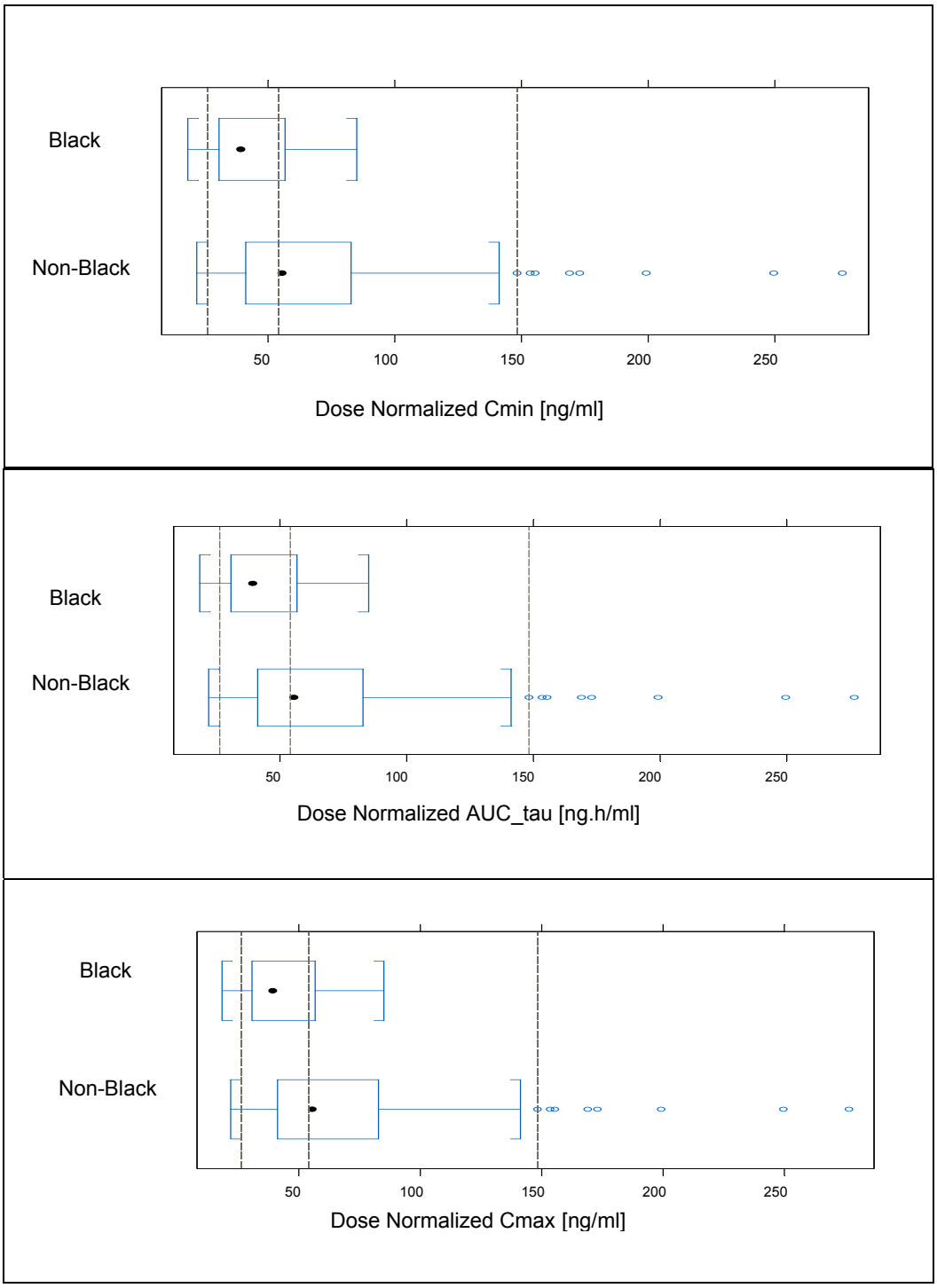


Effect of Gender and Race on Exposure Parameters

79 Male, 62 Female were included in the Non-compartmental covariate assessment analysis, 19 Black, 4 Asian 122 Non-Black. Race and gender did not influence the PK parameters (Figure 77).

Figure 55: Effect of Gender (A), Race (B) on PK Exposure Parameters in Healthy Subjects


Male
Female
50
100
150
200
250
300
Dose Normalized Weight Normalized Cmin [ng/ml]
Male
Female
2000
4000
6000
8000
Dose NormalizeC_tau [ng.h/ml]
Male
Female
1000
2000
3000
4000
Dose Normalized Weight Normalized Cmax [ng/ml]



Compartmental Covariates Assessment

The main objective of the compartmental population PK analysis is to discern whether the covariate relationships were identified correctly, were clinically meaningful, and if they were described accurately in the label.

Structural Model Assessment

Based on goodness of fit plots and OFV value, a two compartment structure for boceprevir patients PK data was selected. This model was first fitted to the healthy subject's data and the PK parameters were estimated. Then the same model was fitted to patient's data fixing the peripheral parameters (Q and Vp) to their previously estimated values (using the dense data in healthy subjects, Vp= 115 L, and Q= 11 L/h). The goodness of fit of the structural model to the data was evaluated (Figure 78). The individual and population predicted concentrations agree well with observed concentrations and are symmetric around the line of unity. Similarly, weighted residuals versus time or observed concentrations with distributed symmetrically around zero and were not skewed at either early/late time points or high/low concentration observations. Relative standard errors were typically less than 20% for all model parameters. The PK parameters of the structural model are presented in Table 60.

Figure 56: Diagnostic Plots for Boceprevir Structural PK Model

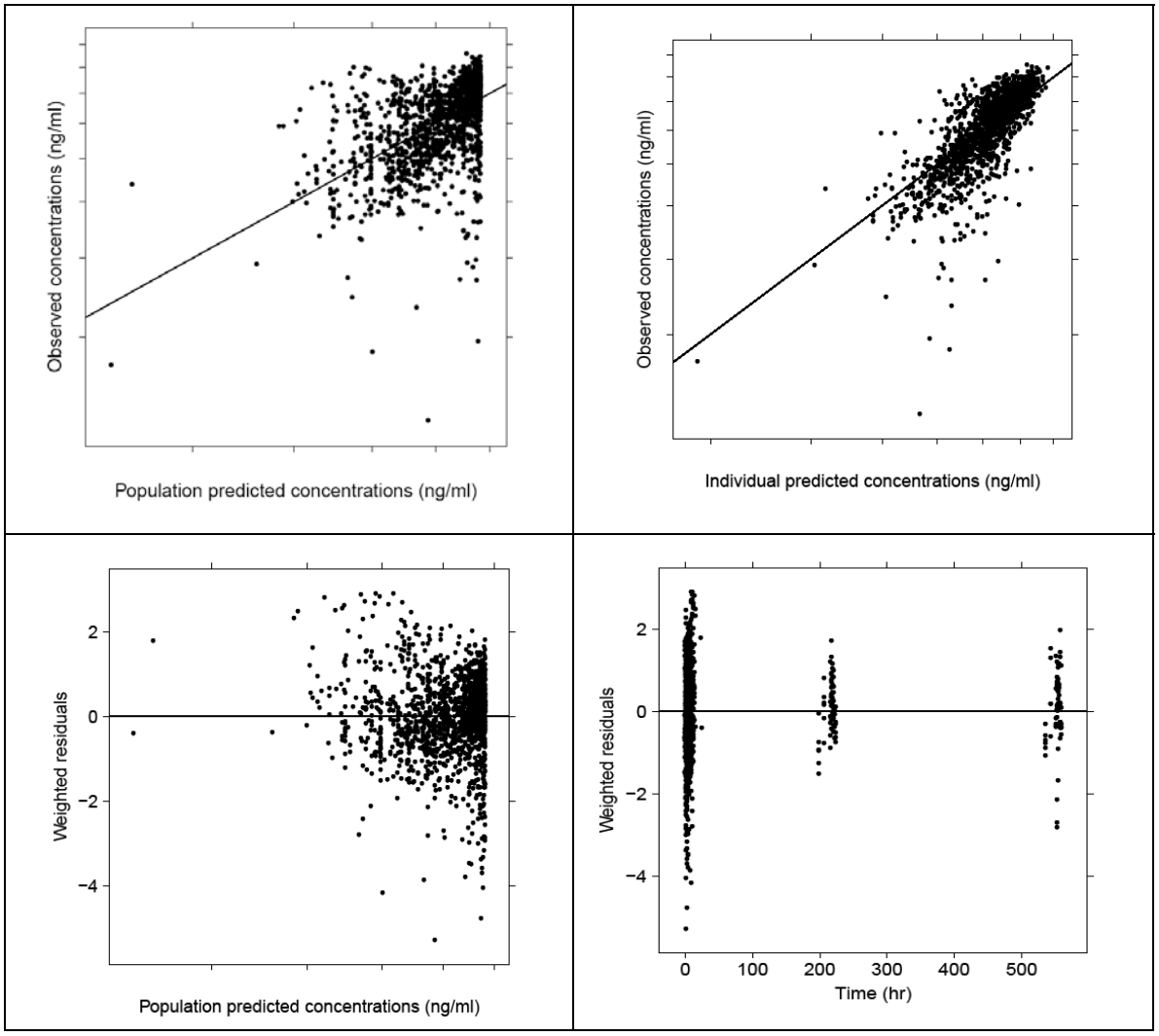


Table 60. Structural Model Parameter Estimates for the Reviewer's Analysis

Fixed-Effects Parameters	Estimate	RSE(%)
CL/F (Apparent Central Clearance, L h^{-1})	181	4.453
Vd/F (Central Volume, L)	176	29.38
Ka (Oral Absorption, h^{-1})	0.302	9.437
Q/F (Inter-compartment clearance, L h^{-1})	11	-
Vp/F (Peripheral Volume, L)	115	-
ALAG1 (Lag time, h)	0.503	4.433
Inter-Individual Variability CL/F (CV%)	55.59	11.54
Inter-Individual Variability Vd/F(CV%)	179.4	21.27
Intra-Individual Variability Parameters (sigma^2)	**Estimate**	**RSE(%)**
Sigma(1)	0.795	3.774

These obtained parameters are relatively in agreement with the sponsor's reported PK parameters, Table 56. The final model patient's CL/F and Vd/F reported by the sponsor were 191 L h^{-1} and 188L, respectively.

Sponsor's Final Model Review

The sponsor's reported a significant gender effect on Ka and CL/F and a significant health status (healthy vs. Patient) effect on Vd/F. The different reported covariates were reevaluation using the reviewer's structural model.

Assessment of the Sponsor's selected covariates:

The addition of the gender effect on Ka or CL/F did not decrease the objective function significantly and did not explain the inter-individual variability for CL/F. Figure 79 shows that gender does not have any significant effect on CL/F and does not differentiate between the inter-individual variability for male and female. This is consistent with the non-compartmental analysis reported earlier. The difference between Vd/F for healthy and patients was not relevant to this analysis as the reviewer focused on the patient population data. In addition, no difference was detected between Vd/F estimated for each study (toxicity experienced patients studies P05101, P04487, P03659 vs. toxicity naïve patients study P05216), Figure 80.

Figure 57: Clearance and Central Volume and the Respective Eta Plots versus Gender.

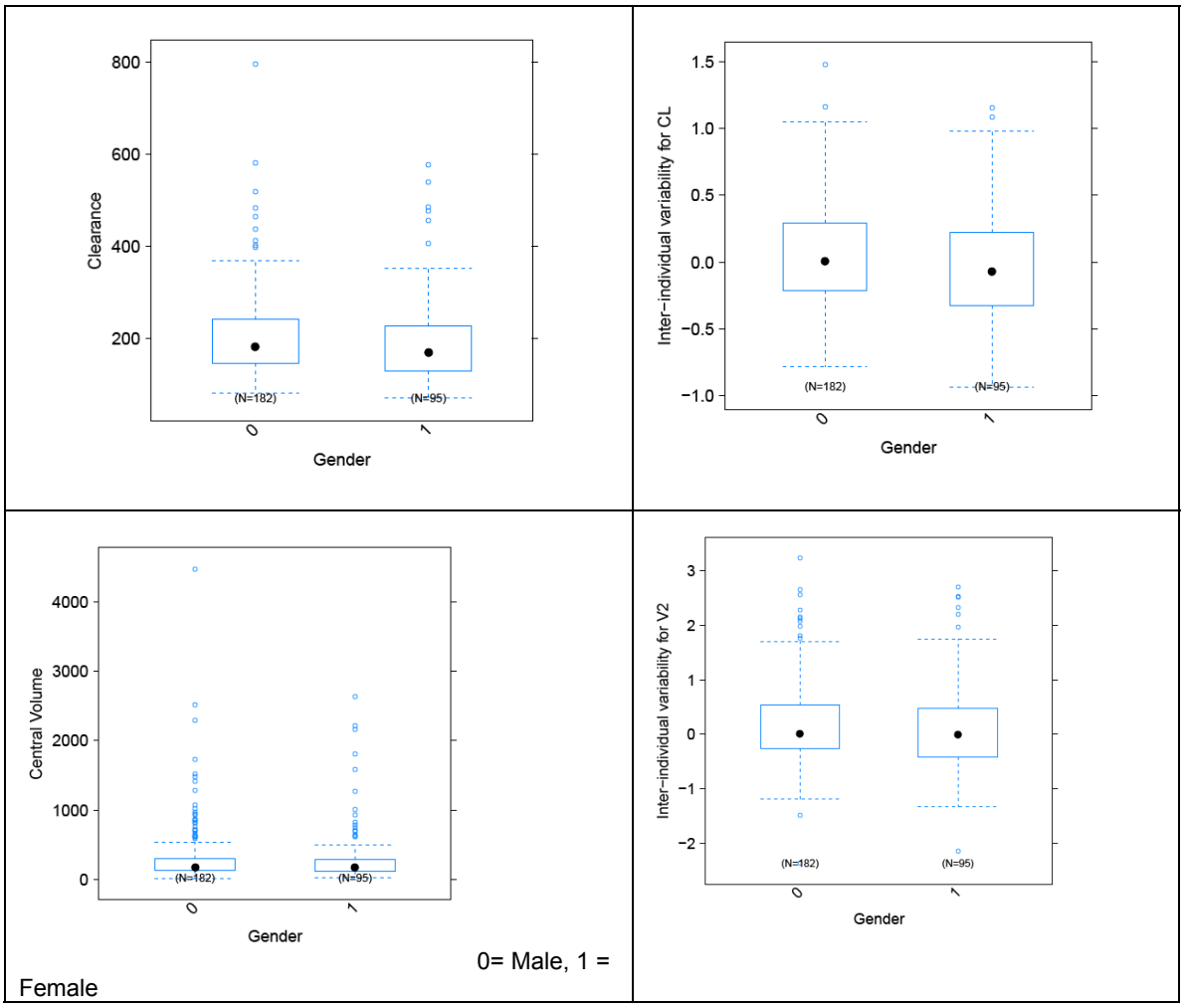
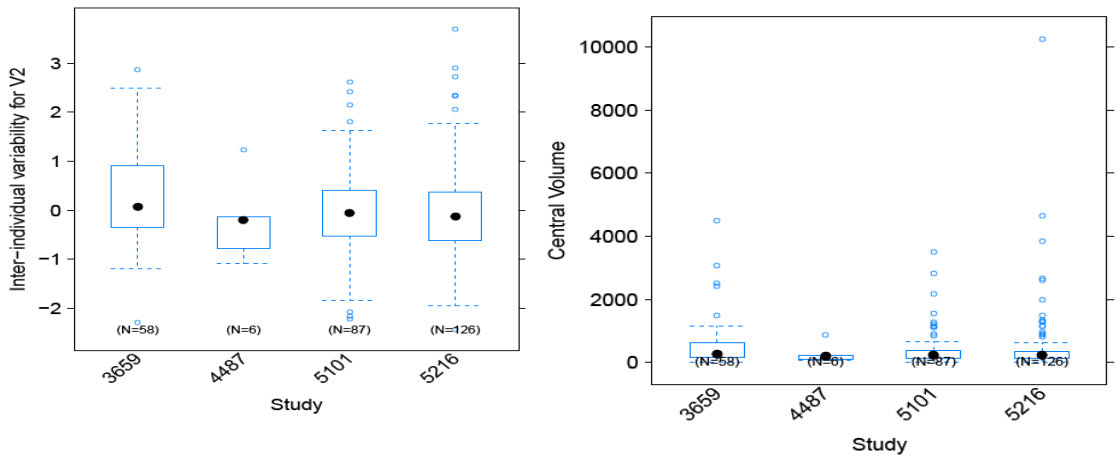


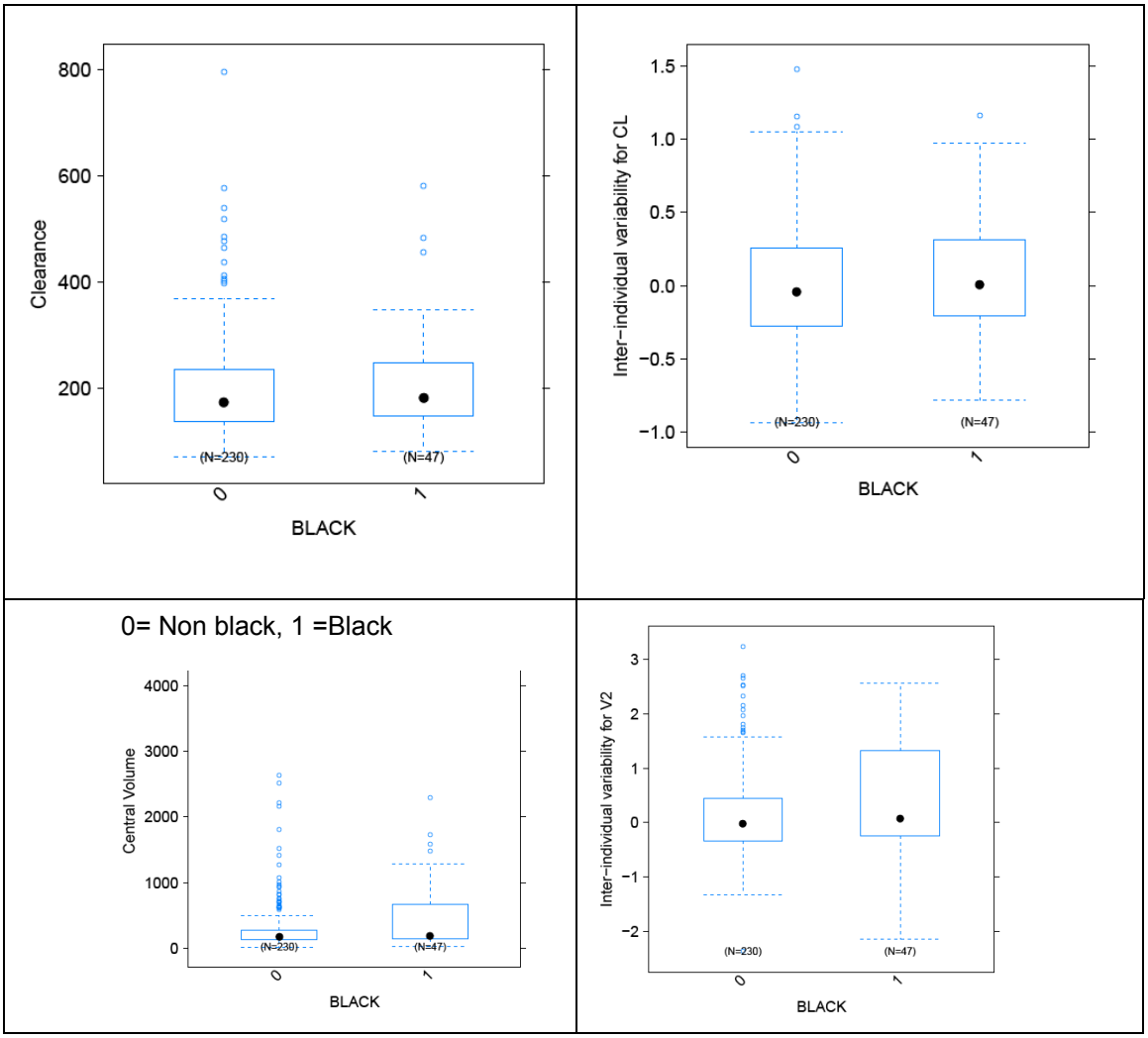
Figure 58: Clearance and Central Volume versus Study.



Assessment of the Label Statement

The label reports no effect of gender, race, or age on the different population PK parameters. This statement was reassessed by testing the effect of the respective covariates on the PK model using patients' sparse data. Gender and race did not significantly explain the variability of Vd/F or CL/F as shown in Figure 59 and Figure 60. This was consistent with the non-compartmental analysis reported earlier. Other covariates such as hepatic function related covariates (AST, ALT) and body weight were evaluated and did not have a significant effect on the variability of the different PK parameters.

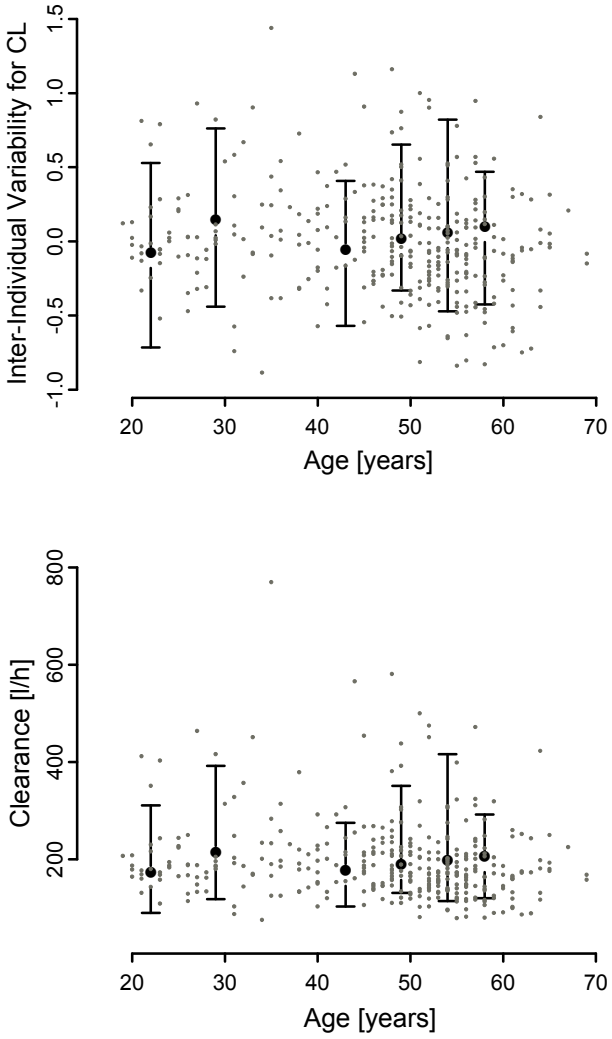
Figure 59: Clearance and Central Volume and Respective Inter-Individual Variability versus Race



Age effect on CL/F significantly decreased the objective function; for a range of age (23 -69) the respective predicted typical value of CL/F was (144 - 243), in

patients. Nevertheless, after assessing the clinical significance of age on clearance it was not considered relevant, for different reasons. First, when age was added to the model it explained only 4% of the inter-subject variability. Second as this drug is hepatically cleared, age effect could be credible only if it caused deterioration in the hepatic functions, nonetheless, AST, ALT did not explain any of the clearance variability. Moreover, to detect if the hepatic functions affect the clearance, the basic model was fitted to healthy and patient data, clearance (mean ± SD) for each group was comparable (199 ± 60.82 for healthy and 189 ± 79.5 for patients), and no trend of decrease in CL was detected with increasing age, Figure 60. Clearance was expressed as median (5^{th} – 95^{th} percentile) for each of 6 quantiles of age values. The quantiles are plotted at the median of their respective age values with confidence intervals overlapping across the studied age 19 to 69.

Figure 60: Clearance and Eta Plot versus Age



In summary the reviewer agrees with the label statement and confirms the absence of the effects of age, gender, or race on boceprevir exposure parameters.

Results for Ribavirin

Ribavirin was dosed BID and accumulates to steady state over at least one month. In the Phase 3 RESPOND-2 (P05101) and SPRINT-2 (P05216) studies, weight-based dosing of 600-1400 mg/day (BID) was used for ribavirin: 600 mg for body weight ≤50 kg, 800 mg for >50-65 kg, 1000 mg for >65-80 kg, 1200 mg for >80-105 kg, and 1400 mg for >105 kg. This is the same as the label dosing recommendation except that the label specifies 800 mg/day up to a weight of 65 kg.

To assess if the weight based dosing provided consistent ribavirin concentrations across the different weight categories, wade[2] model was used to run 200 simulations. Simulations were performed using the subjects' characteristics as well as the dosing and sampling history from the original dataset. From these simulations, concentration-time data were summarized using median and low and high percentiles. The simulated concentrations were plotted then against the different weight categories.

The three compartments, first-order absorption, with re-estimated clearance and its variability, central volume, absorption rate, and overall residual error version of the Wade model was used. The other PK parameters were fixed to their literature reported values.

The typical re-estimated typical clearance for a lean body weight of 60 kg using Wade model was 13.8 L/h, which is slightly lower than the value reported by Wade 18.6 for the same lean body mass, which may reflect differences in the patient population or study conditions in these studies relative to those used to build the published models. Here, concentrations averaged (to three significant digits) 2810 ng/mL at the 4-week visit and 3290 ng/mL).
Figure 62Figure 61 represents ribavirin simulated concentrations (median, 5th - 95th percentile) parallel to theirs matching observed data.

Figure 61: Consistent Ribavirin Concentrations across Weight Categories

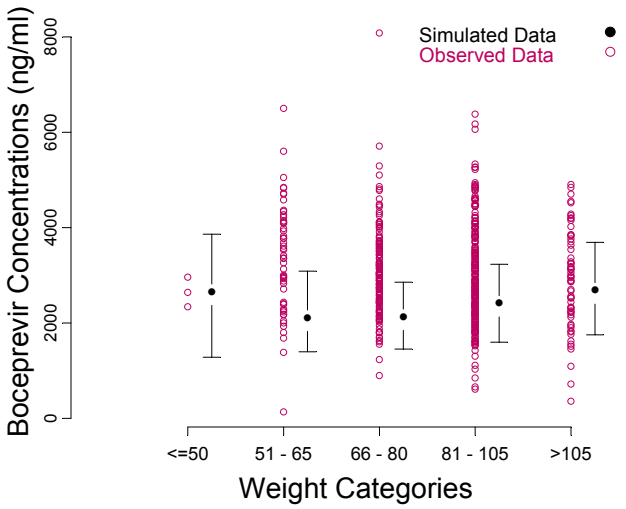
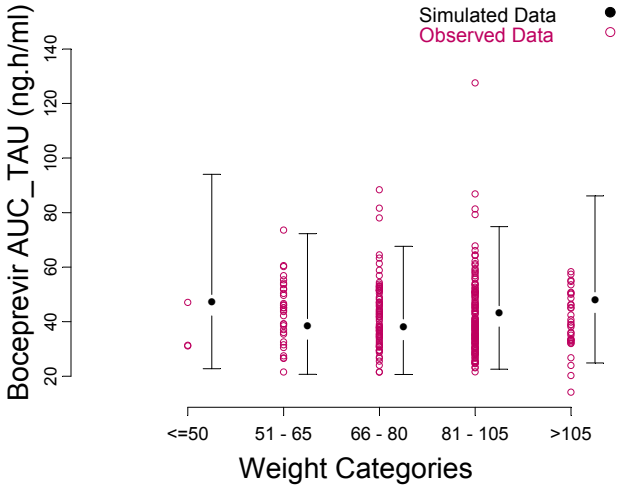


Figure 62 represents ribavirin simulated AUC_T (median, 5^{th} - 95^{th} percentile) parallel to theirs matching observed AUC_T.

Figure 62: Consistent ribavirin AUCs across Weight Categories



The reviewer concluded the consistency in boceprevir exposure across the different weight categories.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnsa\pharmacometrics\Reviews\Ongoing PM Reviews\Boceprevir _NDA 202258_DF\
20100712BOCPopPK.csv	Sponsor's boceprevir basic and final model data	\Boceprevir _NDA 202258_DF\RUN1\PPK_Analyses\NM_Data\Sponsor
RUN1	Sponsor's boceprevir basic model	\Boceprevir _NDA

	script and output	202258_DF\RUN1\PPK_Analyses\Model\RUN1
RUN2	Sponsor's boceprevir final model script and output	\Boceprevir _NDA 202258_DF\RUN2\PPK_Analyses\Model\RUN2
DataPatientRACE.csv	Reviewer's boceprevir basic model data	\Boceprevir _NDA 202258_DF\RUN104\PPK_Analyses\NM_Data\Reviewer\
RUN104	Reviewer's boceprevir basic model model script +output	\Boceprevir _NDA 202258_DF\RUN104\PPK_Analyses\Model\run104
DENSEBOCEPRAVIR.csv	healthy data only to estimate the peripheral parameters and then fix them	\Boceprevir _NDA 202258_DF\RUN300\PPK_Analyses\NM_Data\Reviewer
Run300	Basic model reviewer run on healthy data only to estimate the peripheral, parameters and then fix it in final model reviewer developed on patients only. Model script + output	\Boceprevir _NDA 202258_DF\RUN300\PPK_Analyses\Model\run300
Run301	Basic model reviewer run on healthy data only fixing peripheral parameters to values run300 and comparing OFV.	\Boceprevir _NDA 202258_DF\RUN301\PPK_Analyses\Model\run301
RUN105	Reviewer's boceprevir Basic model model script +output testing dose as covariate on clearance	\Boceprevir _NDA 202258_DF\RUN105\PPK_Analyses\Model\run105
RUN106	Reviewer's boceprevir Basic model model script +output testing age covariate on CL	\Boceprevir _NDA 202258_DF\RUN106\PPK_Analyses\Model\run106
RBVPKNew.csv	Reviewer's and sponsor ribavirine basic model data	\Boceprevir _NDA 202258_DF\RUN200\PPK_Analyses\NM_Data\Reviewer
Run200	Reviewer's and sponsor ribavirin Wade3 model +output	\Boceprevir _NDA 202258_DF\RUN200\PPK_Analyses\Model\run200
Run201	Reviewer's ribavirin Wade3 model simulations +output	\Boceprevir _NDA 202258_DF\RUN201\PPK_Analyses\Model\run201
RBVPKNewSIM.csv	Reviewer's ribavirin Wade3 model simulations data	\Boceprevir _NDA 202258_DF\RUN201\PPK_Analyses\NM_Data\Reviewer
WTeffect2.ssc, DATA_perp.ssc, DATA_perp.ssc, WTeffectAUC.ssc, WTeffectCL.ssc	SPLUS scripts	\Boceprevir _NDA 202258_DF\SPLUS scripts

References

2. Jen JF, Glue P, Gupta S, Zambas D, Hajian G. Population pharmacokinetic and pharmacodynamic analysis of ribavirin in patients with chronic hepatitis C. Ther Drug Monit 2000; 22:555–65.

3. Wade JR, Snoeck E, Duff F, Lamb M, Jorga K. Pharmacokinetics of ribavirin in patients with hepatitis C virus, British Journal of Clinical Pharmacology 2006; 62(6):710–714.

4.5 Genomics Review

NDA Number	202,258
Submission Date	November 10, 2010
Applicant Name	Schering Plough
Drug Name	Boceprevir
Proposed Indication	Treatment of chronic hepatitis C genotype 1 infection
Reviewer	Shashi Amur, Ph.D.
Team Leader	Michael Pacanowski, Pharm.D., M.P.H

1 Background

The current submission is a NDA for boceprevir, an inhibitor of the hepatitis C virus (HCV) non-structural protein 3 (NS3/4A) serine protease. The proposed indication is for the treatment of chronic hepatitis C genotype 1 infection, in combination with peg-interferon alpha and ribavirin (PR), in adult patients (≥18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy.

A polymorphism that is approximately 3 kilobases from the *IL28B* gene (encoding interferon-lambda 3; hereafter referred to as "*IL28B* genotype") is a strong predictor of sustained viral response (SVR) in patients receiving PR therapy, such that carriers of the variant alleles have lower SVR rates.[9] In the two pivotal Phase 3 trials that support boceprevir efficacy, DNA samples were collected from 63% of the subjects. *IL28B* genotype data were submitted for these two trials at the request of the Agency (correspondence dated 27 Sept 2010). The sponsor has not proposed any label language related to *IL28B* genotype.

Inosine triphosphatase (*ITPA*) polymorphisms resulting in ITPA deficiency have been repeatedly associated protection from anemia during the course of PR therapy.[10] As per the Agency's request, the sponsor submitted data and analyses for three *ITPA* polymorphisms using the same PG substudy database used for IL28B analyses on 3 Mar 2011.

The purpose of this review is to evaluate 1) the influence of *IL28B* genotype on response to boceprevir/PR and PR treatment, 2) the influence of ITPA deficiency on anemia-related adverse events to boceprevir/PR and PR treatment, and 3) whether information related to the impact of *IL28B* genotype on boceprevir/PR clinical outcomes should be addressed in the label.

[9] Ge D, et al. Nature 2009;461:399-401.
[10] Fellay, et al. Nature 2010;464:405-408.

2 Submission Contents Related to Genomics

The efficacy and safety of boceprevir are supported by two Phase 2 trials (P03523 [n=595] and P03659 [n=357]) and two Phase 3 trials (P05216 [n=1097] and P05101 [n=403]. DNA samples were collected on a voluntary basis in the two Phase 3 trials, P05216 and P05101, for the purposes of biomarker identification. A retrospective analysis was carried out to determine the distribution of *IL28B* genotypes (rs12979860, rs12980275, and rs8103142) and their relationship to SVR at 24 weeks (primary efficacy endpoint) in subjects receiving PR or boceprevir-containing regimens, including those receiving boceprevir following poor PR response. *IL28B* testing was conducted by (b) (4) Additionally, three *ITPA* polymorphisms were evaluated for their association with anemia in the genetic substudies of P05216 and P05101 as follows: rs1127354 (C>A, missense P32T), rs7270101 (A>C, intronic splicing-altering), and rs6051702 (A>C, tagging SNP). The reports and associated datasets are listed below.

Table 1. Reports and datasets

Reports	**Location**
Exploratory Pharmacogenomic Analysis of IL28B in Phase 3 Studies of Boceprevir (SCH 503034)	\\cdsesub1\EVSPROD\NDA202258\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-hepatitis-c\5353-rep-analys-data-more-one-stud\study-report-pharmacogenomics\study-report-pharmacogenomics.pdf
Exploratory Pharmacogenomic Analysis of ITPA in Phase 3 Studies of Boceprevir (SCH 503034)	\\cdsesub1\EVSPROD\NDA202258\0031\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-hepatitis-c\5353-rep-analys-data-more-one-stud\study-report-itpa\study-report-itpa.pdf
Datasets*	**Location**
Il28cres.xpt (P05101+P05216)	\\cdsesub1\EVSPROD\NDA202258\0001\m5\datasets\integrated-summary-efficacy\analysis\datasets\il28cres.xpt
Il28cres.xpt (P05101)	\\cdsesub1\EVSPROD\NDA202258\ 0004\m5\datasets\p05101\analysis\datasets\il28cres.xpt
Il28cres.xpt (P05216)	\\cdsesub1\EVSPROD\NDA202258\ 0004\m5\datasets\p05216\analysis\datasets\il28cres.xpt
merge_IL28 (b) (4) _Boceprevir.xpt (P05101+P05216)	\\cdsesub1\EVSPROD\NDA202258\0001\m5\datasets\phase-3-pk-pd\analysis\datasets\merge-il28 (b) (4) .sas7bdat
Itpacres.xpt (P05216)	\\cdsesub1\EVSPROD\NDA202258\\0031\m5\datasets\p05216\analysis\datasets\itpacres.xpt
Itpacres.xpt (P05101)	\\cdsesub1\EVSPROD\NDA202258\\0031\m5\datasets\p05101\analysis\datasets\itpacres.xpt

* Deidentified data cannot be linked with original trial records; analysis dataset includes key efficacy and safety variables

Trial P05216 evaluated sustained virologic responses (SVR) at 24 weeks following PR or boceprevir/PR in treatment-naïve subjects with chronic hepatitis C genotype 1. Two cohorts (black [mITT n=149], non-black [mITT n=899]) were randomly assigned to one of three arms (shown below) in a 1:1:1 ratio. Within each cohort, randomization was stratified by baseline viral load (≤400,000 IU/mL vs. >400,000 IU/mL) and HCV subtype (1a vs. 1b; where classified). DNA samples were available from 62% of subjects (653/1048).

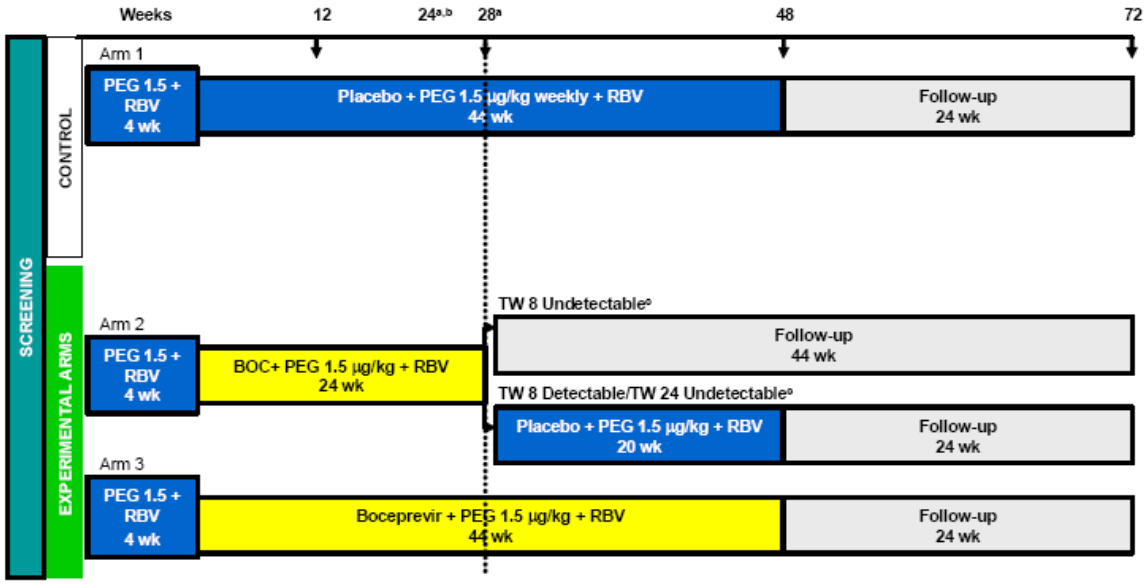


Figure 1. P05216 Study Design

Trial P05101 evaluated SVR at 24 weeks following PR or boceprevir/PR in subjects who failed to achieve SVR on prior treatment with PR. A total of 403 subjects were randomly assigned to one of three arms (shown below) in a 1:2:2 ratio. Randomization was stratified by baseline HCV-RNA level (<400,000 IU/mL vs. >400,000 IU/mL) and HCV subtype (1a vs. 1b; where classified). The mITT population included 394 subjects who received at least one dose of boceprevir or placebo. DNA samples were available from 66% of subjects (259/394).

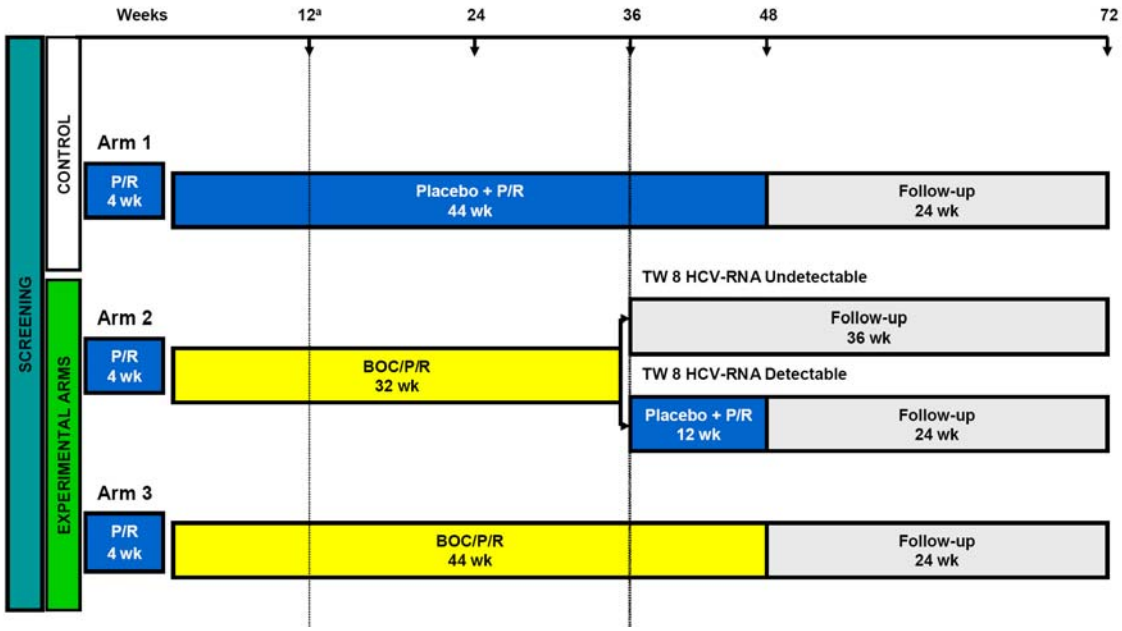


Figure 2. P05101 Study Design

3 Key Questions and Summary of Findings

3.1 Does *IL28B* genotype influence the efficacy of boceprevir/PR?[11]

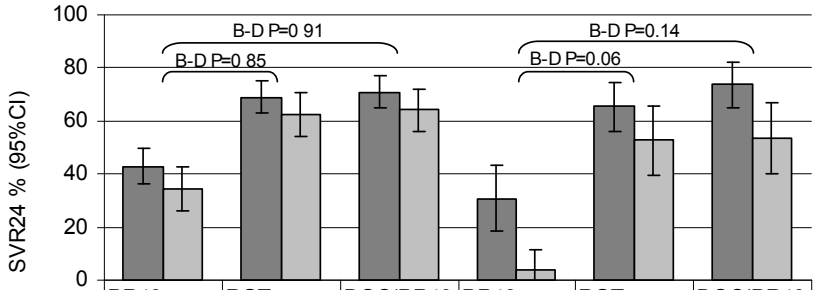
Yes, SVR rates differed significantly by IL28B genotype in subjects receiving PR48; IL28B genotype effects were less apparent in boceprevir-treated subjects. Among C/C subjects, SVR rates in the RGT and boceprevir/PR48 arms did not differ significantly from PR48. However, treatment effects were substantially larger in C/T and T/T subjects. C/C subjects treated with RGT or boceprevir/PR48 had rapid responses, whereas C/C subjects treated with PR48 responded slowly. IL28B genotype was less predictive in previously-treated subjects, but consistent with those observed in treatment-naïve subjects. For PR48, IL28B genotype has predictive performance characteristics that are similar to TW4 responses and has the advantage that subjects need not be exposed to PR to ascertain responsiveness. Despite prognostic imbalances in the substudy, treatment effects in the PG substudy of both trials were similar to the overall trial populations, limiting concerns about bias because of incomplete sampling.

3.1.1 PG substudy bias, confounding, and modeling strategy

Sampling rates were balanced across the treatment arms within each trial. The sponsor reports that several characteristics known to be associated with SVR rates differed between the non-PG mITT relative to PG mITT as follows: the non-PG mITT had more advanced fibrosis in the boceprevir/PR48 arm of P05216; a greater proportion of blacks in all arms of P05101; and a smaller percentage of subjects with high body mass index (BMI) in P05101. SVR rates in the PG substudy populations tended to be higher than the overall and non-PG substudy populations.

As shown in the figure below, the relative treatment effects tended to be similar the PG substudy and non-PG substudy for P05216, but not for P05101. The difference in P05101 appears to be driven by differences in SVR rates for the PR arm, which were 31% in the substudy population and 4% in the non-substudy population (see figure below); 16 of the 17 (94%) sustained responders from the control arm of P05101 participated in the PG substudy compared with only one subject out of 26 in the non-PG group. Subjects consenting to DNA analysis may therefore differ from those not consenting because of preference, attrition, or local regulatory practices. Substudy consent dates and participating sites were not specified in this submission.

[11] Results presented throughout are based on reviewer's analysis unless stated otherwise; the sponsor's analyses were confirmed



	P05216 PR48	P05216 RGT	P05216 BOC/PR48	P05101 PR48	P05101 RGT	P05101 BOC/PR48
PGx-mITT (P05216 N=653; P05101 N=259)	42.9	68.9	71	30.8	65.3	73.6
non-PGx-mITT (P05216 N=395; P05101 N=135)	34.6	62.5	64.3	3.8	52.7	53.7

P-values are for Breslow-Day test for heterogeneity of odds ratios (treatment effect on SVR24) between PG mITT and non-PG mITT.

Figure 3. Heterogeneity of treatment effects in based on substudy participation
Source: Reviewer

Despite prognostic differences between subjects consenting and not consenting to DNA analysis, treatment effects in the PG substudy of both trials were similar to the overall trial populations, as shown in the table below. A slight trend toward smaller treatment effects was observed in P01501. Thus, the treatment effects are not significantly biased because of incomplete sampling.

Table 1. SVR rates for PG substudies vs. overall trial populations

Study	Population	Relative SVR Rate (95% confidence interval)	
		RGT vs. PR48	BOC/PR48 vs. PR48
P05216	PG mITT	1.61 (1.35-1.92)	1.66 (1.39-4.87)
	Overall mITT	1.67 (1.44-1.94)	1.71 (1.48-1.99)
P05101	PG mITT	2.12 (1.38-3.27)	2.39 (1.57-3.65)
	Overall mITT	2.79 (1.80-4.33)	3.06 (1.99-4.73)

Source: Reviewer

3.1.2 Distribution of *IL28B* genotypes

The prevalence of the rs12979860 genotypes in the pooled PG substudy population was as follows: C/C 28.4%, C/T 53.8%, and T/T 17.8%. Genotype frequencies differed significantly by race such that the T/T genotype was more common in black subjects than in non-black subjects. The C/C genotype was less frequent in P05101 consistent with the higher probability of previous treatment failure in this subgroup. None of the SNPs were in Hardy-Weinberg equilibrium in whites (P05101 χ^2 18-23, P05216 χ^2 2.9-4.7), but the frequencies are consistent with those reported in the literature and HapMap.

Table 2. IL28B genotype frequencies by race and trial

Trial	Race	N	rs12979860 (%)			rs12980275* (%)			rs8103142* (%)		
			C/C	C/T	T/T	A/A	A/G	G/G	C/C	C/T	T/T
P05216	**All**	653	30.0	51.2	18.8	31.7	51.5	16.8	19.5	51.7	28.8
	White	540	31.8	52.8	15.4	32.7	52.0	15.2	15.6	53.3	31.1
	Black	94	17.0	42.6	40.4	23.7	50.5	25.8	44.1	43.0	12.9
	Other	16	50.0	43.7	6.3	50.0	37.5	12.5	6.3	43.7	50.0
P05101	**All**	259	24.3	60.6	15.1	25.5	59.8	14.7	15.4	61.8	22.8
	White	232	23.3	64.2	12.5	24.6	62.9	12.5	12.5	65.1	22.4
	Black	22	27.3	31.8	40.9	27.3	36.4	36.4	45.5	36.4	18.2
	Other	5	60.0	20.0	20.0	60.0	20.0	20.0	20.0	20.0	60.0

* rs12979860 missing 3, rs8103142 missing 1

Source: Reviewer

Linkage disequilibrium (LD) between the three tested SNPs was estimated using Haploview. As shown in the below figure, the SNPs were in almost complete LD in whites but not blacks. As such, efficacy and safety results are presented only for rs12979860 since the two other *IL28B* polymorphisms, rs12980275 and rs8103142, will produce similar results. Because of the lower degree of LD between the SNPs in blacks, results are presented for each SNP in blacks in section 3.1.7.2.

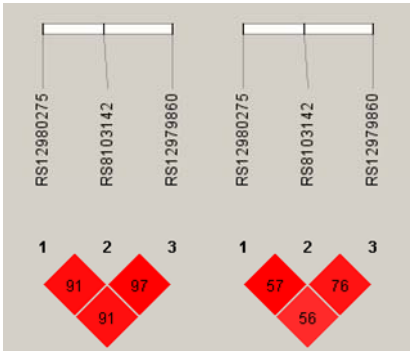


Figure 4. Linkage disequilibrium between IL28B polymorphisms by race

Source: Reviewer

3.1.3 *IL28B* genotype, demographics and baseline characteristics

In both Phase 3 trials, baseline viral load was lower in C/T and T/T subjects. In P05216, HCV subtype 1a was more common in subjects with the *IL28B* C/C and T/T genotypes than was HCV subtype 1b. In P05101, fewer T/T subjects were

sampled from North America and steatosis was higher in T/T subjects. Several prognostic imbalances were noted between the treatment arms within the genotype groups as shown in the table below for key clinical covariates.

Table 3. Baseline clinical and demographic characteristics by IL28B genotype, treatment, and study

Characteristic	C/C				C/T				T/T			
	PG mITT	PR48	RGT	BOC/ PR48	PG mITT	PR48	RGT	BOC/ PR48	PG mITT	PR48	RGT	BOC/ PR48
P05216 N	**196**	**64**	**77**	**55**	**334**	**116**	**103**	**115**	**123**	**37**	**42**	**44**
Race, %												
White	88	88	87	89	86	85	89	83	68	76	67	63
Black	8	8	10	6	12	13	8	15	31	24	31	37
Other	4	5	3	5	2	2	3	2	1	0	2	0
Region, %												
N. America	76	61	82	84	72	75	72	70	75	68	79	77
Europe	20	33	13	15	24	22	24	27	20	27	19	14
Latin America	5	6	5	2	4	3	4	3	6	5	2	9
HCV-RNA, %												
<=400,000	9	8	12	7	7	11	6	4	7	5	10	5
>400,000	91	92	88	93	93	89	94	96	93	95	90	95
>800,000	87	86	86	89	82	72	85	88	86	95	76	88
HCV Subtype*, %												
1a	70	70	64	78	60	64	61	57	72	68	69	80
1b	29	28	34	22	39	35	39	43	28	32	31	20
Other	1	2	2	0	1	1	0	0	0	0	0	0
P05101 N		**13**	**28**	**22**		**29**	**62**	**66**		**10**	**11**	**18**
Race, %												
White	86	77	89	86	95	93	97	94	74	100	64	67
Black	9	15	11	5	5	7	3	5	23	0	36	28
Other	5	8	0	9	1	0	0	2	3	0	0	6
Region, %												
N. America	83	85	79	86	61	55	65	61	59	30	64	72
Europe	17	15	21	14	39	45	35	39	41	70	36	28
HCV-RNA, %												
<=400,000	2	92	100	100	4	97	92	98	13	80	91	89
>400,000	98	8	0	0	96	3	8	2	87	20	9	11
>800,000	98	92	100	100	84	76	84	88	74	70	91	67
HCV Subtype*, %												
1a	67	77	54	77	55	59	58	50	49	40	36	61
1b	33	23	46	23	45	41	42	48	51	60	64	39
Other	0	0	0	0	<1	0	0	2	0	0	0	0
Failure, %												
Nonresponse	35	46	71	64	50	62	48	56	44	30	55	50
Relapse	65	54	29	36	50	38	52	44	56	70	45	50

(b) (4) result used where available, otherwise (b) (4) result used

Source: Reviewer

3.1.4 Modeling strategy to address bias and confounding

Considering the observed prognostic imbalances between treatment arms and genotypes, multivariable analysis was performed to adjust for potentially confounding factors. The reviewer used three different modeling strategies as follows:

- Model 1: Treatment, race (black, white, other) and stratification variables (baseline HCV-RNA and HCV genotype) entered as forced covariates.

- Model 2: Treatment, race and stratification variables entered as forced covariates; additional forced covariates that were predictive of SVR in the at least one of the treatment arms in the PG mITT (at P<0.1), based on univariate logistic regression, were as follows: age, race, BMI, prior response (for P05101), cirrhosis, fibrosis (0/1/2 vs. 3/4), platelet count, and ALT.

- Model 3: Treatment, race and stratification variables entered as forced covariates; additional variables were included in the model based on the stepwise method with entry at P<0.2 and retention at P<0.1: sex, age, BMI, weight, steatosis, region, cirrhosis, fibrosis, HCV-RNA (continuous), platelets, and ALT (note 43 subjects were removed from this analysis due to missing data for one or more of these factors).

All analyses were stratified by protocol, genotype and/or treatment arm. Results for model 1 are presented throughout; consistency of estimates across the models was evaluated.

3.1.5 Primary efficacy outcomes – SVR at 24 weeks by *IL28B* genotype

The applicant presented retrospective analyses of association of the *IL28B* genotypes to SVR, which generally compared C/T and T/T subjects to C/C subjects within the treatment arms in the pooled trials. In treatment-naïve subjects (P05216), the PR arm had a much higher SVR in the C/C genotype group (78%) compared to those with C/T (28%) or T/T (27%) genotype subjects (P<0.0001), confirming earlier published data from the IDEAL trial.[12] In the boceprevir-containing arms, the SVR rates in the C/T and T/T genotype subjects were also lower, but the difference among genotype groups was smaller than the difference observed in the PR arm. In treatment-experienced subjects (P05101), T/T subjects had the highest SVR rate in the PR arm, although this subgroup consisted of 10 subjects, decreasing the reliability of the estimates. SVR rates in the boceprevir-containing arms tended to be lower among C/T and T/T subjects as compared to C/C subjects. The lack of significant genotype effects within the P05101 treatment arms may be related to the smaller sample size and enrichment for prior PR-nonresponders.

[12] Ge D, et al. Nature 2009;461:399-401.

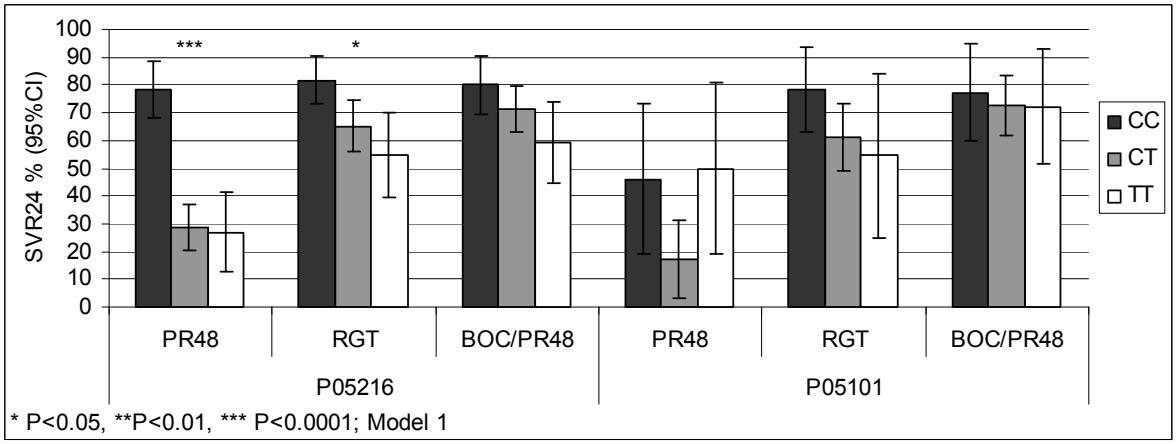


Figure 5. SVR rates by IL28B genotype, treatment arm, and trial
Source: Reviewer

An additional analysis was carried out using pooled data from P05101 and P05216. Consistent with the individual study results, SVR rates in subjects with the C/C genotype was 2.3-2.8-fold higher than that seen in subjects with C/T or T/T genotype in the PR arm. SVR rates across treatment arms were similar in subjects with the C/C genotype (73% in the PR48 arm, 81% in the RGT arm, and 79% in the BOC/PR arm). In contrast, among T allele carriers the SVR rates were higher 2.4- and 2.7-fold higher in the RGT and boceprevir/PR arms, respectively.

To examine whether treatment effects were heterogeneous across the genotype groups, crude unadjusted odds ratios were calculated for each boceprevir-containing arm relative to PR in the *IL28B* genotype strata (not shown). Breslow-Day testing for homogeneity of treatment effects revealed significant differences in treatment effects across *IL28B* genotype groups for RGT vs. PR48 (P=0.0348) and BOC/PR48 vs. PR48 (P=0.0047). Significant heterogeneity was not observed in P05101.

Multivariate logistic regression was used to model relative treatment effects while adjusting for potentially confounding factors and to test genotype × treatment interactions. In P05216, the boceprevir-containing arms were not significantly different than PR alone in the C/C subgroup, whereas boceprevir produced significantly higher SVR rates in subjects with the C/T and T/T genotypes. Treatment effects were statistically heterogeneous across the genotype groups (genotype × treatment P-interaction=0.01). In P05101, the boceprevir-containing arms tended to have higher SVR rates compared to PR alone, regardless of genotype (genotype × treatment P-interaction=0.39). While this may be expected because this trial is enriched for nonresponders, relative treatment effects by genotype in P05101 should be viewed with caution owing to the small number of subjects.

Table 4. Treatment comparisons by IL28B genotype x treatment interactions

	N	SVR, n/N (%)			Odds Ratio (95% Confidence Interval)*		P†	P-int†
		PR48	*RGT-BOC*	*BOC/PR48*	*RGT-BOC vs PR48*	*BOC/PR48 vs PR48*		
P05216								
C/C	196	50/64 (78)	63/77 (82)	44/55 (80)	1.14 (0.48-2.70)	1.21 (0.48-3.04)	0.9137	
C/T	334	33/116 (28)	67/103 (65)	82/115 (71)	6.24 (3.34-11.6)	8.26 (4.44-15.4)	<0.0001	0.0052
T/T	123	10/37 (27)	23/42 (55)	26/44 (59)	3.81 (1.39-10.4)	4.91 (1.79-13.5)	0.0055	
P05101								
C/C	63	6/13 (46)	22/28 (79)	17/22 (77)	4.04 (0.86-18.9)	4.35 (0.91-20.9)	0.1260	
C/T	157	5/29 (17)	38/62 (61)	48/66 (73)	8.18 (2.50-26.8)	15.7 (4.75-52.1)	<0.0001	0.5965
T/T	39	5/10 (50)	6/11 (55)	13/18 (72)	1.29 (0.19-8.63)	3.74 (0.62-22.5)	0.2799	

* Model 1 covariate selection strategy, models 2 and 3 produced similar results; note quasi-complete separation of data points for all models, unadjusted model for drug effect produced similar results without convergence warning
† P-value based on global test

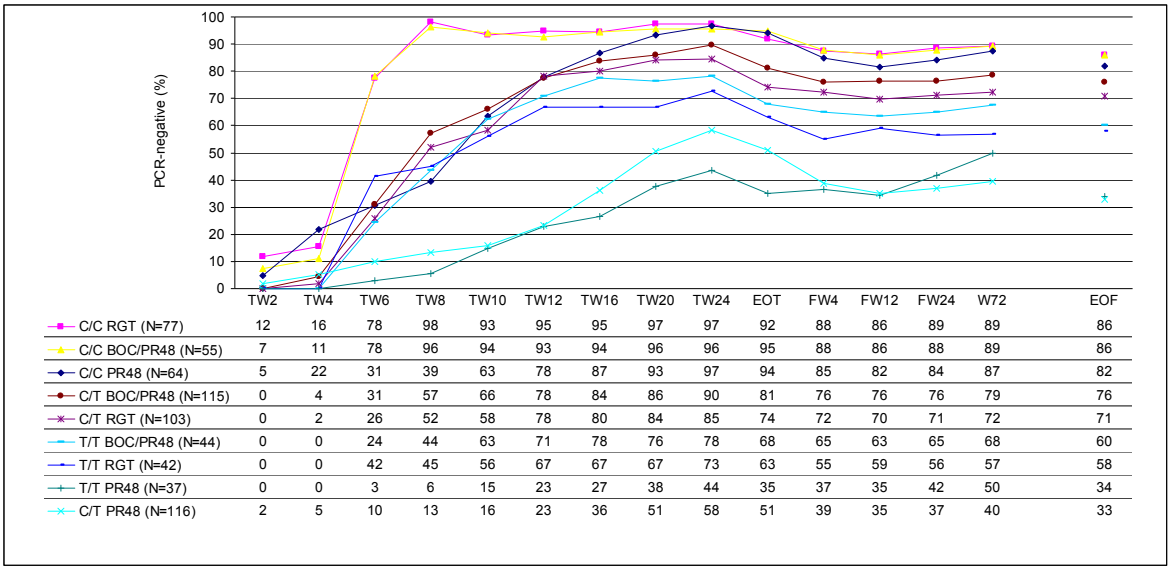
Source: Reviewer

3.1.6 Selected secondary efficacy outcome and supportive analyses

3.1.6.1 Early virologic response (EVR; TW2, TW4, TW6, TW8, TW12), FW12, W72[13]

Response rates (PCR-negative) at each time point in P05216 are shown in the figure below. T/T and C/T subjects treated with PR48 had the lowest response rates throughout the trial. In contrast, C/C subjects receiving PR48 had high sustained response rates reaching maximum values at TW24. C/C patients treated with RGT or boceprevir/PR48 had a rapid response, the majority of which had occurred by TW8. At week 72, C/C subjects on any therapy had the highest response rates, followed by C/T and T/T subjects receiving boceprevir-containing regimens, followed by C/T and T/T subjects receiving PR48.

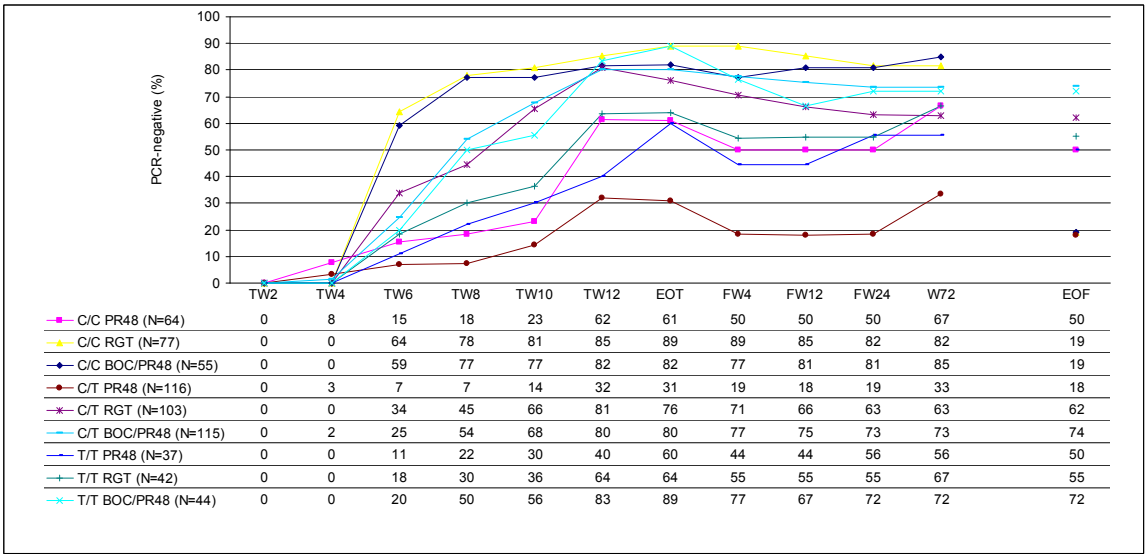
[13] Futility rules were applied at TW12 in P05101 and TW24 in P05216 if subjects remained detectable



	TW2	TW4	TW6	TW8	TW10	TW12	TW16	TW20	TW24	EOT	FW4	FW12	FW24	W72	EOF
C/C RGT (N=77)	12	16	78	98	93	95	95	97	97	92	88	86	89	89	86
C/C BOC/PR48 (N=55)	7	11	78	96	94	93	94	96	96	95	88	86	88	89	86
C/C PR48 (N=64)	5	22	31	39	63	78	87	93	97	94	85	82	84	87	82
C/T BOC/PR48 (N=115)	0	4	31	57	66	78	84	86	90	81	76	76	76	79	76
C/T RGT (N=103)	0	2	26	52	58	78	80	84	85	74	72	70	71	72	71
T/T BOC/PR48 (N=44)	0	0	24	44	63	71	78	76	78	68	65	63	65	68	60
T/T RGT (N=42)	0	0	42	45	56	67	67	67	73	63	55	59	56	57	58
T/T PR48 (N=37)	0	0	3	6	15	23	27	38	44	35	37	35	42	50	34
C/T PR48 (N=116)	2	5	10	13	16	23	36	51	58	51	39	35	37	40	33

Figure 6. Virologic response (PCR-negative) over time by genotype and treatment in P05216. (subjects with data at each point, time point omitted if missing >25%; TW20, TW24, FW12, FW 12, FW24, FW72 missing >10%). Source: Reviewer

Response rates (PCR-negative) at each time point in P05216 are shown in the figure below. Subjects of all genotypes receiving boceprevir had the highest response rates throughout. Individuals with the C/C genotype demonstrated an early sustained response, as in P05216.



	TW2	TW4	TW6	TW8	TW10	TW12	EOT	FW4	FW12	FW24	W72	EOF
C/C PR48 (N=64)	0	8	15	18	23	62	61	50	50	50	67	50
C/C RGT (N=77)	0	0	64	78	81	85	89	89	85	82	82	19
C/C BOC/PR48 (N=55)	0	0	59	77	77	82	82	77	81	81	85	19
C/T PR48 (N=116)	0	3	7	7	14	32	31	19	18	19	33	18
C/T RGT (N=103)	0	0	34	45	66	81	76	71	66	63	63	62
C/T BOC/PR48 (N=115)	0	2	25	54	68	80	80	77	75	73	73	74
T/T PR48 (N=37)	0	0	11	22	30	40	60	44	44	56	56	50
T/T RGT (N=42)	0	0	18	30	36	64	64	55	55	55	67	55
T/T BOC/PR48 (N=44)	0	0	20	50	56	83	89	77	67	72	72	72

Figure 7. Virologic response (PCR-negative) over time by genotype and treatment in P05101. (subjects with data available at each point, timepoint omitted if missing >25%; FW72 missing >10%)
Source: Reviewer

3.1.6.2 PR response at TW4

PR responses during at the run-in period were analyzed for both trials pooling the treatment arms. The PG substudy dataset consists of the mITT population who

received at least one dose of boceprevir and does not include subjects that discontinued treatment prior to week 4, thus biasing selection of PR-tolerant individuals and PR-responders. As shown in the table below, mean changes in HCV-RNA and response rates ($\geq$1-$\log_{10}$ decrease or $\geq$2-$\log_{10}$ decrease) were lower among subjects with carrying the T allele. In P05101, only three subjects (1 C/C, 2 C/T) were PCR-negative at 4 weeks, whereas in P05216, PCR-negative rates at 4 weeks were significantly higher in C/C subjects as compared to C/T and T/T subjects.

Table 5. Changes in viral load during 4-week PR lead-in period by IL28B genotype and trial*

				TW4 Response Rates		
Trial	**Genotype**	**N**	**HCV-RNA $\log_{10}$ change, Mean (SD)**	**$\geq$1-$\log_{10}$ decrease n (%)**	**$\geq$2-$\log_{10}$ decrease n (%)**	**PCR-negative‡ n (%)**
P05216	**C/C**	196	-3.75 (1.16)	191 (97)	178 (91)	32 (16)
	C/T	334	-1.85 (1.26)	244 (73)	129 (39)	13 (4.0)
	T/T	123	-1.37 (1.12)	68 (55)	33 (27)	0 (0)
	P†		<0.0001	4.9×10^{-22}	5.5×10^{-43}	3.2×10^{-9}
P05101	**C/C**	63	-3.53 (1.28)	59 (95)	55 (87)	1 (1.6)
	C/T	157	-1.82 (0.99)	124 (79)	60 (38)	2 (1.3)
	T/T	39	-1.56 (0.99)	24 (62)	12 (31)	0 (0)
	P†		<0.0001	3.2×10^{-4}	2.2×10^{-12}	…

* The PG substudy dataset consists of the mITT population, which does not include subjects that discontinued treatment prior to week 4, thus biasing selection of PR-tolerant or PR-responsive subjects (which would bias results toward null)
† P-values based on analysis of variance or χ^2 test
‡ missing 11 values

Source: Reviewer

3.1.7 Sensitivity analyses for primary efficacy endpoint

3.1.7.1 Subgroup analyses

The sponsor conducted separate and combined analyses of P05101 and P05216 to evaluate at *IL28B* genotype effects in various subgroups. Despite wide confidence intervals in some small subgroups, the results suggested that point estimates for *IL28B* genotype as a predictor of SVR were generally consistent across subgroups defined by trial, race, sex, age, baseline HCV-RNA, HCV genotype, BMI, weight, ALT, fibrosis, and steatosis, with no obvious effect modifiers noted in either trial. Results for P05216 are shown below.

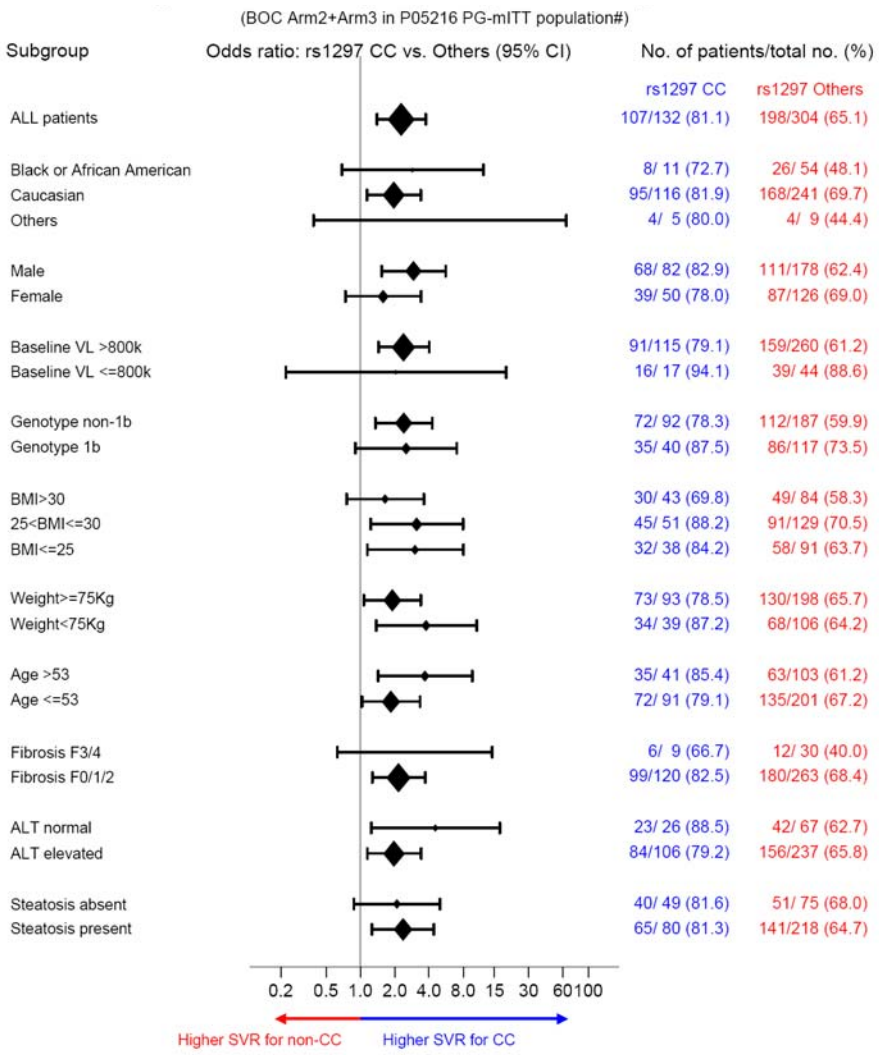


Figure 8. Subgroup analysis of IL28B genotype relationship with SVR in boceprevir-treated subjects in trial P05216

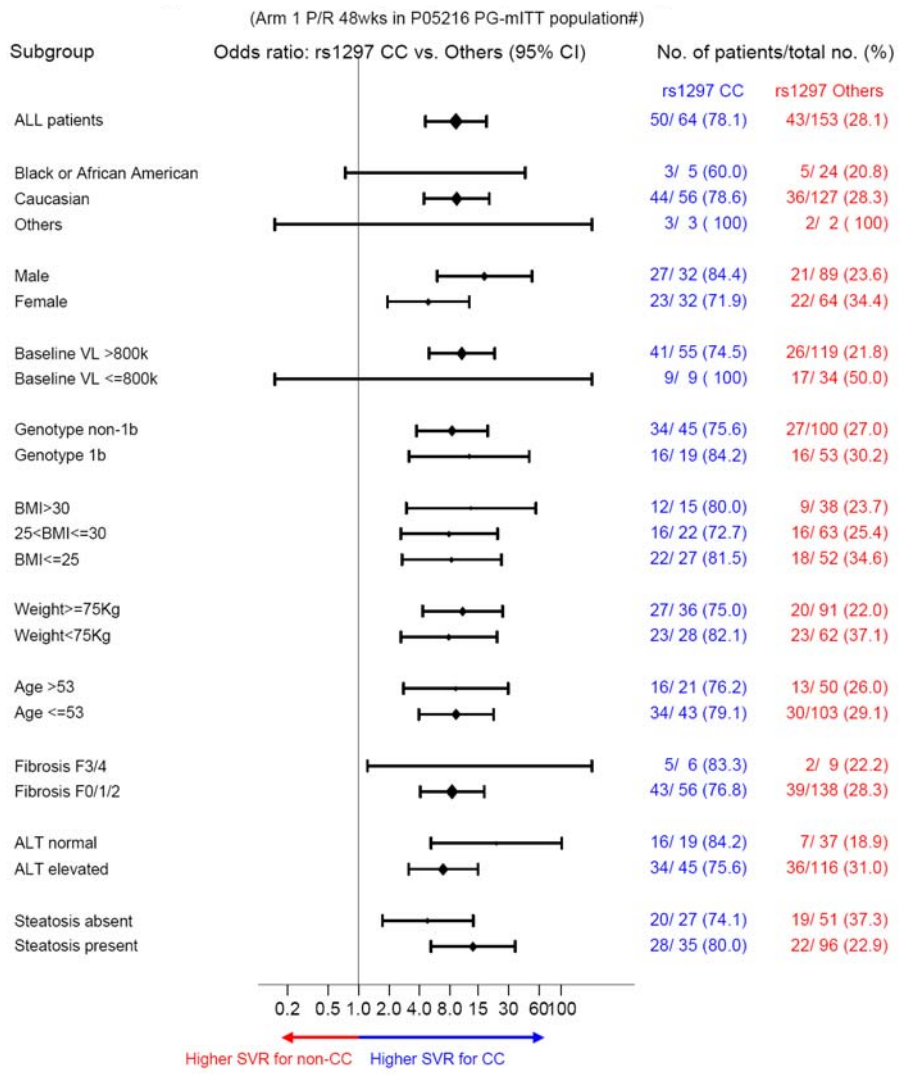


Figure 9. Subgroup analysis of IL28B genotype relationship with SVR in PR-treated subjects in trial P05216

3.1.7.2 Race and comparative performance of rs12979860, rs12980275, and rs8103142 in black subjects

The majority of the participants in the two Phase 3 trials were non-black (86-88%) and thus, pooled data were analyzed. Black subjects with C/C genotype had higher SVR rates as compared to the C/T or T/T genotype. Blacks treated with boceprevir/PR had higher SVR rates compared to blacks in the PR arm with the matching genotype. Similar to observations in the overall population, boceprevir/PR treatment appeared to increase response rates considerably in the C/T and T/T genotype subjects and to have minimum impact on the C/C genotype subjects in black and non-black subjects. Again, the numbers of black subjects in *IL28B* genotype subgroups are small, limiting definitive conclusions about differences in *IL28B* genotype effects on SVR in blacks vs. non-blacks.

Table 6. SVR rates by race, IL28B genotype, treatment, and trial

Protocol Nos. P05216 and P05101

	% (Number) of Subjects								
	CC			CT			TT		
	All	Blacks	Non-blacks	All	Blacks	Non-blacks	All	Blacks	Non-blacks
Pooled P05101 + P05216									
Arm 1: PR 48	72.73 (56/77)	57.14 (4/7)	74.29 (52/70)	26.21 (38/145)	29.41 (5/17)	25.78 (33/128)	31.91 (15/47)	0/9 (0)	39.47 (15/38)
Arm 2: RGT	80.95 (85/105)	63.64 (7/11)	82.98 (78/94)	63.64 (105/165)	50.00 (5/10)	64.52 (100/155)	54.72 (29/53)	47.06 (8/17)	58.33 (21/36)
Arm 3: BOC/PR 48	79.22 (61/77)	75.00 (3/4)	79.45 (58/73)	71.82 (130/181)	50.00 (10/20)	74.53 (120/161)	62.90 (39/62)	57.14 (12/21)	65.85 (27/41)
P05101									
Arm 1: PR 48	46.15 (6/13)	50.00 (1/2)	45.45 (5/11)	17.24 (5/29)	0 (0/2)	18.52 (5/27)	50.00 (5/10)	0 (0/0)	50.00 (5/10)
Arm 2: RGT	78.57 (22/28)	66.67 (2/3)	80.00 (20/25)	61.29 (38/62)	100.00 (2/2)	60.00 (36/60)	54.55 (6/11)	50.00 (2/4)	57.14 (4/7)
Arm 3: BOC/PR 48	77.27 (17/22)	0 (0/1)	80.95 (17/21)	72.73 (48/66)	33.33 (1/3)	74.60 (47/63)	72.22 (13/18)	80.00 (4/5)	69.23 (9/13)
P05216									
Arm 1: PR 48	78.13 (50/64)	60.00 (3/5)	79.66 (47/59)	28.45 (33/116)	33.33 (5/15)	27.72 (28/101)	27.03 (10/37)	0 (0/9)	35.71 (10/28)
Arm 2: RGT	81.82 (63/77)	62.50 (5/8)	84.06 (58/69)	65.05 (67/103)	37.50 (3/8)	67.37 (64/95)	54.76 (23/42)	46.15 (6/13)	58.62 (17/29)
Arm 3: BOC/PR 48	80.00 (44/55)	100.00 (3/3)	78.85 (41/52)	71.30 (82/115)	52.94 (9/17)	74.49 (73/98)	59.09 (26/44)	50.00 (8/16)	64.29 (18/28)

BOC=boceprevir 800 mg TID; PR=pegylated interferon 1.5 µg/kg once weekly + ribavirin 600 to 1400 mg/day; RGT=response-guided therapy; SVR=sustained virologic response.

[a] IL28B genotype is based on rs12979860.

Source Data: Table 3, Table 3.1, and Table 3.2 in Section 12.2.1.10, Section 12.2.2.10, Section 12.2.3.10.

Source: Sponsor's report

Consistent with the LD estimates provided in section 3.1.2, SVR rates within the studies' treatment arms were similar across the three SNPs (average absolute difference in SVR between the SNPs being 0.8%). Additional analyses of the other SNPs were not performed in whites due to high LD. Since r^2 values tended to be lower in blacks, each SNP was analyzed independently to determine which best predicts response. rs12979860 provided the best fitting model in terms of differentiating HCV-RNA changes at 4 weeks (using general linear model), reflecting PR response, and SVR for PR and the boceprevir-containing regimens (table below).

Table 7. Changes in viral load after 4-week PR lead-in period and SVR by IL28B genotype and treatment in black subjects (trial P05216)

		HCV-RNA $\log_{10}$ decrease at 4 weeks, mean (SD)	SVR, n/N (%)		
		All arms	*PR48*	*RGT-BOC*	*BOC/PR48*
rs12979860	C/C	-3.16 (1.25)	3/5 (60)	5/8 (62)	3/3 (100)
	C/T	-1.46 (1.22)	5/15 (33)	3/8 (38)	9/17 (53)
	T/T	-1.19 (1.12)	0/9 (0)	6/13 (46)	8/16 (50)
rs12980275	A/A	-2.47 (1.65)	4/8 (50)	4/7 (57)	5/7 (71)
	A/G	-1.53 (1.21)	4/15 (27)	7/14 (50)	10/18 (56)
	G/G	-1.16 (1.06)	0/6 (0)	3/7 (43)	5/11 (46)
rs8103142	C/C	-1.18 (1.14)	2/12 (17)	6/14 (43)	7/15 (47)

	C/T	-1.81 (1.43)	6/14 (43)	4/8 (50)	10/18 (56)
	T/T	-2.78 (1.20)	0/3 (0)	4/6 (67)	3/3 (100)

Source: Reviewer

3.1.7.3 Prior treatment failure – relapsers and nonresponders

In study P05101, subjects that had failed previous treatment – both prior non-responders and relapser – had higher SVR rates in boceprevir/PR than the PR arm. Because of the small numbers in the PR arm, it is difficult to analyze the SVR based on genotype. Response rates by *IL28B* genotype in previous non-responders and relapsers to PR therapy are shown below. Adding boceprevir to PR appears to have a beneficial effect in both nonresponder and relapser subjects of all *IL28B* genotypes.

Table 8. SVR rates by IL28B genotype and previous response in trial P05101

Protocol No. P05101

	% (Number) of Subjects		
	CC	**CT**	**TT**
Nonresponders			
Arm 1: PR 48	33.33 (1/3)	0 (0/14)	33.33 (1/3)
Arms 2 + 3: BOC/PR	60.00 (9/15)	55.32 (26/47)	45.45 (5/11)
Relapsers			
Arm 1: PR 48	50.00 (5/10)	33.33 (5/15)	57.14 (4/7)
Arms 2 + 3: BOC/PR	85.71 (30/35)	74.07 (60/81)	77.78 (14/18)

BOC=boceprevir 800 mg TID; PR=pegylated interferon 1.5 µg/kg once weekly + ribavirin 600 to 1400 mg/day; RGT=response-guided therapy; SVR=sustained virologic response.

[a] IL28B genotype is based on rs12979860.

Source Data: Table 2.1.1 and Table 2.1.2 in **Section 12.2.1.10**.

Source: Sponsor's report

3.1.8 Predictive utility of *IL28B* and early PR48 responses for selected endpoints

The number needed to treat (NNT) to achieve one SVR for the bocepravir-containing regimens as compared to PR48 are shown in the following table for each genotype group. Among treatment-naive C/C subjects, the number NNT with boceprevir is 9 to 18 times higher than C/T and T/T subjects. However, treatment-experienced patients tend to benefit from boceprevir-containing regimens without regard to genotype.

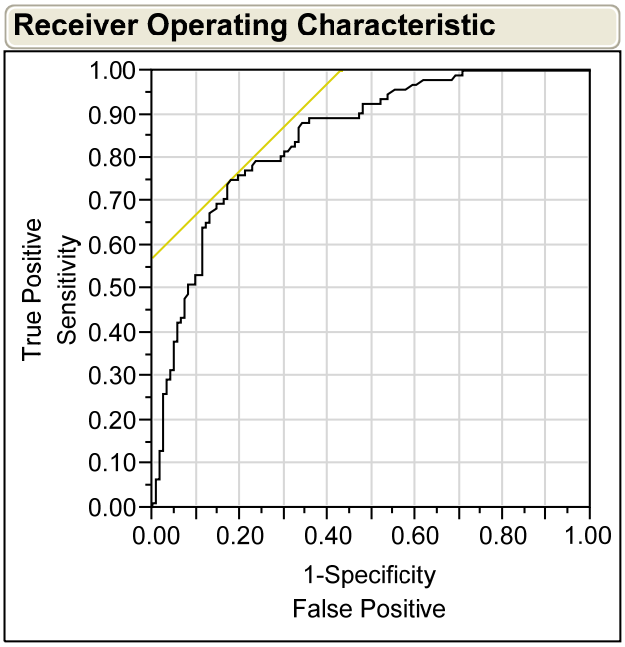
Table 9. Number needed to treat to achieve one SVR by IL28B genotype

Trial	rs12979860 Genotype	NNT	
		RGT vs. PR48	BOC/PR48 vs. PR48
P05216	C/C	27	53
	C/T	3	3
	T/T	4	4
P05101	C/C	4	4
	C/T	3	2
	T/T	22	5

Source: Reviewer

Predictive markers may have utility in clinical decision-making for treatment-naive subjects. To identify non-genetic response predictors, stepwise logistic regression was performed for SVR for each treatment arm in P05216, as described in section 3.1.4. Significant predictors of SVR in PR-treated subjects were *IL28B* genotype and baseline viral load, while predictors of SVR in boceprevir-treated patients were *IL28B* genotype, baseline viral load, race, and cirrhosis. Post-randomization response metrics were also allowed in a separate analysis. TW4 response (undetectable) was predictive of SVR for PR but not boceprevir. TW8 response (undetectable), reflecting addition of boceprevir, was predictive of boceprevir response and resulted in loss of *IL28B* genotype from the model for boceprevir. When the change in HCV RNA at 4 weeks (continuous) was allowed into the model, *IL28B* genotype was no longer predictive of response to either PR or boceprevir; *IL28B* genotype also dropped out of the model with inclusion of the 8-week change in HCV RNA. HCV genotype, baseline ALT, and BMI inconsistently entered into the various models.

Since TW4 response was a strong predictor of SVR, the optimal threshold for 4-week changes in HCV RNA was determined using ROC curve analysis of SVR for subjects in the PR48 arm, in an effort to identify individuals most likely to benefit from PR48 alone. The optimal cutpoint based on the ROC curve is approximately -2.55 (true positive n=69, true negative n=101, false positive n=22, false negative n=23); the PPV at this threshold is 75%. Cutpoints larger than -2.55 (i.e., greater changes in HCV RNA) minimize false positives (i.e., those categorized as being PR48 responder who do not have and SVR; maximizing PPV), in whom boceprevir might be inappropriately withheld. The maximum PPV based on HCV RNA changes was 85-90%, which generally required a conservative threshold of -4 (amounting to approximately the 20th percentile).



Using SVR24locf='1' to be the positive level

Area Under Curve = 0.84791

Figure 10. Receiver operating characteristic curves for change in viral load during 4-week PR lead-in period in P05216

Source: Reviewer

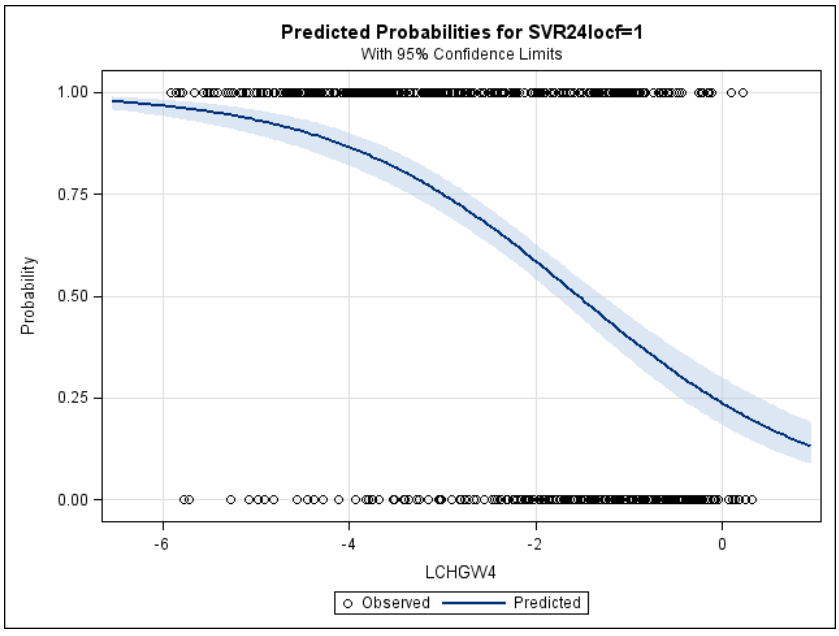


Figure 11. Predicted probability of response based on change in viral load during 4-week PR lead-in period in P05216

Source: Reviewer

Among treatment-naïve C/C subjects, PR48 produced SVR rates that were similar to the boceprevir-containing regimens. Consequently, the utility of *IL28B* genotype in treatment-decision making as compared to early drug response measures (e.g., TW4 PCR negativity) were assessed. The clinical performance characteristics of the key response predictors are summarized in the following table. PPV in the PR arm reflects the likelihood of SVR if PR is continued, which is probably the most useful parameter in determining whether to add boceprevir. The PPV for *IL28B* genotype was approximately 78%. As noted above, a 2.5-log_{10} decrease in HCV RNA at TW4 optimally differentiates responders from nonresponders; the PPV for this threshold is 75%. Increasing the TW4 response threshold improves specificity and PPV at the cost of lower sensitivity and NPV. Considering all parameters, *IL28B* genotype performs about as well as the TW4 2.5-log_{10} change in HCV RNA (except sensitivity). *IL28B* genotype and TW4 responses are less sensitive and have lower NPV for predicting boceprevir responses, although the sensitivity and PPV remain high. Taken together, C/C genotype and early responses to PR predict response positive outcomes for both PR48 and boceprevir. *IL28B* genotype appears to perform as well as early PR responses in terms of predicting SVR.

Table 10. Clinical performance characteristics of IL28B genotype and early response profiles for SVR in trial P05216

P05216	PR48				BOC (RGT+BOC/PR48)			
	Sens (TP/ TP+FN)	**Spec** (TN/ TN+FP)	**PPV** (TP/ TP+FP)	**NPV** (TN/ TN+FN)	**Sens** (TP/ TP+FN)	**Spec** (TN/ TN+FP)	**PPV** (TP/ TP+FP)	**NPV** (TN/ TN+FN)
rs12979860 Pos=CC Neg=CT	**0.60** 50/83	**0.86** 83/97	**0.78** 50/64	**0.72** 83/116	**0.42** 107/256	**0.73** 69/94	**0.81** 107/132	**0.32** 69/218
rs12979860 Pos=CC Neg=TT	**0.83** 50/60	**0.66** 27/41	**0.78** 50/64	**0.73** 27/37	**0.69** 107/156	**0.60** 37/62	**0.81** 107/132	**0.43** 37/86
rs12979860 Pos=CC Neg=CT,TT	**0.54** 50/93	**0.89** 110/124	**0.78** 50/64	**0.72** 110/153	**0.35** 107/305	**0.81** 106/131	**0.81** 107/132	**0.35** 106/304
TW4 1-log_{10} Pos $\geq$1-log_{10} Neg>1-log_{10}	**0.98** 91/93	**0.35** 44/124	**0.53** 91/171	**0.96** 44/46	**0.88** 269/305	**0.52** 68/131	**0.81** 269/332	**0.65** 68/104
TW4 2.5-log_{10} Pos $\geq$2.5-log_{10}* Neg<2.5-log_{10}	**0.75** 70/93	**0.81** 101/124	**0.75** 70/93	**0.81** 101/124	**0.57** 174/305	**0.82** 107/131	**0.88** 174/198	**0.45** 107/238
TW4 4-log_{10} Pos $\geq$4-log_{10} Neg <4-log_{10}	**0.38** 35/93	**0.94** 117/124	**0.83** 35/42	**0.67** 117/175	**0.24** 74/305	**0.92** 121/131	**0.88** 74/84	**0.34** 121/352
PCRW4 Pos=undetectable Neg=undetectable	**0.21** 19/92	**0.99** 122/123	**0.95** 19/20	**0.63** 122/195	**0.07** 22/298	**0.98** 126/129	**0.88** 22/25	**0.31** 126/402

TP=true positive, C/C or TW4 responder with SVR; FP=false positive, C/C or TW4 responder without SVR; FN=false negative, C/T, T/T or TW4 nonresponder with SVR, TN=true negative, C/T, T/T or TW4 nonresponder without SVR
Sensitivity is the proportion of subjects with SVR predicted to be responders; Specificity is the proportion of subjects without SVR predicted to be nonresponders; PPV is the proportion of subjects predicted to be responders with SVR; NPV is the proportion of subjects predicted to be nonresponders without SVR
* Optimal cutpoint based on receiver operating characteristic curve analysis

Source: Reviewer

As expected, TW4 responses and *IL28B* genotype were highly correlated. Of the subjects that were PCR-negative at TW4, 71% were C/C, 29% were C/T, and

none were T/T. Approximately 38% of the subjects with ≥1-log$_{10}$ decline had the C/C genotype; approximately 58% of the subjects with ≥2.5-log$_{10}$ decline had the C/C genotype.

Table 11. Distribution of TW4 response (PR only) in pooled treatment arms of P05216 by IL28B genotype

Genotype	N	TW4 PCR*		TW4 1-log$_{10}$ decline		TW4 2.5-log$_{10}$ decline	
		Negative n *row %* *col %*	Positive n *row %* *col %*	≥1-log$_{10}$ ↓ n *row %* *col %*	<1-log$_{10}$ ↓ n *row %* *col %*	≥2.5-log$_{10}$ ↓ n *row %* *col %*	<2.5-log$_{10}$ ↓ n *row %* *col %*
C/C	195	32 *16.4* *71.1*	163 *83.6* *27.3*	191 *97.5* *38.0*	5 *2.6* *3.3*	170 *86.7* *58.4*	26 *13.3* *7.2*
C/T	328	13 *4.0* *28.9*	315 *96.0* *52.8*	244 *73.1* *48.5*	90 *27.0* *60.0*	97 *29.0* *33.3*	237 *71.0* *65.5*
T/T	119	0 *0* *0*	119 *100* *19.9*	68 *55.3* *13.5*	55 *44.7* *36.7*	24 *19.5* *8.3*	99 *80.5* *27.4*
Total	642	45	597	503	150	291	291
* missing data for 11 subjects							

Source: Reviewer

SVR rates by *IL28B* genotype as a function of TW4 response are shown in the following table. Subjects who were TW4 responders (defined by ≥1-log$_{10}$ decline consistent with the sponsor's proposed labeling), had higher response rates than TW4 nonresponders. Consistent with the findings for the overall trial population, those with the C/T and T/T genotypes had lower SVR rates following PR48, even if early responses were demonstrated. SVR rates were similar across the genotype groups in the boceprevir-containing arms. Almost no C/C subjects had <1-log$_{10}$ decline, limiting analysis in this subgroup. Collectively, subjects who have early responses more commonly have the C/C genotype. Those with early responses at TW4 who also have the C/C genotype tend to respond most favorably to PR48 (not differentiating from boceprevir-containing arms), whereas those with early responses and the C/T or T/T genotypes tend to have lower response rates, benefitting from the addition of boceprevir.

Table 12. SVR rates by TW4 response, IL28B genotype, and treatment in P05216

TW4 Response Subgroup	rs12979860	SVR, n/N (%)		
		PR48	*RGT-BOC*	*BOC/PR48*
PG mITT	**All**	**93/124 (43)**	**153/222 (69)**	**152/214 (71)**
	C/C	50/64 (78)	63/77 (82)	44/55 (80)
	C/T	33/116 (28)	67/103 (65)	82/115 (71)
	T/T	10/37 (27)	23/42 (55)	26/44 (59)
TW4 ≥1-log$_{10}$ decline	**All**	**91/171 (53)**	**138/168 (82)**	**131/164 (80)**
	C/C	50/62 (81)	63/76 (83)	42/53 (79)
	C/T	32/90 (36)	56/69 (81)	69/85 (81)

	T/T	9/19 (47)	19/23 (83)	20/26 (77)
TW4 <1-log$_{10}$ decline	**All**	**2/44 (4.4)**	**15/54 (28)**	**21/50 (42)**
	C/C	0/2 (0)	0/1 (0)	2/2 (100)
	C/T	1/26 (3.8)	11/34 (32)	13/30 (43)
	T/T	1/18 (5.6)	4/19 (21)	6/18 (33)
TW4 ≥2.5-log$_{10}$ decline	**All**	**70/93 (75)**	**96/106 (91)**	**78/92 (85)**
	C/C	47/58 (81)	59/66 (89)	38/46 (83)
	C/T	18/29 (62)	31/33 (94)	29/35 (83)
	T/T	5/6 (83)	6/7 (86)	11/11 (100)
TW4 <2.5-log$_{10}$ decline	**All**	**23/124 (19)**	**57/116 (49)**	**74/122 (61)**
	C/C	3/6 (50)	4/11 (36)	6/9 (67)
	C/T	15/87 (17)	36/70 (51)	53/80 (66)
	T/T	5/31 (16)	17/35 (49)	15/33 (45)
TW4 undetectable	**All**	**19/20 (95)**	**13/14 (93)**	**9/11 (82)**
	C/C	14/14 (100)	11/12 (92)	5/6 (83)
	C/T	5/6 (83)	2/2 (100)	4/5 (80)
	T/T	0/0 (0)	0/0 (0)	0/0 (0)
TW4 detectable	**All**	**73/195 (37)**	**137/205 (67)**	**139/197 (71)**
	C/C	36/50 (72)	52/65 (80)	38/48 (79)
	C/T	28/109 (26)	62/98 (63)	78/108 (72)
	T/T	9/36 (25)	23/42 (55)	23/41 (56)

Source: Reviewer

3.2 Are *IL28B* or *ITPA* genotypes associated with the safety of boceprevir/PR?[14]

Nonspecific TEAEs and hematologic safety data were included in the deidentified PG substudy dataset; data on SAEs and other drug-specific AEs were not available. Nearly all subjects experienced a TEAE in the PG substudy, most of which occurred on day 1. As such, PG analysis of TEAEs was not possible.

Anemia is a known adverse event related to PR, and boceprevir reportedly causes an additional 1 g/dl decrease in Hgb. In the PG substudy, the median time to first Hgb <10 mg/dl among subjects who had a Hgb < 10 g/dl in both studies was 71 days (IQR 44-137), corresponding to the middle of the treatment periods.

IL28B genotype was not associated with the minimum observed Hgb during treatment, time to first Hgb <10 g/dl, or hemoglobin change from baseline during treatment in any of the treatment arms (not shown).

Three *ITPA* polymorphisms were assayed in the genetic substudy of P05216 and

[14] Results presented throughout are based on reviewer's analysis unless stated otherwise; the sponsor's analyses were confirmed

P05101 as follows: rs1127354 (C>A, missense P32T), rs7270101 (A>C, intronic splicing-altering), and rs6051702 (A>C, tagging SNP). Anemia rates were approximately similar between treatment-naïve and treatment experienced subjects, so pooled PG analysis was conducted. Since haplotype determination is not amenable to clinical testing, the reviewer parameterized the *ITPA* genotypes as a composite on the basis of functional effects on ITPA activity as follows (in a manner similar to the sponsor's analysis): rs1127354 C and rs7270101 A homozygotes = 0 (normal), heterozygotes at either rs1127354 or rs7270101 = 1 (normal-moderate), heterozygotes at both rs1127354 and rs7270101 = 2 (low-moderate), and rs1127354 A or rs7270101 C homozygotes = 3 (low; since two subjects were homozygous for the low activity allele of rs1127354 and seven subjects were homozygous for low activity allele of rs7270101, these groups were combined despite the greater penetrance of rs1127354).

Various anemia-related endpoints are summarized according to the *ITPA* composite genotype in the following table. Baseline hemoglobin did not differ by *ITPA* genotype. The incidence of all anemia-related adverse events differed significantly according to *ITPA* genotype in both arms (P<0.001), except hemoglobin <10 g/dL and ribavirin dose modification in the PR arm. No significant *ITPA* genotype x treatment interactions were identified using logistic or general linear models.

Table 12. Anemia-related adverse events by *ITPA* composite genotype* and treatment in P05216 and P05101

P05216+P05101	**PR**					**Pooled PR/BOC**				
	ITPA 0	**ITPA 1**	**ITPA 2**	**ITPA 3**	**P**	**ITPA 0**	**ITPA 1**	**ITPA 2**	**ITPA 3**	**P**
N	189	70	5	3		427	198	10	6	
Minimum Hgb	10.5 (1.2)	11.3 (1.5)	12.9 (0.7)	10.8 (2.6)	<0.0001	9.9 (1.3)	10.4 (1.3)	11.4 (1.5)	10.2 (1.1)	<0.0001
Hgb change	-4.2 (1.3)	-3.6 (1.3)	-2.0 (0.6)	-2.9 (2.4)	<0.0001	-5.0 (1.4)	-4.6 (1.2)	-3.1 (1.8)	-4.2 (1.7)	<0.0001
Hgb % change	-28.5 (7.8)	-24.3 (8.2)	-13.1 (2.9)	-20.6 (17.5)	<0.0001	-33.4 (8.4)	-30.5 (7.2)	-21.1 (11.8)	-28.5 (9.5)	<0.0001
Hgb<10 g/dL	70 (37)	17 (24)	0 (0)	1 (33)	0.0995	234 (55)	82 (41)	1 (10)	4 (67)	0.0008
EPO use	57 (30)	14 (20)	0 (0)	1 (33)	0.0028	201 (47)	69 (35)	1 (10)	3 (50)	0.0050
Rib. dose modification	37 (20)	9 (13)	1 (20)	2 (67)	0.9870	140 (33)	50 (25)	0 (0)	1 (17)	0.0364
DAIDS Grade 3/4†	81 (43)	15 (21)	0 (0)	1 (33)	0.0045	291 (68)	107 (54)	1 (10)	2 (33)	<0.0001

Values are mean (SD) or n (%)
* Based on rs1127354 or rs7270101 genotype; ITPA 0 = no ITPA variants, ITPA 1 = heterozygous at one locus, ITPA 2 = heterozygous at both loci, ITPA 3 = homozygous at either locus
† DAIDS (Division of AIDS) toxicity criteria. Derived from Hgb nadir and change values; Grade 3/4 defined as Hgb $\leq$8.9 g/dL or change $\geq$4.5 g/dL

Similar to the results presented above, hemoglobin changes at 4 weeks, reflecting the 4-week PR lead-in phase were larger in subjects without any *ITPA* variants.

Table 13. Hemoglobin changes by *ITPA* composite genotype*

P05216+P05101	PR+BOC/PR				P
	ITPA 0	ITPA 1	ITPA 2	ITPA 3	
N	602	263	15	9	
Week 4 Hgb	11.8 (1.4)	13.2 (1.4)	14.1 (1.5)	13.3 (1.7)	<0.0001
Week 4 Hgb change	-3.0 (1.3)	-1.7 (1.1)	-0.5 (1.3)	-0.8 (0.8)	<0.0001

Values are mean (SD) or n (%)
* Based on rs1127354 or rs7270101 genotype; ITPA 0 = no ITPA variants, ITPA 1 = heterozygous at one locus, ITPA 2 = heterozygous at both loci, ITPA 3 = homozygous at either locus

These findings support the sponsor's haplotype-based analysis and analyses by rs6051702 genotype.

4. Summary and Conclusions

Substudy bias and prognostic imbalances: Subjects consenting to DNA analysis differed from those not consenting in terms of baseline characteristics and treatment effects. However, treatment effects in the PG substudy of both trials were similar to the overall trial populations, limiting concerns about bias because of incomplete sampling. Prognostic imbalances were between the treatment arms within the *IL28B* genotype strata were handled by statistical adjustment and sensitivity analyses, and the results were consistent across multiple models.

IL28B genotype effects on PR and BOC/PR response in treatment-naïve subjects: The findings of this PG substudy confirm earlier reports of *IL28B* genotype effects. SVR rates differed significantly by *IL28B* genotype in subjects receiving PR48; *IL28B* genotype effects were less apparent in boceprevir-treated subjects. Among C/C subjects, SVR rates in the RGT and boceprevir/PR48 arms did not differ significantly from PR48. However, treatment effects were substantially larger in C/T and T/T subjects. C/C subjects treated with RGT or boceprevir/PR48 had rapid responses, the majority of which had occurred by TW8, whereas C/C subjects treated with PR48 responded slowly, with maximal response rates occurring at 24 weeks. The *IL28B* genotype relationship with SVR was robust to adjustment for other clinical predictors and was consistent across various subgroups.

IL28B genotype effects on PR and BOC/PR response in treatment-experienced subjects: *IL28B* genotype was less predictive in previously-treated subjects, although the trends in the PR48 arm were consistent with those observed in treatment-naïve subjects. The lack of significant genotype effects within the P05101 treatment arms may be related to the smaller sample size and enrichment for prior PR-nonresponders.

Predictive utility of IL28B genotype in treatment-naïve subjects: *IL28B* genotype was highly predictive of SVR in subjects treated with PR. Responses at 4 weeks

(changes in viral load or PCR-negativity) were highly predictive of response. The optimal threshold for decision-making based on changes in viral load at 4 appears to be approximately a 2.5-$\log_{10}$ decrease, such that those with greater reductions may respond favorably to PR alone. *IL28B* genotype has predictive performance characteristics that are similar to TW4 responses and has the advantage that subjects need not be exposed to PR to ascertain responsiveness.

Alternative polymorphisms near the IL28B gene: Three SNPs near the *IL28B* gene were tested in the current submission. These were nearly perfectly correlated in whites, but not blacks. Among blacks, rs12979860 appeared to differentiate responses most.

ITPA and anemia: Consistent with published observations, genetic variants of *ITPA* that result in ITPA deficiency were protective against anemia in subjects receiving PR with or without boceprevir, and did not appear to have any specificity to boceprevir. The small number of subjects that were homozygous at either locus (n=9, 1%) precludes definitive conclusions about this subgroup.

Ongoing trials and IL28B genotyping: The program also has one ongoing Phase 2 trial (P05411) and three ongoing Phase 3 trials (P05514, P05685 and P06086). *IL28B* genotyping is being performed in P05411 and P06086, but not P05514 and P05685.

5. Recommendations

The Genomic Group has reviewed the *IL28B* pharmacogenomic substudies submitted with NDA 202,258. The results support a large and robust effect of *IL28B* genotype on PR response, with or without concomitant boceprevir. Based on the potential clinical utility of *IL28B* genotype information, descriptive results of the pharmacogenomic substudy should be included in labeling bearing appropriate precautions about the retrospective nature of the analyses.

5.1 Label recommendations

Recommended label additions are noted in underlined blue text, deletions are noted in ~~red strikethrough~~ text.

(b) (4)

5.2 Post-marketing studies

Conduct a trial evaluating shorter treatment durations of PR48 and boceprevir/PR48 in patients with the *IL28B* rs12979860 C/C genotype.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUBEN C AYALA
04/15/2011

JEFFRY FLORIAN
04/15/2011

SHASHI AMUR
04/15/2011

MICHAEL A PACANOWSKI
04/15/2011
Concur

PRAVIN R JADHAV
04/15/2011

SARAH M ROBERTSON
04/15/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**202-258**
Application Date:	10-NOV-2010
Date of Receipt:	15-NOV-2010
Proprietary Name:	Victrelis™
Established Name:	Boceprevir
Code Name/#:	SCH 503034; HCV-Y
Pharmacological Classification:	Antiviral
Formulation:	Immediate release hard gelatin capsules
Strength:	200 mg
Applicant:	Schering Corporation (Merck)
Submission Type:	Original NDA
Legal Basis for Submission:	505(b)
Chemical Type:	1 (NME)
Submission Priority:	Priority
Reviewer:	Mark R. Seggel
GRMP Goal:	15-APR-2011
PDUFA Goal:	13-MAY-2011

BACKGROUND

Boceprevir is an antiviral agent for the treatment of chronic hepatitis C virus infection in adult patients (≥18 years of age). It is used in combination with peginterferon alpha and ribavirin. Boceprevir is a BCS Class IV drug. The drug product is manufactured using a (b) (4) . Excipients include those typically found in solid oral dosage forms. The formulation also contains (b) (4) sodium lauryl sulfate (SLS). This anionic surfactant is included in (b) (4) The daily dosage is 800 mg (4 capsules) three times a day for up to (b) (4) Boceprevir capsules are supplied in cartons of 28 twelve-count bottles, each bottle containing a one day supply. The product is stored under refrigeration until dispensed to the patient.

***Proposed Dissolution Method*:** USP Apparatus 2 (paddle) at 50 RPM with 900-mL of dissolution medium containing a 50 mM sodium phosphate buffer at pH 6.8 and 0.1% of sodium lauryl sulfate. Spiral capsule sinkers, 316 SS, 0.84" L x 0.385" W capacity, 5 coils, (b) (4)

***Dissolution Acceptance Criteria*: Q (b) (4) at 60 minutes.**

RECOMMENDATION

The proposed dissolution method is adequately discriminating. The acceptance criterion has been revised at our request, from Q (b) (4) at 45 minutes to Q (b) (4) at 60 minutes, will ensure consistent bioavailability of the drug product. It is, therefore, recommended that this application, as amended, be approved from the biopharmaceutics perspective.

{see electronic signature page}
Mark R. Seggel

Date

{see electronic signature page}
Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

Date

cc: P.Marroum, A.Dorantes, H.Mahayni, S.Abraham, S.Miller, D.Matecka

9 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK R SEGGEL
04/08/2011

PATRICK J MARROUM
04/08/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA202258**	**Brand Name**	**Victrelis**
OCP Division (I, II, III, IV, V)	**IV**	**Generic Name**	**Boceprevir**
Medical Division	**DAVP**	**Drug Class**	**NS3 Protease Inhibitor**
OCP Reviewer	**Ruben Ayala**	**Indication(s)**	**HCV treatment**
OCP Team Leader	**Sarah Robertson**	**Dosage Form**	**200 mg capsules**
Pharmacometrics Reviewer	**Jeffry Florian**	**Dosing Regimen**	**800 mg TID**
Pharmacogenomics Reviewer	**Shashi Amur**	**Route of Administration**	**Oral**
Date of Submission	**11/15/2010**	**Sponsor**	**Schering-Plough**
Estimated Due Date of OCP Review	**04/11/2011**	**Priority Classification**	**Priority review**
Medical Division Due Date			
PDUFA Due Date	**05/15/2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**1**		
Tabular Listing of All Human Studies	**X**	**1**		
HPK Summary	**X**	**1**		
Labeling	**X**	**1**		
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		
Isozyme characterization:	**X**			
Blood/plasma ratio:	**X**	**1**		
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) -	**X**	**4**		
Healthy Volunteers-				
single dose:	**X**	**2**		
multiple dose:	**X**	**1**		
Patients-				
single dose:				
multiple dose:	**X**	**2**		
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**2**		
fasting / non-fasting multiple dose:	**X**	**1**		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**3**		
In-vivo effects of primary drug:	**X**	**3**		
In-vitro:	**X**	**5**		
Subpopulation studies -				
ethnicity:	**X**	**1**		
gender:				
pediatrics:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:				
renal impairment:	**X**	**1**		
hepatic impairment:	**X**	**1**		
PD -				
Phase 2:				
Phase 3:		**2**		
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		
Phase 3 clinical trial:	**X**	**2**		
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**3**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			
Literature References	**X**			
Total Number of Studies	**16**			

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	All P2/P3 studies used commercial formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

At this moment, we have not identified major potential review issues in the submission.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Ruben Ayala, Pharm.D. 12/13/2010

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUBEN C AYALA
12/13/2010

SARAH M ROBERTSON
12/14/2010