CLINICAL PHARMACOLOGY REVIEW

NDA/SDN	203094/191 (location of trial report) (b) (4) (location of datasets)
Submission Type	Efficacy supplement (S-13 for use with atazanavir [ATV] (b) (4)
Applicant Name	Gilead
Submission Date	SDN 191: 1/31/2019 (b) (4)
Generic Name	Cobicistat (COBI, c)
Brand Name	TYBOST™
Dosage Form (Strength)	Tablet (150 mg)
Indication	Treatment of HIV-1 Infection
Review Team	Mario Sampson, PharmD, Vikram Arya, PhD

Contents

1 Background

COBI, in combination with ATV or DRV, is approved for use in adults (TYBOST™). ATV/c (ATV co-administered with COBI) was approved based on Phase 3 Trial 114 which compared the safety and efficacy of ATV/c versus ATV/ritonavir (RTV, r), and a relative bioavailability (relBA) trial comparing the PK of ATV administered with RTV versus COBI. In Trial 114, ATV/c was noninferior to ATV/r and in the relBA trial, ATV exposures were similar (PK parameter ratios and 90% confidence intervals within 80-125%) when administered with COBI or RTV.

DRV/c (DRV co-administered with COBI) was initially approved based solely on a relBA trial comparing the PK of DRV administered with RTV versus COBI. In this trial, mean C_{max} and AUC ratios were similar while the geometric mean ratio (GMR) of DRV C_{tau} values were lower when administered with COBI vs RTV (C_{tau} ratio of 0.69; 90% CIs = 0.59, 0.82). Lower DRV C_{tau} values in the DRV/c arm were attributed to a greater proportion of subjects with higher concentrations of DRV between the 20 hour and 24-hour timepoints in the DRV/r arm (NDA 203094, Clinical Pharmacology review dated 3/22/13, page 65). The mean 31% lower C_{tau} values were not considered to be clinically significant. Subsequently, SYMTUZA™ (a fixed dose combination of DRV/c/emtricitabine/tenofovir alafenamide) was approved based on efficacy and safety findings from Phase 3 trials.

Of note, the approved dose of ATV when co-administered with RTV for patients weighing ≥35 kg is 300 mg (REYATAZ™). The approved dose of DRV when co-administered with RTV for patients with no DRV resistance-associated mutations is 675 mg for patients weighing 35 - <40 kg and 800 mg for patients weighing ≥40 kg (PREZISTA™).

(b) (4) provide an interim report for trial GS-US-216-0128 (Trial 0128). Trial 0128 is enrolling subjects aged 3 months - <18 years; the interim report contains PK data for adolescents (ages 12 - <18 years and weighing ≥25 kg). The primary basis of approval of ATV/c (b) (4) in adolescents is based on demonstrating similarity of systemic exposures of ATV (administered as ATV/c) (b) (4) between adolescents and adults.

(b) (4)

2 Overall Clinical Pharmacology Recommendations

We recommend the approval of S-13 (COBI in combination with ATV for patients ≥35 kg)

(b) (4)

3 Labeling Recommendations

3.1 Section 2.2 – Dosage and Administration in Pediatric Patients

(b) (4)

3.1.2 ATV dosing for patients weighing 35 (b) (4) kg

Proposed ATV dosing when co-administered with COBI for patients weighing 35 (b) (4) kg is 300 mg. There was one subject (b) (4) who received ATV 200 mg (per protocol) with COBI or RTV at the time of intensive PK. Subjects in Trial 0128 had intensive PK measured during RTV- and COBI-containing therapy and ATV exposures were overall comparable when co-administered with COBI and RTV (Table 4). ATV AUC and C_{tau} ratios were generally near one throughout the weight range of subjects enrolled in Trial 0128 (Figure 1, Figure 2). Thus, for subjects weighing 35 (b) (4) kg (b) (4), based on the totality of information, similar ATV exposures are expected when ATV 300 mg is co-administered with COBI or RTV, hence, the review team agrees with the proposed ATV dosing of 300 mg when co-administered with COBI for patients in the 35 (b) (4) kg (b) (4)

(b) (4)

(b) (4)

3.2 (b) (4)

(b) (4)

4 Trial 0128 – Summary and Results

The adolescent cohort of Trial 0128 enrolled HIV-1 infected, virologically-suppressed subjects aged 12 - <18 years of age and weighing ≥25 kg. Subjects had to be on an antiretroviral (ARV) regimen including ATV/r or DRV/r prior to enrollment. Objectives included PK, efficacy, and safety. Subjects switched from ATV/r to ATV/c or DRV/r to DRV/c on day 1 and continued treatment for 48 weeks. Intensive PK was measured on day -1 ± four days (RTV-containing regimen) and on day 10 ± four days (COBI-containing regimen).

Twenty-two adolescents were enrolled; 14 on ATV and 8 on DRV. Body weight at the time of the day 10 intensive PK visit ranged from 32.5 – 81.3 kg. Per protocol (original version), adolescent ATV and DRV dosing was determined based on body weight while COBI dosing was 150 mg QD (Table 1).

Table 1. Dosing of Trial 0128 medications for subjects weighing ≥25 kg.

Weight range (kg)	QD ATV dose (mg)	QD DRV dose (mg)	QD COBI dose (mg)
30 - <40 kg	200	675	150
≥40 kg	300	800	150

Source: Trial 0128 protocol.

ATV/c results

When compared to adults, mean ATV exposures from ATV/c were higher in adolescents (Table 2). Exposure-related adverse events associated with ATV in adults include increased bilirubin, PR interval prolongation, and QT interval prolongation (NDA 21567 Clinical Pharmacology review dated 6/20/2003). However, threshold ATV C_{max} and AUC values that should not be exceeded have not been established. We observed that when co-administered with ATV alone (ATV administered without ritonavir), clarithromycin increased ATV AUC (GMR = 1.28; 90% confidence interval (CI) = 1.16, 1.43) to a similar magnitude as observed in Trial 0128. No ATV dose adjustment is recommended for this interaction (REYATAZ labeling). The review team concluded that the higher mean ATV exposures in adolescents after administration of ATV/c are not clinically significant. This is consistent with proposed Tybost labeling which states that the

safety profile of ATV/c in adolescents is similar to the safety profile of ATV/c in ARV treatment-naïve adults.

Table 2. Comparison of ATV PK parameters in adolescents and adults administered ATV/c.

ATV PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	Adolescents in Study GS-US-216-0128 (Test, N = 14)	Adults in Studies GS-US- 216-0105, GS-US-216-0114 (Reference, N = 30)	
AUC_{tau} (h•ng/mL)	51654.40	39960.83	129.26 (100.99, 165.45)
C_{max} (ng/mL)	4375.00	3537.60	123.67 (97.93, 156.17)
C_{tau} (ng/mL)	986.68	576.46	171.16 (100.21, 292.34)

GLSM = geometric least-squares mean

Source: Trial report.

The proposed ATV dosing in Tybost labeling is 300 mg for patients weighing ≥35 kg. However, the 14 adolescents on ATV/c included one subject weighing 32.5 kg and one subject weighing 39.7 kg who each received 200 mg ATV. These subjects received 200 mg ATV (instead of 300 mg ATV) because when the trial was initiated, approved ATV dosing with RTV for patients weighing 35 - <40 kg was 200 mg. During the trial, approved ATV dosing with RTV for patients weighing 35 - <40 kg was revised to 300 mg and the protocol was later amended to dose ATV according to local country prescribing information (response to IR, page 3). The removal of these two subjects did not impact the ratio of adolescent-to-adult geometric mean PK parameters (Table 3).

Table 3. Comparison of geometric mean ATV PK parameters in adolescents and adults administered ATV/c after removal of two subjects who did not receive ATV 300 mg.

ATV PK parameter	Adolescents (test, N = 12)	Adults (reference, N = 30)	Ratio of geometric means (test/reference)
AUC_{tau} (ng*h/mL)	49475	39961	1.24
C_{max} (ng/mL)	4321	3538	1.22
C_{tau} (ng/mL)	908	576	1.58

Source: Reviewer calculations. Adult values are from Table 3 and adolescent values are from the pp dataset.

4.1 Review Team's Assessment of ATV/c Dosing for Patients Weighing ≥ 35 kg:

(b) (4)

ATV dosing for patients weighing 35 (b) (4) kg

Proposed ATV dosing when co-administered with COBI for patients weighing 35 (b) (4) kg is 300 mg. As previously mentioned, there was one subject (b) (4) who received ATV 200 mg (per protocol) with COBI or RTV at the time of intensive PK. (b) (4) Further, subjects in Trial 0128 had intensive PK measured during RTV- and COBI-containing therapy and ATV exposures were overall comparable when co-administered with COBI and RTV (Table 4). ATV AUC and C_{tau} ratios were generally near one throughout the weight range of subjects enrolled in Trial 0128 (Figure 1, Figure 2). Thus, for subjects weighing 35 (b) (4) kg (b) (4), based on the totality of information, similar ATV exposures are expected when ATV 300 mg is co-administered with COBI or RTV, hence, the review team agrees with the proposed ATV dosing of 300 mg when co-administered with COBI for patients in the 35 (b) (4) kg (b) (4).

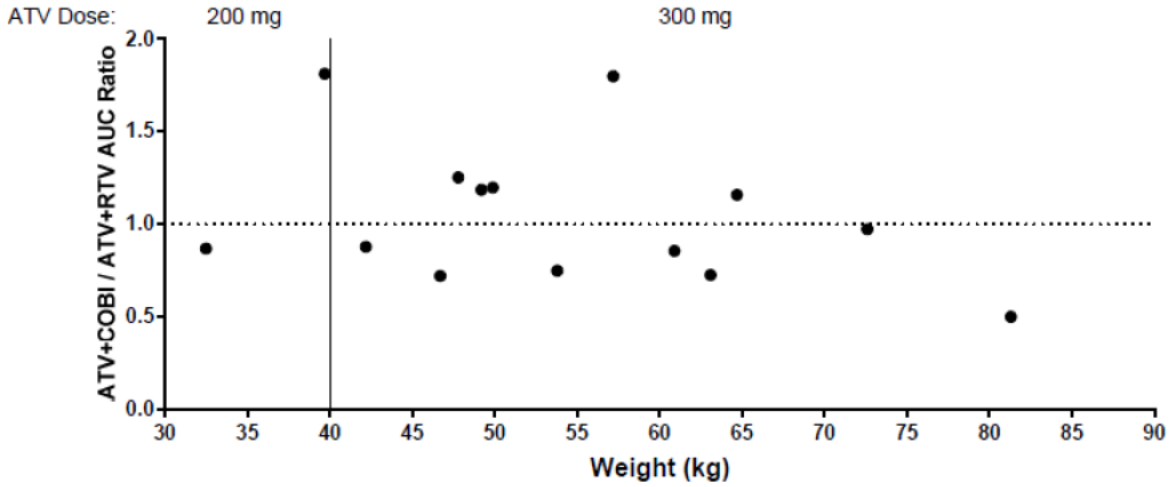
Table 4. Comparison of ATV exposures in adolescents when co-administered with COBI vs RTV.

ATV PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	ATV/co Day 10 (Test, N = 14)	ATV/r Day -1 (Reference, N = 14)	
AUC_{tau} (h•ng/mL)	51654.40	52344.42	98.68 (83.31, 116.90)
C_{max} (ng/mL)	4375.00	4811.54	90.93 (75.01, 110.23)
C_{tau} (ng/mL)	986.68	1177.30	83.81 (53.01, 132.51)

GLSM = geometric least-squares mean
PK parameters for the test group were from Day 10 intensive PK assessment when ATV was boosted by COBI.
PK parameters for the reference group were from Day -1 intensive PK assessment when ATV was boosted by RTV.

Source: Trial report.

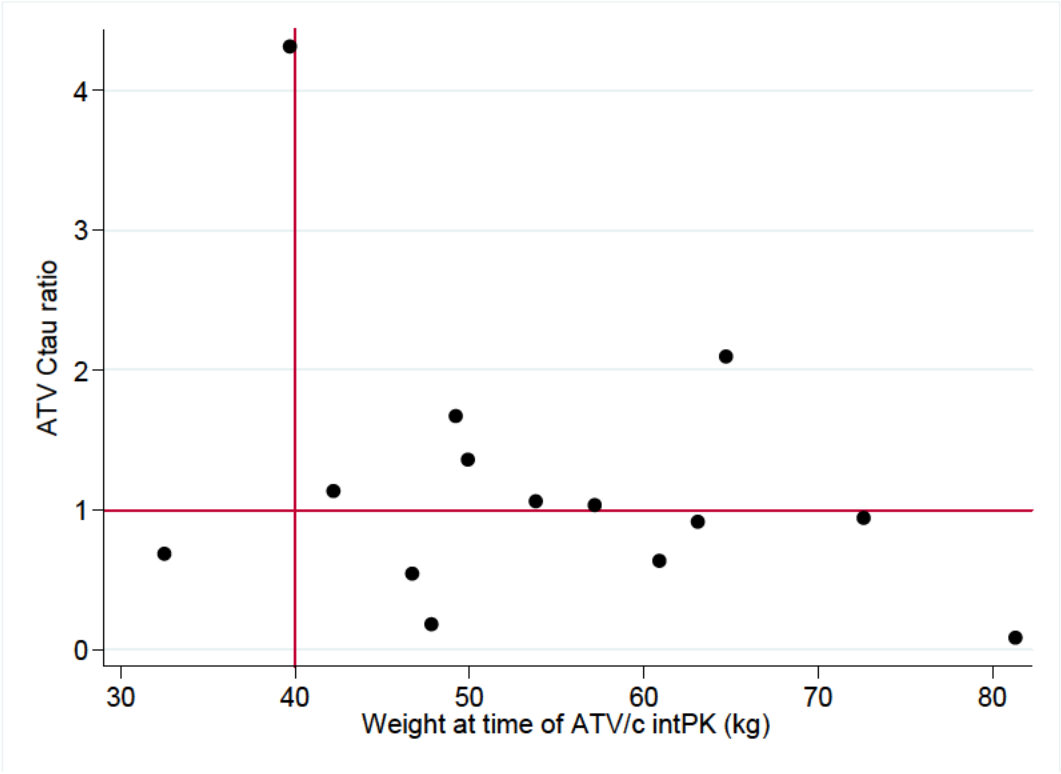
Figure 1. ATV AUC ratio (ATV/c / ATV/r) as a function of body weight in Trial 0128.



AUC ratios were calculated by dividing AUC with ATV/COBI by AUC with ATV/RTV for each individual participant.
Sources: Study GS-US-216-0128 Table 15.10.1.2.1 and Listing 16.2.4.1

Source: Response to IR, page 3.

Figure 2. ATV C_{tau} ratio (ATV/c / ATV/r) as a function of body weight in Trial 0128.



Source: plotted by reviewer from PP dataset.

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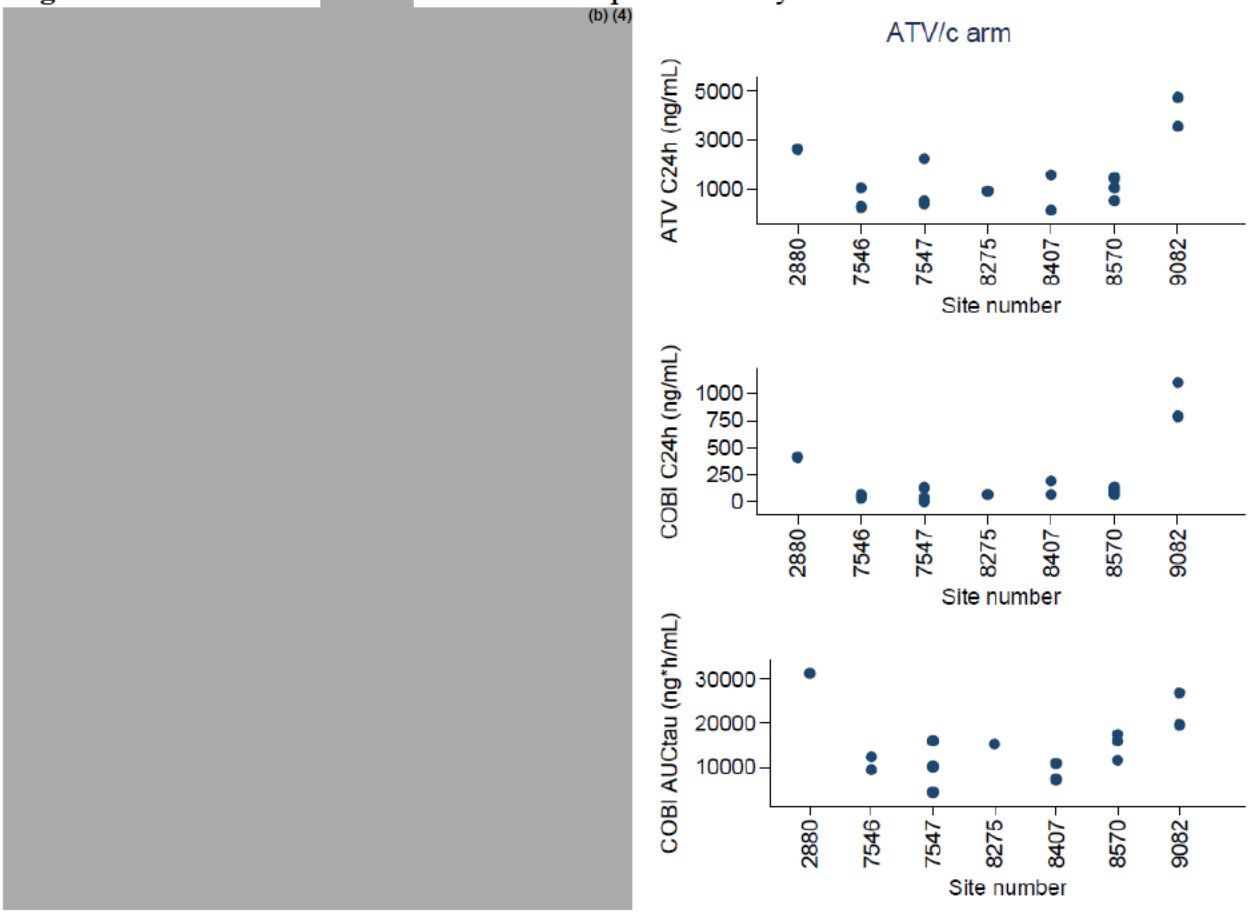
Inspections

We requested clinical and analytical site inspections of Trial 0128. There was only one analytical site and because the Office of Study Integrity and Surveillance (OSIS) had recently inspected the site, they declined to conduct an on-site inspection of the analytical site (NDA 203094 review dated 4/29/2019).

Subjects were enrolled at seven clinical sites. (b) (4) We requested clinical inspections at these two sites; St. Jude Children's Research Hospital (site 2800, n=3 enrolled) and Children's Hospital Colorado (site 8407, n=4 enrolled). Clinical inspections were conducted at these sites and the inspector concluded that the clinical data were reliable to support a regulatory decision (NDA 203094, OSIS review dated 7/17/2019).

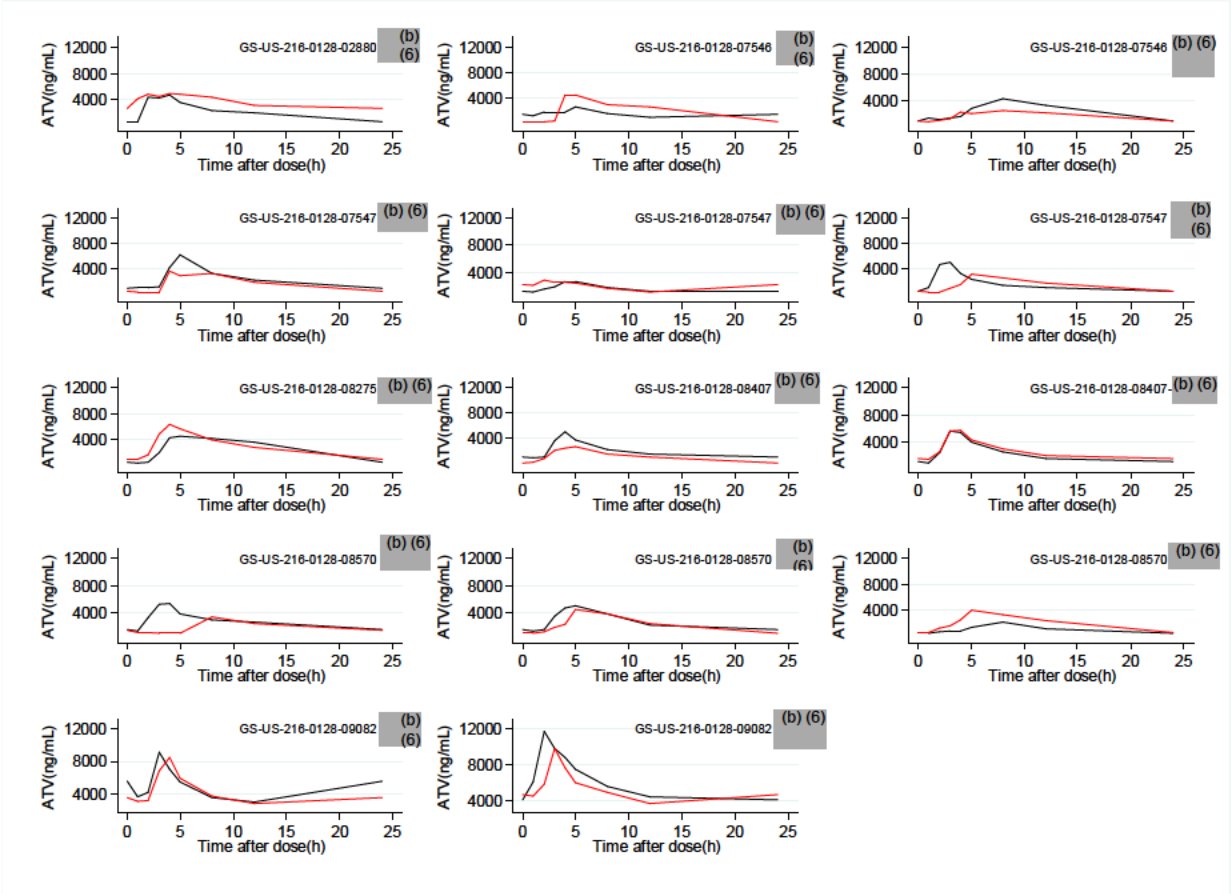
Figure 4. Selected ATV (b) (4) and COBI PK parameters by clinical site.



Source: plotted by reviewer from PP dataset.

The clinical inspection review noted a protocol deviation at site 8407. Per protocol, subjects were to take study medication at approximately the same time each day. Subjects were to record dose times for the 9 days leading up to intensive PK visits on day -1 and day 10. The inspector noted that among all four subjects enrolled at this site (subjects (b) (6)), dose times of COBI varied by 2-4 hours among the days and recommended that we consider if this deviation affects the PK results. This deviation can potentially impact whether subjects are at steady-state at the intensive PK visit. At the intensive PK visit, doses were administered at the clinic and the actual time (instead of the nominal time) elapsed since dosing was used for PK assessments, hence the deviation in dosing times prior to the intensive PK visit is not expected to affect the estimation of steady state PK parameters. Because steady state ATV (b) (4) concentration-time profiles were comparable after co-administration with RTV vs COBI in all subjects (Figure 5, Figure 6), we concluded that the dose time deviations are not likely to significantly impact our overall assessment.

Figure 5. ATV concentration-time profiles in adolescents on ATV/r or ATV/c.



Source: Plotted by reviewer from pp dataset. Black = day -1 ATV/r intensive PK; Red = day 10 ATV/c intensive PK.

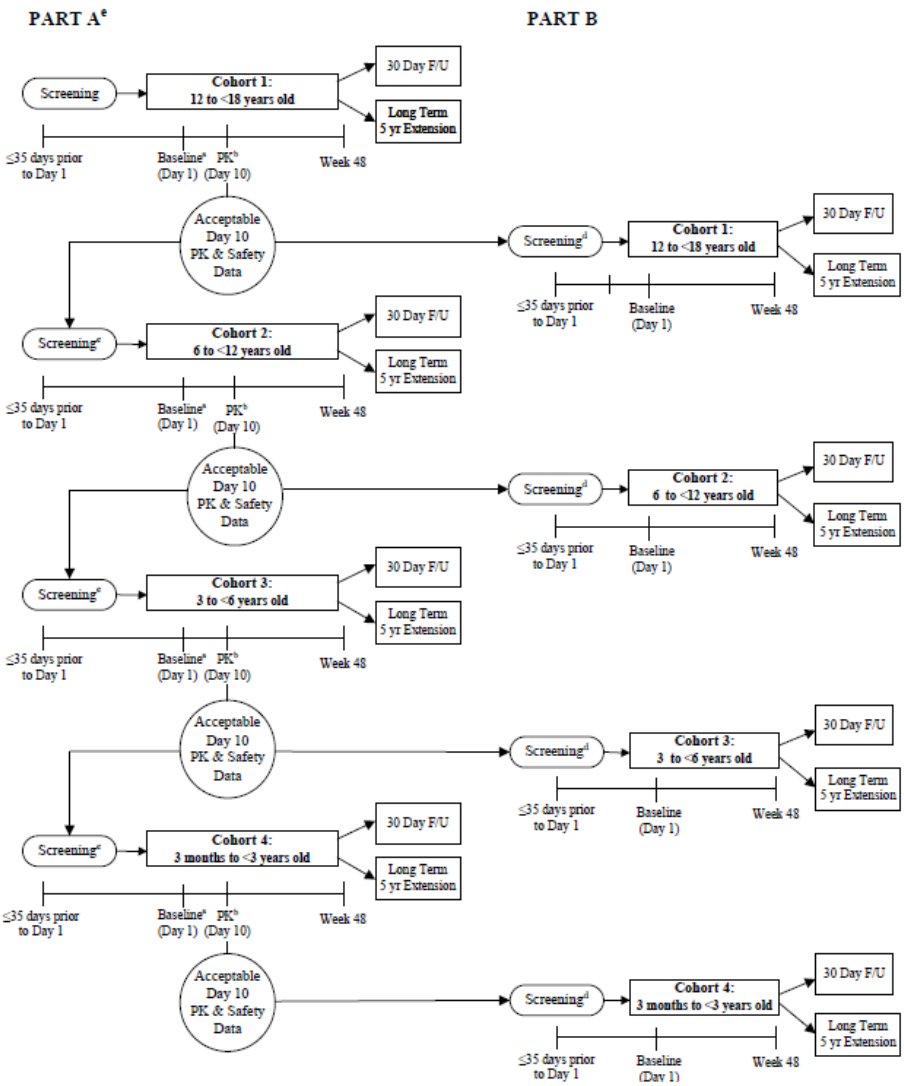

(b) (4)

5 Review of Trial 0128

Note that while Trial 0128 is ongoing and will enroll subjects aged 3 months to <18 years, results in the interim report are available only for the adolescent cohort.

Study title	A Phase 2/3, Multicenter, Open-label, Multicohort, Two-Part Study Evaluating Pharmacokinetics (PK), Safety, and Efficacy of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir (DRV/co), Administered with a Background Regimen (BR) in HIV-1 Infected, Treatment-Experienced, Virologically Suppressed Pediatric Subjects
Study period	1/16/2014 – 5/30/2018 (last subject observation for this report)

STUDY SUMMARY (As Reported by the Applicant)
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS
Objectives: Primary: PK and dose confirmation Secondary: Safety, tolerability, and antiviral activity
Design and study schema:



a Prior to Day 1, subjects discontinue RTV and initiate once-daily COBI coadministered with DRV or ATV plus their BR.
b Subjects participate in an Intensive PK.
c Screening will be initiated after analysis of intensive PK samples and confirmation of COBI exposure in the previous age cohort.
d Part B screening will be initiated after analysis of intensive PK samples and confirmation of COBI exposure in corresponding age cohort in Part A.
e In each cohort, if the minimum number of either ATV/co or DRV/co subjects completes their Day 10 intensive PK visit before the other, then the data from that treatment are to be analyzed. Upon acceptable COBI and PI safety and PK data through Day 10, Part B of that cohort and Part A of the subsequent cohort will proceed to be opened for that treatment. Part A for the treatment that does not complete enrollment is to remain open until the minimum number of subjects complete their Day 10 intensive PK visit.

Population: HIV-infected, treatment-experienced, virologically suppressed, male and female subjects aged 3 months to <18 years on a stable background ARV regimen containing ATV/r or DRV/r. To be eligible, subjects on DRV must have no history of DRV resistance-associated mutations.

Dose selection: Only dose selection for adolescents is described (dose selection for younger age cohort will be added to subsequent reports). Only COBI dosing is addressed in the dose selection section. It is noted that COBI 150 mg (the dose used in this study) is approved for adolescents as a component of GENVOYA™ and STRIBILD™.

Reviewer comment: While not stated explicitly, for a given weight group, it appears that doses of ATV and DRV were selected to match the dose when co-administered with RTV.

Study drug administration: COBI is to be given with food and with the subject's protease inhibitor (ATV or DRV) at approximately the same time each day. Study medication was to be taken at the clinic on intensive PK days (day -1 and day 10).

Formulation: Approved ATV capsules (REYATAZ™) and DRV tablets (PREZISTA™) were used. COBI 150 mg tablets were provided by Gilead.

Reviewer comment: The trial report does not state that approved COBI 150 mg was used in this study. However, the description of the tablet in the report matches the description in TYBOST™ labeling. It appears the approved COBI 150 mg tablet was used in the study.

Prohibited concomitant medications: By protocol amendment 6, prohibited concomitant medications included acid reducing agents (H2RA or PPIs if <40 kg and on ATV) alfuzosin, modafinil, telithromycin, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, voriconazole, astemizole, terfenadine, rifampin, rifapentine, rifabutin, amiodarone, quinidine, dronedarone, lorasidone, bepridil, apixaban, rivaroxaban, ergot derivatives, cisapride, St. John's Wort, echinacea, simvastatin, lovastatin, cerivastatin, pimozide, norgestimate, ethinyl estradiol, midazolam, triazolam, sildenafil (for PAH) and irinotecan.

Prohibited ARVs in the background regimen include saquinavir, indinavir, nelfinavir, double protease inhibitor (PI) regimens, raltegravir, elvitegravir, efavirenz, nevirapine, delaviridine, maraviroc, etravirine, rilpivirine, dolutegravir and investigational antiretroviral agents.

PK sampling: In part A of the adolescent cohort, intensive PK assessment occurred on day -1 (for ATV/r or DRV/r) and on day 10 (for ATV/c or DRV/c). Sampling times were pre-dose, and 1, 2, 3, 4, 5, 8, and 12 hours post-dose. Analytes measured were ATV, DRV, and COBI.

Also in part A of the adolescent cohort, sampling of trough samples occurred at baseline (pre-dose), and 20-28 hours post-dose at weeks 12, 24, and 48. In part B, 20-28 hour post-dose samples were taken on weeks 4, 12, 24, 32, and 48.

Reviewer comments: The trial report states that intensive PK samples were to be taken up to 12 hours post-dose while PK datasets contained concentrations for samples taken 24 hours post-dose.

Bioanalytical methods: Bioanalytical methods were stated to be fully validated and samples analyzed within the duration of stability (
Table 9, Table 10).

Table 9. Summary of ATV, (b) (4) and COBI bioanalytical method validation.

Parameter	ATV	(b) (4)	COBI
Calibrated Range (ng/mL)	10 to 5000		5 to 2500
Interassay Precision (%CV)	3.8 to 5.5		3.4 to 5.7
Interassay Accuracy Range (%RE)	−2.4 to −0.1		−3.0 to 2.0
Stability in Frozen Matrix (days)	721 at −70°C		121 at −10°C to −30°C 1297 at −60°C to −80°C

%CV = percentage coefficient of variation; %RE = percentage relative error

Source: Trial report.

Table 10. Links to method validation and study sa

	ATV	[redacted] (b) (4)	COBI
Method validation report	42-0830		60-1343
Sample analysis report	60-1384A		60-1384C

RESULTS

Demographics

Twenty-two subjects were enrolled; 14 on ATV/c and eight on DRV/c. Subjects were approximately two-thirds male and the most prevalent racial group was Asian (Table 11).

Table 11. Demographics in the adolescent cohort of Trial 0128.

Characteristic	Cohort 1 Part A: Age 12 to < 18 Years		
	ATV/co (N = 14)	DRV/co (N = 8)	Total (N = 22)
Age (years)			
N	14	8	22
Mean (SD)	14 (2.0)	14 (1.5)	14 (1.8)
Median	14	15	14
Q1, Q3	12, 16	13, 15	12, 16
Min, Max	12, 17	12, 16	12, 17
Sex at Birth			
Male	10 (71.4%)	4 (50.0%)	14 (63.6%)
Female	4 (28.6%)	4 (50.0%)	8 (36.4%)
Race			
Asian	8 (57.1%)	0	8 (36.4%)
Black	2 (14.3%)	3 (37.5%)	5 (22.7%)
White	4 (28.6%)	3 (37.5%)	7 (31.8%)
Other	0	2 (25.0%)	2 (9.1%)
Ethnicity			
Hispanic or Latino	4 (28.6%)	3 (37.5%)	7 (31.8%)
Not Hispanic or Latino	10 (71.4%)	5 (62.5%)	15 (68.2%)
Baseline Body Weight (kg)			
N	14	8	22
Mean (SD)	54.6 (13.43)	55.0 (13.25)	54.8 (13.05)
Median	52.7	53.7	52.7
Q1, Q3	46.5, 63.3	45.8, 62.8	46.5, 63.3
Min, Max	32.3, 81.4	37.2, 78.0	32.3, 81.4

Source:

Protocol Deviations

Seventeen protocol deviations were reported. Only one of these deviations occurred before week 4 (intensive PK, the primary endpoint, was completed by day 10 ± 4 days). The deviation occurring before week 4 occurred for subject (b) (6) on day 10 and the deviation was stated to be "day 10 intensive PK was completed in error; retest not obtained". The most common deviations were drug compliance <70% (n=8) and retest of virologic rebound not performed (n=5). The Applicant concluded that the deviations did not affect the study results.

Reviewer comments: We do not think the reported deviations affected the PK results. The intensive PK deviation occurred in subject (b) (6) who received incorrect (b) (4) dosing and was excluded from the (b) (4) dataset. As described in section 4.2, unreported protocol deviations were identified at one of two clinical sites that were inspected. Study medication was to be taken at approximately the same time each day, and dosing times were to be recorded in the days leading up to intensive PK visits. At site 8407 all four enrolled subjects recorded dosing times deviating by 2-4 hours. Based on comparable concentration-time profiles of ATV (b) (4) after co-administration with RTV vs COBI for all subjects, we concluded these deviations were unlikely to have affected the PK results.

Concomitant medications

Use of concomitant medications was not described in the Trial report.

Reviewer comments: Use of concomitant medications are typically summarized in Trial reports. In our review of concomitant medications listed in the cm dataset, we did not observe use of prohibited concomitant ARVs in background regimens (Table 12) or use of prohibited non-ARVs. The most commonly used concomitant non-ARV medications were influenza vaccine (n=21), ibuprofen (n=18), and paracetamol/acetaminophen (n=9).

Table 12. Reported medications denoted as current antiretroviral medication.

Reported Name of Drug, Med, or Therapy	Freq.	Percent	Cum.
DESCOVY	2	2.99	2.99
NRTI: ABACAVIR (ABC)	4	5.97	8.96
NRTI: DIDANOSINE (DDI)	1	1.49	10.45
NRTI: DIDANOSINE EC (DDI)	1	1.49	11.94
NRTI: EMTRICITABINE (FTC)	1	1.49	13.43
NRTI: EPZICOM/KIVEXA (ABC+3TC)	8	11.94	25.37
NRTI: LAMIVUDINE (3TC)	8	11.94	37.31
NRTI: TENOFOVIR DF (TDF)	7	10.45	47.76
NRTI: TRUVADA (FTC+TDF)	5	7.46	55.22
NRTI: ZIDOVUDINE (AZT)	1	1.49	56.72
PI: ATAZANAVIR (ATV)	16	23.88	80.60
PI: DARUNAVIR (DRV)	8	11.94	92.54
PI: RITONAVIR (RTV)	4	5.97	98.51
TDF/FTC(300/200)	1	1.49	100.00
Total	67	100.00	

Source: Reviewer's analysis of the cm dataset.

Pharmacokinetics

See section 4 for PK results.

Efficacy

Among subjects with virologic data at week 48, 13/14 (93%) of subjects on ATV/c (b) (4) remained virologically suppressed. (b) (4)

Safety

There were no deaths during the study.

Five serious AEs were reported: these included clavicle and foot fracture (n=1), substance abuse (n=1), bipolar disorder (n=1), appendicitis (n=1), and chest pain (n=1).

Two subjects discontinued the study due to an AE; both subjects were on DRV/c. AEs leading to discontinuation in one subject included hyperlipidemia (started day 173), acanthosis nigricans (started day 222), and an SAE of bipolar disorder (study day unspecified). The last dose was taken on day 614. The other subject's AEs included Becker's naevus (day 56) and chest pain (day 73). The last dose was on day 56.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Was bioanalytical method performance acceptable? ☑ Yes ☐ No
- Did protocol deviations affect the integrity of the study? ☐ Yes ☑ No
- Did use of prohibited concomitant medications affect the integrity of the study? ☐ Yes ☑ No

Study Results

Are the study results acceptable as reported by the sponsor? ☑ Yes ☐ No

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