CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204569Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Suvorexant (MK-4305)
PRODUCT (Brand Name):	Belsomra
NDA:	204569
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	5, 10, 15, 20 mg
INDICATION:	Insomnia
NDA TYPE:	Complete Response Resubmission
SUBMISSION DATE:	February 14, 2014
SPONSOR:	Merck & Co., Inc.
REVIEWER:	Hristina Dimova, Ph.D.
PHARMACOMETRICS REVIEWER:	Satjit Brar, Pharm.D., Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

1.0 EXECUTIVE SUMMARY

An original New Drug Application (NDA) was submitted for suvorexant to the Agency on August 30, 2012 for treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. On June 28, 2013, FDA issued a Complete Response (CR) Letter, stating that the application cannot be approved in its present form and requested the following information:

- 10 mg tablet must be available at time of approval as the starting dose
- For patients expected to have significantly higher plasma levels of suvorexant (e.g. patients taking concomitant CYP3A4 inhibitors), a 5 mg tablet strength is needed
- A safety update is required in the resubmission

On February 14, 2014, the sponsor submitted a Complete Response NDA 204569 addressing the deficiencies outlined in the FDA CR letter. Based on the subsequent feedback from the Agency, including the 19-Jun-2013 CMC meeting on the proposal for development of a 10 mg tablet, the 27-Sep-2013 End of Review Conference, and the FDA's 18-Dec-2013 response to Merck's CMC submission in which the FDA agreed that the combination of the in vitro dissolution data for the 5 mg and 10 mg tablets, along with relevant clinical data from the original NDA, support biowaivers.

This submission contains CMC information and two Phase 1 relative bioavailability studies completed since the original NDA application was reviewed (P055, P056), providing supportive data for the 5 mg and 10 mg tablets. At the End of Review Conference, the FDA concurred with the sponsor's plan not to update the clinical modules in the original application based on the limited new clinical safety data to be included in the resubmission.
Therefore, only the results of the Phase 1 relative bioavailability studies will be discussed in this review.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP)/ Division of Clinical Pharmacology-1 has reviewed the Clinical Pharmacology information submitted to NDA 204569 Complete Response and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

Study P055: A Study to Evaluate the Relative Bioavailability of a Suvorexant Low Dose Formulation in Healthy Subjects under Fasting Conditions

Primary objective: To evaluate the relative bioavailability between four 5 mg Suvorexant Tablets and one 20 mg Suvorexant Tablet after a single-dose in healthy subjects under fasting conditions

Study Design	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study*
Study Population	Healthy male (12) and female (12) subjects from 18 to 55 years of age, with a BMI from 18.5 to 30.0 kg/m^2
Treatment Groups	In each period, subjects received one of the following two treatments: Treatment A Test Product: four 5 mg tablets Treatment B Reference Product: one 20 mg tablet
Dose and Administration	Trt A (four 5mg) or B (one 20 mg tablet) were administered after an overnight fast of at least 10 hours with 240 mL of water. The washout between drug administrations for each subject was 5 days (± 3 hours).
PK Sampling: plasma	In each period 15 samples were collected prior to dosing (0-hour) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 48 and 72 hours after drug administration.
Analysis	LC-MS/MS method for suvorexant Calibration Range: 1.00 to 1000.00 ng/mL
PK Assessment	Suvorexant AUC_{0-t}, AUC_{inf}, C_{max}, T_{max} and $t_{1/2}$
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry
PD Assessment	None

* Subjects were randomly assigned to one treatment sequence:

	Treatment	
Sequence	Period 1	Period 2
AB	A	B
BA	B	A

Bioanalytical Assay:
Plasma concentrations of suvorexant were determined using a validated liquid chromatography-tandem mass spectrometric detection (LC-MS/MS) method (method DM-909). This method was developed and validated by Merck Research Laboratories and was later transferred and validated (b) (4) (for details, see Section 2.6 of the Clinical Pharmacology NDA 204569 Review in DARTTS, Apr 30, 2013).

The performance of the assay during the analysis of the samples from study P055 was acceptable, see table below.

Assay performance

Analyte			Suvorexant (MK-4305)	
Method:			HPLC/MS/MS	
Standard Curve:	Range:		1.00 to 1000.00 ng/mL	
	R^2:		>0.998	
	Precision:		≤ 3.0%	
	Accuracy:		≤ |2.5|%	
LOQ:			1.00 ng/mL	
QC:		3 ng/mL	150 ng/mL	750 ng/mL
	Precision:	3.3%	1.9%	3.1%
	Accuracy:	-0.3%	-2.1%	0.1%

Comment: The bioanalytical method was found acceptable, with inter-day and intra-day accuracy and precision being <15%.

Pharmacokinetic Results:

All 24 subjects were included in the pharmacokinetic (PK) and statistical data analyses. One subject (Subject 0003) missed the 72 h sample collection time point in Period 1 and did not complete Period 2 due to an adverse event (AE), loose stools, this subject was included in the PK and statistical analyses.

Non-zero pre-dose concentration levels were obtained at the beginning of Period 2 as detailed in the table below. However, all measured pre-dose levels were less than 5% of the subject's corresponding C_{max} value, therefore all pre-dose levels were maintained in the PK analysis without baseline correction.

Subject	*Seq*	*Period*	*Trt*	*Pre-dose Conc. (µM)*	*Cmax (µM)*	*Pre-dose Conc./Cmax (%)*	*Decision*
5	AB	2	B	0.00322	1.02	0.31	Include
9	BA	2	A	0.00674	1.27	0.53	Include
15	BA	2	A	0.00271	0.809	0.33	Include
21	BA	2	A	0.00339	0.766	0.44	Include

The pharmacokinetics of suvorexant following single-dose administration of four 5 mg tablets and one 20 mg tablet were similar, as assessed by $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}. Although not pre-specified, the 90% confidence interval of the GMR of these parameters is within the bioequivalence (BE) interval of 80.00-125.00%.

Suvorexant PK Parameters

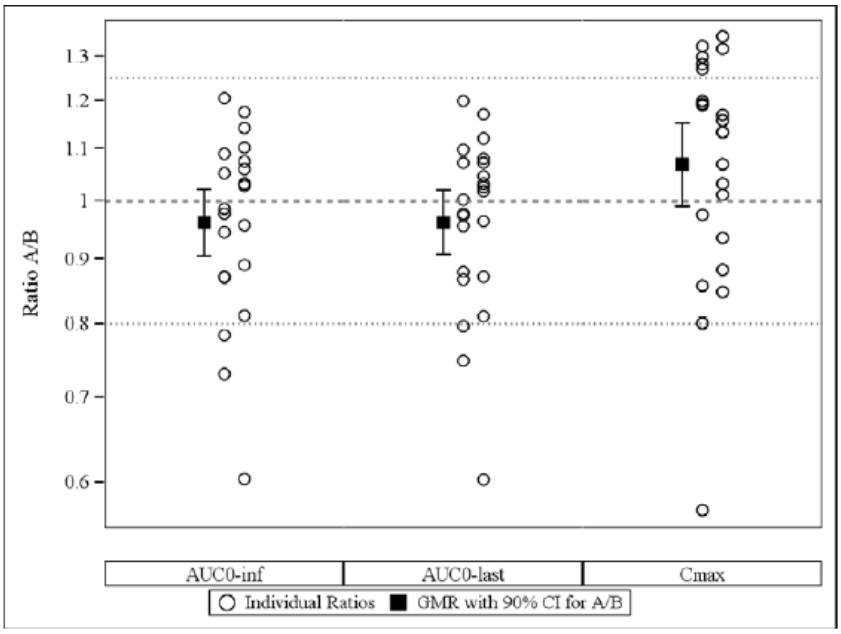
Based on Measured Plasma MK-4305 (Suvorexant) Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
$AUC_{0\text{-last}}$	A	24	8.12	6.87 - 9.61	A vs B	96.13	90.65 - 101.93	11.5
(hr·µM)	B	23	8.45	7.14 - 10.0		-	-	-
$AUC_{0\text{-inf}}$	A	24	8.45	7.13 - 10.0	A vs B	96.13	90.53 - 102.08	11.8
(hr·µM)	B	23	8.79	7.42 - 10.4		-	-	-
C_{max}	A	24	0.762	0.672 - 0.864	A vs B	106.83	99.14 - 115.12	14.7
(µM)	B	23	0.713	0.611 - 0.832		-	-	-
			Median	*Range*				
T_{max}	A	24	1.00	1.00- 3.00				
(hr)	B	23	2.00	0.50- 4.00				
			GM	*CV(%)***				
$t_{½}$	A	24	12.8	31.8				
(hr)	B	23	12.5	32.2				

** Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$*
*** $CV(\%) = 100*sqrt(exp(s^2)-1)$, where s^2 is the observed between-subjects variance on the natural log-scale.*

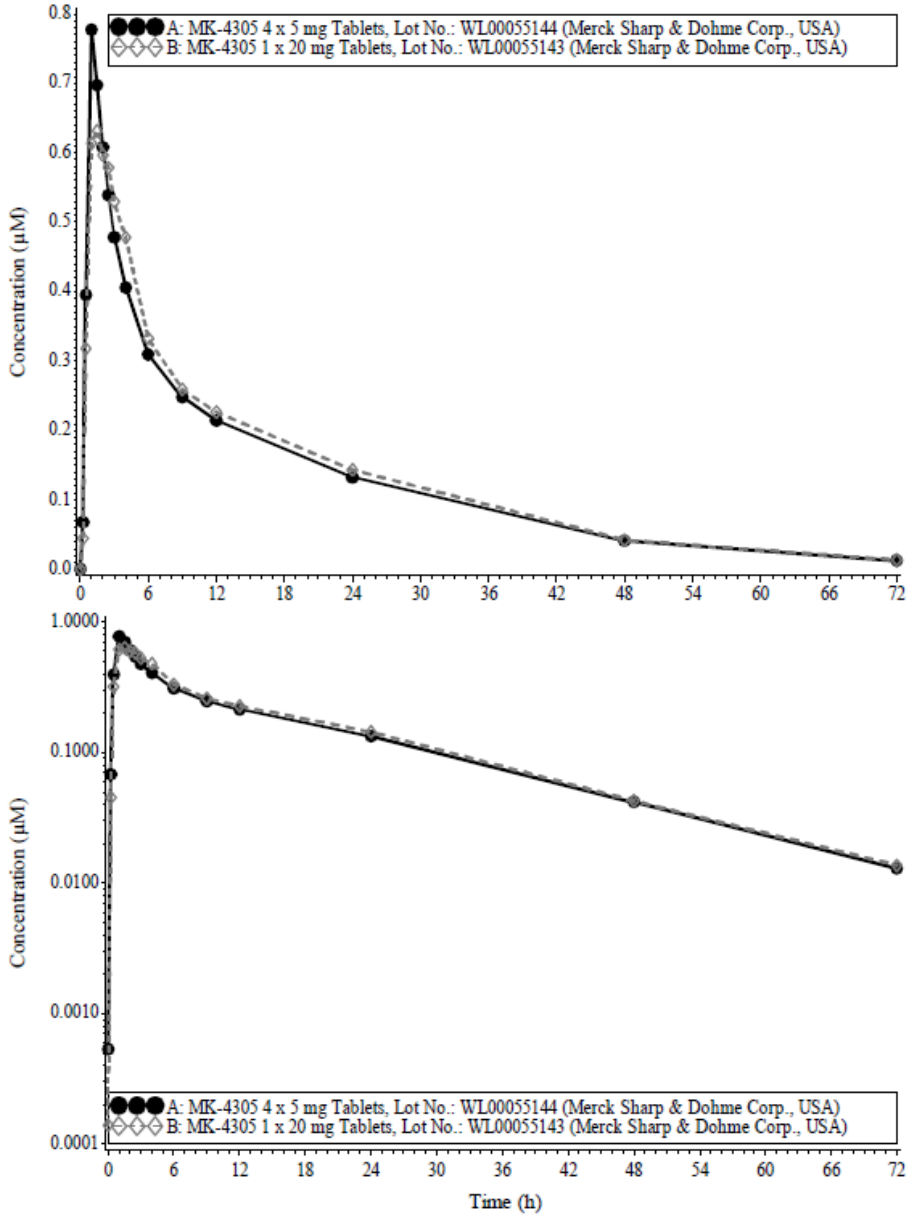
Treatment A: MK-4305 4 x 5 mg Tablets, Lot No.: WL00055144 (Merck Sharp & Dohme Corp., USA)
Treatment B: MK-4305 1 x 20 mg Tablet, Lot No.: WL00055143 (Merck Sharp & Dohme Corp., USA)

Individual Subject Ratios, GMR and the 90% CI for MK-4305 (Suvorexant) Contrast A vs. B



Treatment A: MK-4305 4 x 5 mg Tablets, Lot No.: WL00055144 (Merck Sharp & Dohme Corp., USA)
Treatment B: MK-4305 1 x 20 mg Tablet, Lot No.: WL00055143 (Merck Sharp & Dohme Corp., USA)

Mean MK-4305 (Suvorexant) Plasma Concentration-Time Profiles
A: n = 24 / B: n = 23
(top panel: linear scale / bottom panel: log-linear scale)



Safety:

No serious adverse events (AEs) were reported during the conduct of this study.
Subject 0003 was discontinued from the study prior to Period 2 due to an AE.
None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results. Somnolence was the most frequent AE as expected based on the intended pharmacology of suvorexant.

Study P056: A Study to Evaluate the Relative Bioavailability of a Suvorexant Novel Lower Dose Formulation in Healthy Subjects under Fasting Conditions

Primary objective: To evaluate the relative bioavailability between two 10 mg MK-4305 (Suvorexant) Tablets and one 20 mg Suvorexant Tablet after a single-dose in healthy subjects under fasting conditions

Study Design	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study*
Study Population	Healthy male (20) and female (16) subjects from 18 to 55 years of age, with a BMI from 18.5 to 30.0 kg/m^2
Treatment Groups	In each period, subjects received one of the following two treatments: Treatment A Test Product: two 10 mg tablets Treatment B Reference Product: one 20 mg tablet
Dose and Administration	Treatment A (two 10 mg) or B (one 20 mg tablet) were administered after an overnight fast of at least 10 hours with 240 mL of water. The washout between drug administrations for each subject was 5 days (± 3 hours).
PK Sampling: plasma	In each period 15 samples were collected prior to dosing (0-hour) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 48 and 72 hours after drug administration.
Analysis	LC-MS/MS method for suvorexant Calibration Range: 1.00 to 1000.00 ng/mL
PK Assessment	Suvorexant AUC_{0-t}, AUC_{inf}, C_{max}, T_{max} and $t_{1/2}$
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry
PD Assessment	None

* Subjects were randomly assigned to one treatment sequence:

	Treatment	
Sequence	Period 1	Period 2
AB	A	B
BA	B	A

Bioanalytical Assay:
Plasma concentrations of suvorexant were determined using a validated LC-MS/MS method (method DM-909). This method was developed and validated by Merck Research Laboratories and was later transferred and validated (b) (4) (for details, see Section 2.6 of the Clinical Pharmacology NDA 204569 Review in DARTTS, Apr 30, 2013).

The performance of the assay during the analysis of the samples from study P056 was acceptable, see table below.

Assay performance

Analyte			Suvorexant (MK-4305)	
Method:			HPLC/MS/MS	
Standard Curve:	Range:		1.00 to 1000.00 ng/mL	
	R^2:		>0.998	
	Precision:		≤ 3.5%	
	Accuracy:		≤ |1.8|%	
LOQ:			1.00 ng/mL	
QC:		3 ng/mL	150 ng/mL	750 ng/mL
	Precision:	3.3%	2.5%	2.4%
	Accuracy:	-0.3%	-3.0%	-2.9%

Comment: The bioanalytical method was found acceptable, with inter-day and intra-day accuracy and precision being <15%.

Pharmacokinetic Results:

Subjects 0016 and 0017 were discontinued due to illicit drug use prior to Period 2 dosing. In addition, Subject 0014 missed the 72-hour sample collection in Period 1 (Treatment A). According to the protocol, all available data from Subjects 0014 Period 1 (Treatment A), 0016 Period 1 (Treatment A), 0017 Period 1 (Treatment B) were included in the PK analyses.

Subject 0025 missed the 48-hour sample collection in Period 2 (Treatment A). In addition, Subject 0025 did not have a quantifiable suvorexant concentration at 72 hours in either period. Consequently, the missed sample for Subject 0025 led to PK parameters being evaluated over truncated sampling intervals in both study periods: 0 to 48 in Period 1 and 0 to 24 in Period 2.

However, the estimated $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and t½ were similar between the study periods for Subjects 0014 and 0025. In addition, based upon table below, the percentage extrapolation was still <20%. Therefore, 35 subjects were included in the PK dataset for Treatment A and 35 subjects were included in the PK dataset for Treatment B.

Between-Period Comparison of Selected Parameters for Subjects 0014 and 0025

Sbj	*Seq*	*Per*	$AUC_{0\text{-last}}$ (hr·µM)	$AUC_{0\text{-inf}}$ (hr·µM)	$AUC_{0\text{-last}}/AUC_{0\text{-inf}}$ (%)	$t_{½}$ (hr)	*LQCT* (hr)
14	**AB**	**1**	16.0	19.7	81.3	20.8	***47.2***
14	**AB**	**2**	15.8	16.6	95.2	17.4	71.8
Ratio Period 1 /Period 2			***1.01***	***1.19***	***0.85***	***1.20***	
25	**BA**	**2**	6.78	8.00	84.8	9.09	***24.0***
25	**BA**	**1**	6.72	6.86	98.0	8.62	47.6
Ratio Period 2 /Period 1			***1.01***	***1.17***	***0.87***	***1.05***	

None of the subjects had pre-dose concentrations greater than 5% of their respective C_{max} in a given period and no subjects experienced emesis within 4 hours of drug administration.

The pharmacokinetics of suvorexant following single-dose administration of two 10 mg tablets and one 20 mg tablet were similar, as assessed by $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}. Although not pre-specified, the 90% confidence interval of the GMR of these parameters lie within the BE interval of 80.00-125.00%.

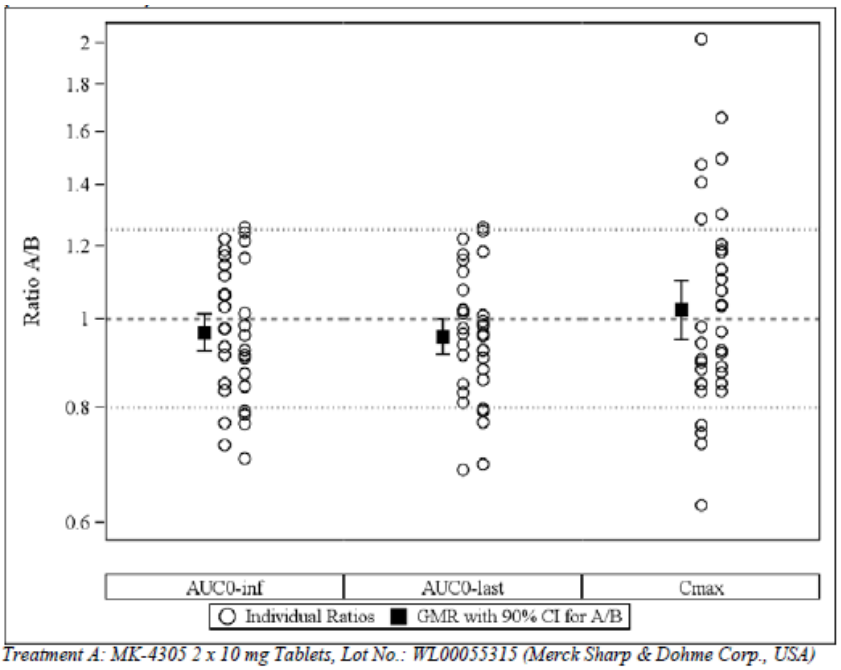
Suvorexant PK Parameters

Based on Measured Plasma MK-4305 (Suvorexant) Concentrations

Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
$AUC_{0\text{-last}}$	**A**	35	7.09	5.95 - 8.45	**A vs B**	95.71	91.54 - 100.06	10.8
(hr·µM)	**B**	35	7.41	6.25 - 8.78		-	-	-
$AUC_{0\text{-inf}}$	**A**	35	7.36	6.14 - 8.82	**A vs B**	96.65	92.23 - 101.29	11.4
(hr·µM)	**B**	35	7.61	6.40 - 9.05		-	-	-
C_{max}	**A**	35	0.697	0.628 - 0.773	**A vs B**	102.28	94.97 - 110.15	18.1
(µM)	**B**	35	0.681	0.605 - 0.767		-	-	-
			Median	*Range*				
T_{max}	**A**	35	1.00	0.50- 3.00				
(h)	**B**	35	1.50	0.50- 4.00				
			GM	*CV(%)***				
$t_{½}$	**A**	35	11.5	38.3				
(h)	**B**	35	11.5	35.7				

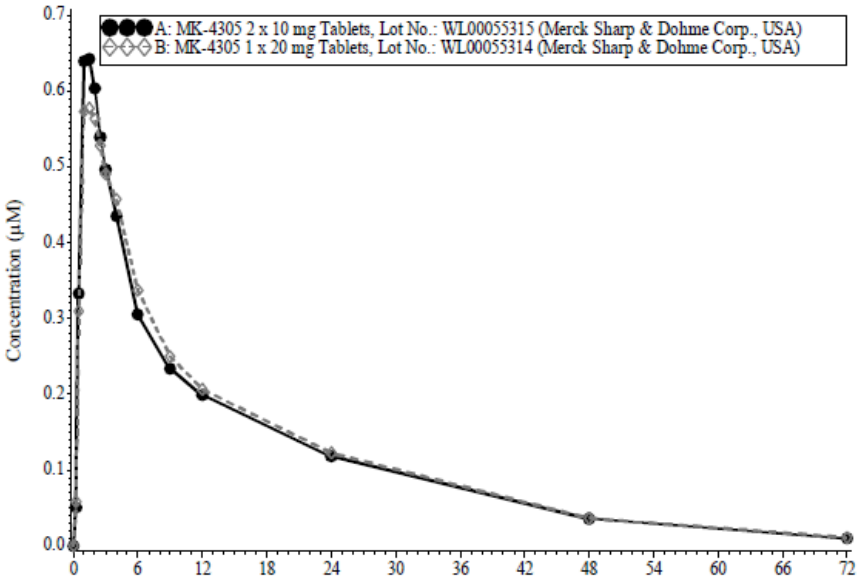
** Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$*
*** $CV(\%) = 100*sqrt(exp(s^2)-1)$, where s^2 is the observed between-subjects variance on the natural log-scale.*
Treatment A: MK-4305 2 x 10 mg Tablets, Lot No.: WL00055315 (Merck Sharp & Dohme Corp., USA)
Treatment B: MK-4305 1 x 20 mg Tablets, Lot No.: WL00055314 (Merck Sharp & Dohme Corp., USA)

Individual Subject Ratios, GMR and the 90% CI for MK-4305 (Suvorexant) Contrast A vs. B



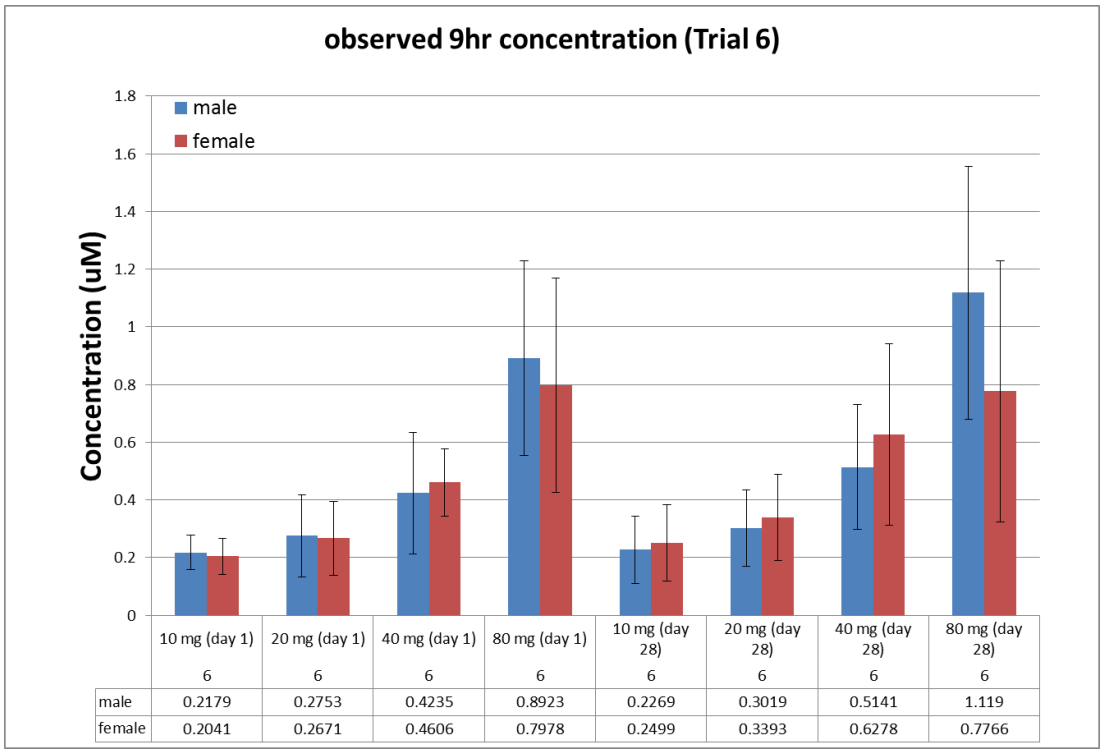
Treatment A: MK-4305 2 x 10 mg Tablets, Lot No.: WL00055315 (Merck Sharp & Dohme Corp., USA)
Treatment B: MK-4305 1 x 20 mg Tablets, Lot No.: WL00055314 (Merck Sharp & Dohme Corp., USA)

Mean MK-4305 (Suvorexant) Plasma Concentration-Time Profiles
A: n = 35 / B: n = 35 (linear scale)

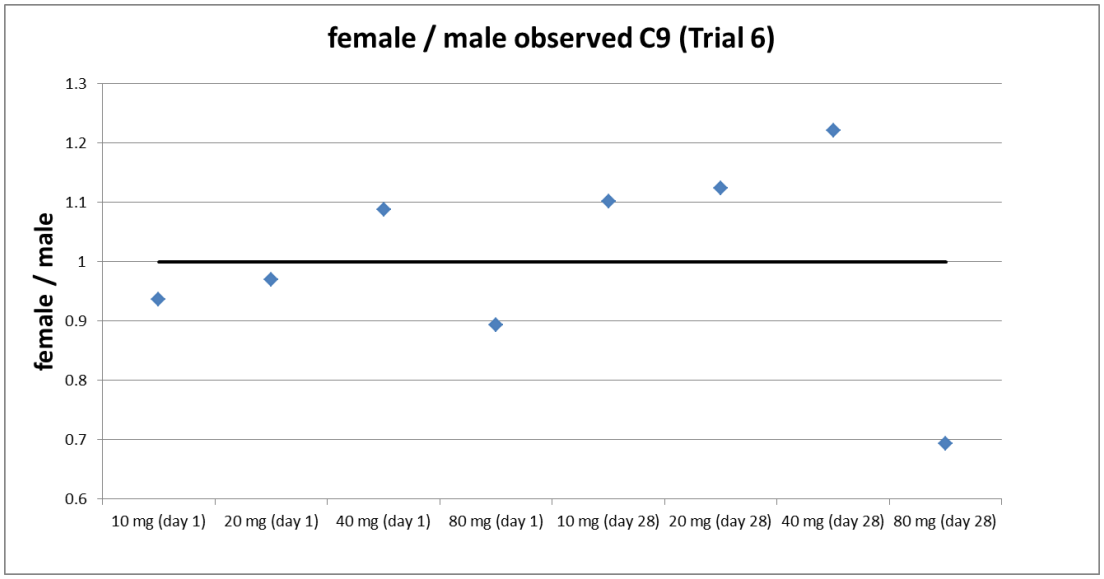


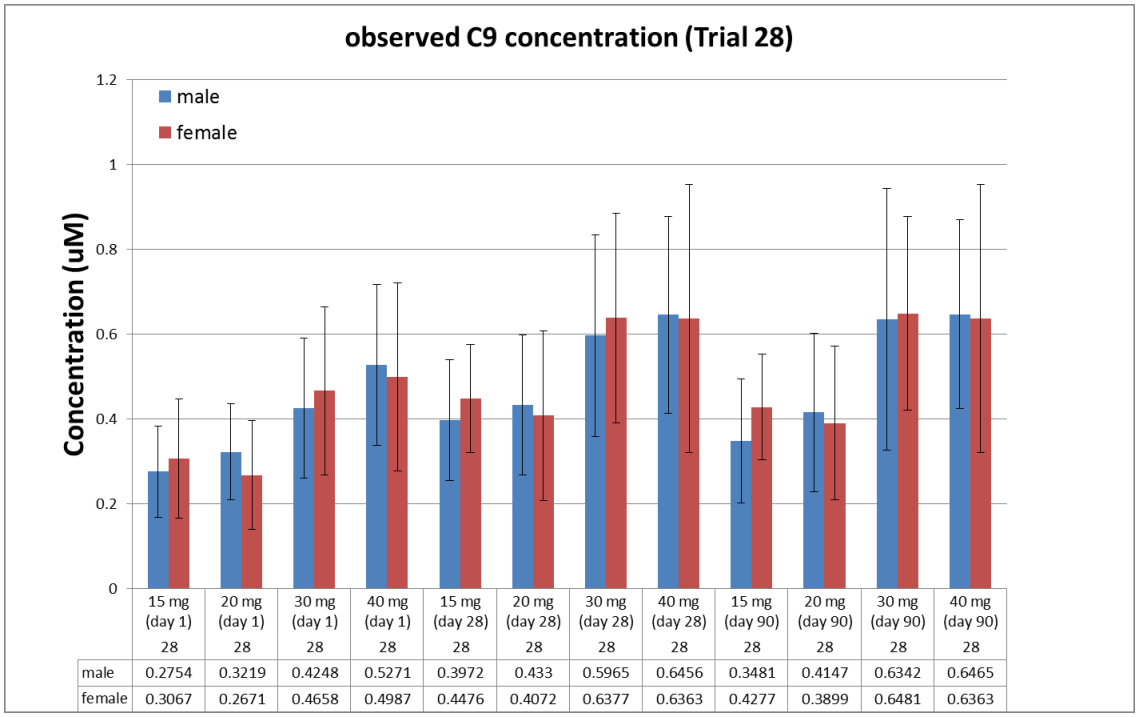
Safety Results:
No subjects were discontinued due to adverse events (AEs). No serious AEs were reported during the conduct of this study. Somnolence was the most frequent AE as expected based on the intended pharmacology.

An additional analysis was conducted by pharmacometrics (Dr. Satjit Brar) to justify the labeling change proposed by the sponsor about the effect of gender on suvorexant average concentration 9 hours after dosing (C9), see Special Populations Rationale on page 15. The analysis demonstrated that there is no conclusive difference in C9 between male and female patients in the Phase 2 (Trial 6) and the two Phase 3 trials (Trials 28 and 29).
Therefore, the labeling change proposed by the sponsor was accepted.

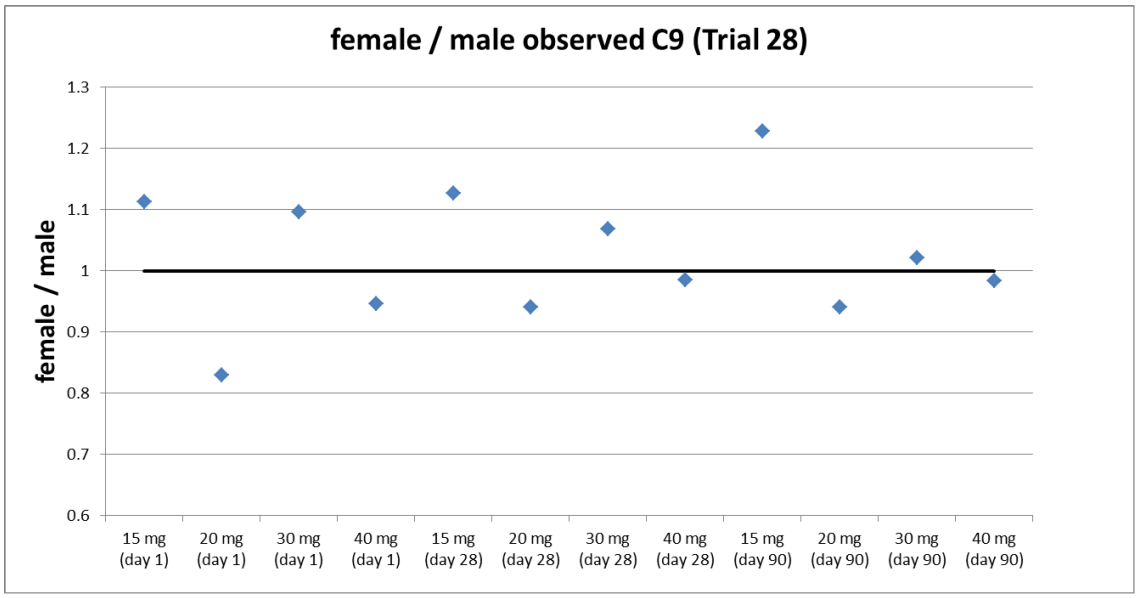


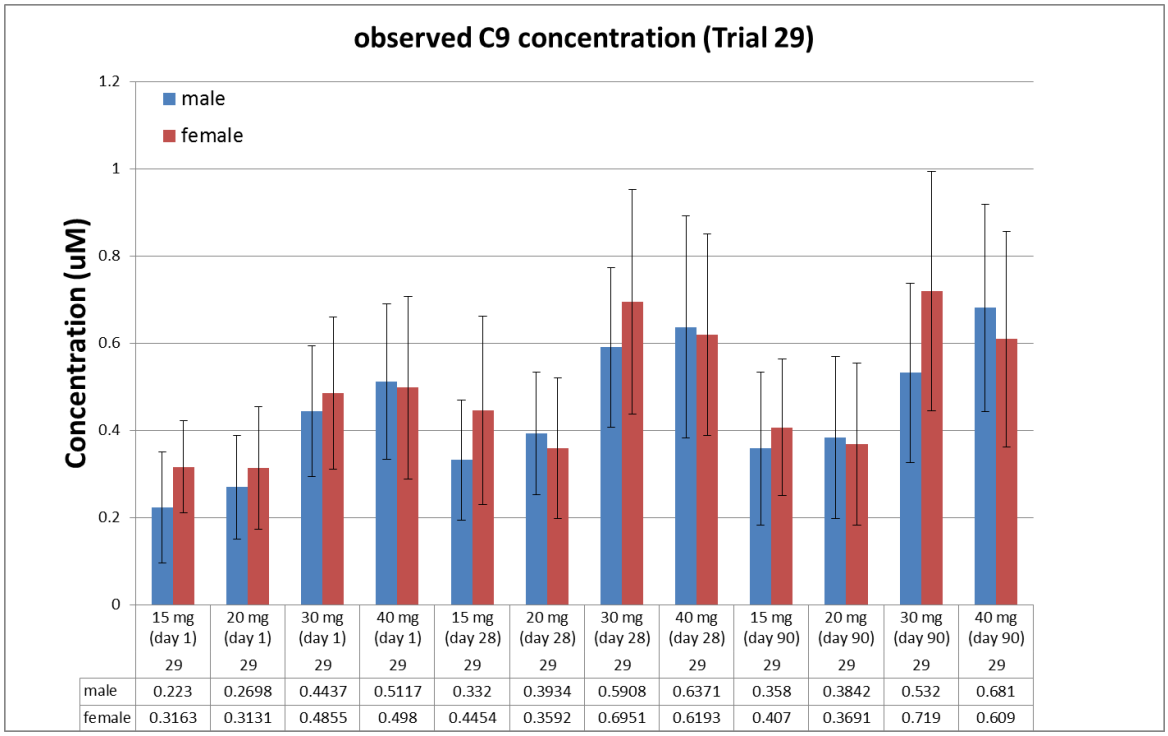
	10 mg (day 1)	20 mg (day 1)	40 mg (day 1)	80 mg (day 1)	10 mg (day 28)	20 mg (day 28)	40 mg (day 28)	80 mg (day 28)
	6	6	6	6	6	6	6	6
male	0.2179	0.2753	0.4235	0.8923	0.2269	0.3019	0.5141	1.119
female	0.2041	0.2671	0.4606	0.7978	0.2499	0.3393	0.6278	0.7766



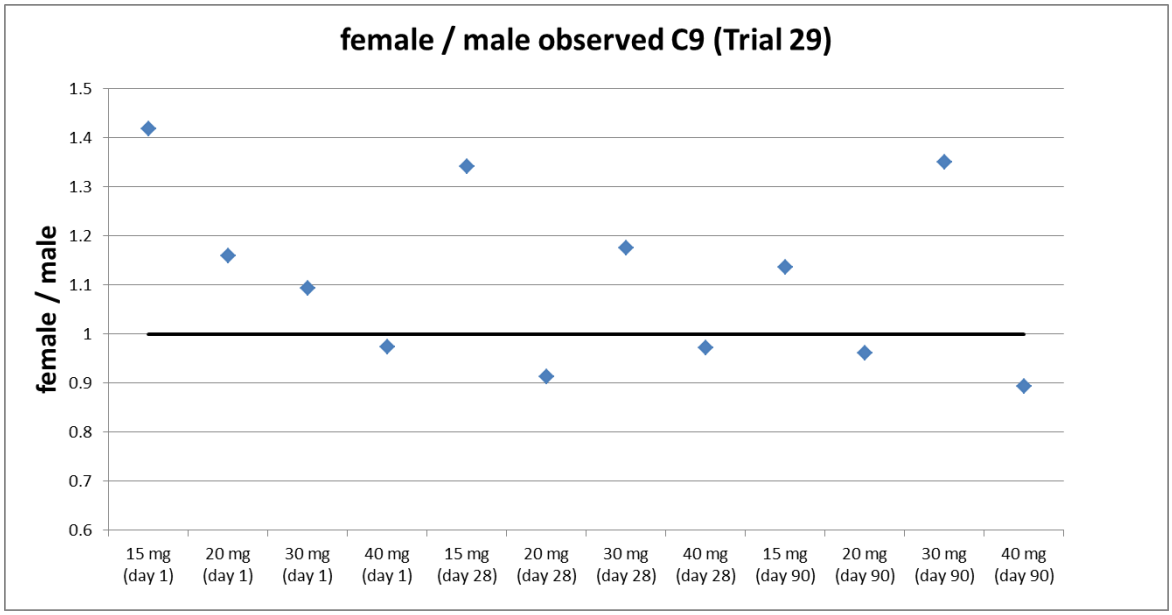


	15 mg (day 1)	20 mg (day 1)	30 mg (day 1)	40 mg (day 1)	15 mg (day 28)	20 mg (day 28)	30 mg (day 28)	40 mg (day 28)	15 mg (day 90)	20 mg (day 90)	30 mg (day 90)	40 mg (day 90)
	28	28	28	28	28	28	28	28	28	28	28	28
male	0.2754	0.3219	0.4248	0.5271	0.3972	0.433	0.5965	0.6456	0.3481	0.4147	0.6342	0.6465
female	0.3067	0.2671	0.4658	0.4987	0.4476	0.4072	0.6377	0.6363	0.4277	0.3899	0.6481	0.6363





	15 mg (day 1)	20 mg (day 1)	30 mg (day 1)	40 mg (day 1)	15 mg (day 28)	20 mg (day 28)	30 mg (day 28)	40 mg (day 28)	15 mg (day 90)	20 mg (day 90)	30 mg (day 90)	40 mg (day 90)
	29	29	29	29	29	29	29	29	29	29	29	29
male	0.223	0.2698	0.4437	0.5117	0.332	0.3934	0.5908	0.6371	0.358	0.3842	0.532	0.681
female	0.3163	0.3131	0.4855	0.498	0.4454	0.3592	0.6951	0.6193	0.407	0.3691	0.719	0.609



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/s/

HRISTINA DIMOVA
06/25/2014

SATJIT S BRAR
06/25/2014

YUXIN MEN
06/26/2014

ONDQA BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-569, Resubmission	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DNP		
Applicant:	Merck Sharp & Dohme Corp.	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D	
Trade Name:	(b) (4) Tablets	**Acting Biopharmaceutics Supervisor:** Richard Lostritto, Ph.D	
Generic Name:	Suvorexant Film-Coated IR Tablets	**Date Assigned:**	Feb 15, 2014
Indication:	Treatment of Insomnia	**Date of Review:**	June 23, 2014
Formulation/strength	Immediate Release Tablet/5 mg, and 10 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**Desired Completion Date**
Feb 15, 2014 May 30, 2014	Feb 15, 2014	June 25, 2014
Type of Submission:	Resubmission	
Biopharmaceutics Review Focus:	• Dissolution method and acceptance criterion • Dissolution data supporting the biowaiver request for the 5 mg and 10 mg tablets	

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Background

Suvorexant (MK-4305), an orexin receptor antagonist, is being proposed for the treatment of insomnia. NDA 204-569 for suvorexant was originally submitted on Aug 30, 2012. The NDA was found acceptable from biopharmaceutics perspective[1]; however, a CR letter was issued on June 28, 2013 due to safety concerns. In the CR letter, the FDA stated that the 10 mg tablet strength must be available at the time of approval as the starting dose and that the 5 mg tablet strength is needed for patients expected to have significantly higher plasma levels of suvorexant (e.g., patients taking concomitant CYP3A4 inhibitors).

CURRENT SUBMISSION

This resubmission to NDA 204569 contains the Applicant's responses to the deficiencies outlined in the FDA's CR letter dated June 28, 2013, following review of the initial NDA submission of August 30, 2012.

In response to the FDA's recommendation, the 30 mg and 40 mg strengths are no longer being planned for marketing. Therefore, in the current resubmission, the Applicant is seeking approval of the 5 mg and 10 mg strengths of Suvorexant IR tablets. The following information was included to support the approval of these two lower strengths:

- Side by side comparison of the formulations (components and composition)
- Dissolution profile comparisons in the QC media for two additional batches per strength
- In vivo dose-proportionality which included the two strengths under review. This study is being reviewed by OCP.

[1] Biopharmaceutics review for NDA 204569 original submission entered in DARRTS by Sandra Suarez on Sep 2012.

The Biopharmaceutics review is focused on the review of the following:

1. Dissolution data supporting the proposed dissolution method
2. Acceptance of the proposed dissolution acceptance criterion
3. Additional dissolution profile comparisons

1. Dissolution Method and Acceptance Criterion:

The following method and acceptance criterion are been proposed for the 5 and 10 mg strengths for QC purposes:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	75 rpm	900mL QLA sinker	37°C	0.4% SDS in water	Q = (b) (4) in 30 min

The dissolution method (b) (4) is acceptable. The method showed good discriminating ability towards several critical process parameters. In a teleconference held on May 28, 2014, the Applicant agreed to revise the dissolution acceptance criterion to ***Q***= (b) (4) ***in 30 min*** and submit further justification to support it. The data submitted on June 30, 2014, further support the implementation of the recommended dissolution acceptance criterion for both strengths. (b) (4) It is noted that the setting of this criterion was based on data linking the in vitro dissolution data to in vivo PK data[1].

2. Dissolution Profile Comparisons

In response to the FDA's requests sent on Dec 2013, the Applicant provided dissolution profiles comparison for two additional batches per strength. The *f2* similarity values for all the batches and strengths were higher than 50, indicating that the lower strengths and the higher strengths have proportional in vitro and in vivo performance.

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed the resubmission to NDA 204-469 and its amendments submitted on Feb 15, 2014 and June 6, 2014. The dissolution data and additional information provided in all these submissions support the approval of 5 and 10 mg strengths.

The following dissolution method and acceptance criterion for the 5 mg and 10 mg the strengths of Suvorexant IR Tablets are acceptable and have agreed upon with the Applicant (refer to submission dated May 30, 2014):

USP Apparatus	Paddle Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	75 rpm	900mL QLA sinker	37°C	0.4% SDS in water	Q = (b) (4) in 30 min

From Biopharmaceutics perspective, the resubmission to NDA 204-469 is recommended for APPROVAL.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. RLostritto

BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Suvorexant, also known as MK-4305 is a New Molecular Entity (NME). It is an orally active, potent, and reversible orexin receptor antagonist (ORA) and is anticipated to be the first in class ORA for the treatment of patients with insomnia. A CR letter was issued on June 28, 2013 due to safety concerns. In the CR letter, FDA stated that the 10 mg tablet strength must be available at time of approval as the starting dose and that the 5 mg tablet strength is needed for patients expected to have significantly higher plasma levels of suvorexant (e.g., patients taking concomitant CYP3A4 inhibitors).

Merck submitted to FDA a proposal for the development of the lower strengths, which was discussed on June 19, 2013. The Applicant described their plans to develop 5 mg and 10 mg tablets (b) (4) and based on available CMC data on the 15 mg, 20 mg, 30 mg and 40 mg tablets, the Applicant anticipated that information pertaining to manufacture and control of the 5 mg and 10 mg strengths including in vitro dissolution and stability data would support review and approval of these lower dose strengths, without additional clinical data.

PREVIOUS COMMUNICATIONS BETWEEN APPLICANT and FDA

Meeting: The meeting package dated Aug 15, 2013 included several Biopharmaceutics questions and the following comments were conveyed to the Sponsor on Sep 25, 2013:

1. The approved dissolution method for the higher strengths is appropriate for the lower strengths provided that the following is met:
    - The dissolution profiles for the 5 mg and 10 mg strengths do not differ significantly from the higher strengths in such a way that the discriminating ability is lost.

      (b) (4)
    - The dissolution acceptance criterion for these strengths should be set based on the performance of the registration/commercial/ stability batches and may not be the same as that approved for higher strengths

2. We remind you that if you are not planning on doing any dose proportionality studies to support the approval of these strengths, a biowaiver request of the BA studies should be included in the NDA submission. The biowaiver will be granted if the following requirement are met:

    - The proposed lower and higher strengths of your product have the same dosage form;

      (b) (4)
    - The lower and highest strength products have the same manufacturing process; and

- Dissolution profile comparisons between the higher and lower strengths in three different media meet the f2 similarity requirements.

Teleconference: On a teleconference dated Sep 27, 2013, the FDA clarified that the approved IVIVC cannot not be used as a surrogate for BA/BE given that it was a Level C correlation which only took into consideration Cmax. Under these conditions, the correlation could only be used to support the drug product specification ranges for some attributes (b) (4) Therefore, the approval of the lower strengths should be based on a dose- proportionally study. Alternatively, this study could be waived if the requirements stated in the submitted preliminary comments (as listed on the background section) are met. FDA suggested that if *f2* testing fails, the Applicant may consider relying on in vivo data to justify/support the approval of these strengths in such a way that if dissolution of the new strengths (5 mg and 10 mg) using the QC method is demonstrated to be within the bounds established from pivotal clinical studies (e.g. 15 mg data from Protocol 051), a new PK study may not be required.

Submission: On a submission dated Oct 28, 2013, the Applicant included dissolution profiles comparisons with similarity testing (*f2* and multivariate) in three different media as well as formulation information in support of the biowaiver of the BA/BE studies for the 5 mg and 10 mg strengths. The reviewer[2] concluded that the data submitted support the claim of 5 mg, 10 mg and 15 mg being dose proportional.

The submission package included the following questions which were conveyed to the Applicant after a submission received in which the Applicant proposed to conduct an in vivo dose-proportionality study:

> **Question 1:** Does Agency agree that the similarity observed in the dissolution data for 10 mg and the available clinical experience supports a biowaiver of additional clinical characterization for the 10 mg strength?
>
> **Response:**
> Yes, we agree.
>
> **Question 2:** Does Agency agree that the similarity observed in the dissolution data for 5 mg and the available clinical experience supports a biowaiver of additional clinical characterization for the 5 mg strength?
>
> **Response:**
> Yes, we agree.
>
> **Additional Comment to be conveyed to the Applicant:**
> Provide dissolution profile comparisons for two additional batches per strength at the time of NDA resubmission.

[2] Biopharmaceutics Review entered in DARRTS by Dr. Suarez on Nov 2013.

APPROVED DISSOLUTION METHOD AND ACCEPTANCE CRITERION

The following dissolution method and acceptance criterion was approved as a QC method for the 15 mg, 20 mg, 30 mg and 40 mg strengths of Suvorexant IR, tablets[1]:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	75 rpm	900mL QLA sinker	37°C	0.4% SDS in water	Q = (b) (4) in 30 min

DRUG PRODUCT

The components and composition of Suvorexant IR tablets are summarized in Table 1.

Table 1. SUVOREXANT TABLETS COMPOSITION

Components	Quality Reference	Function	(b) (4)	Amount per Tablet (mg) 5 mg	Amount per Tablet (mg) 10 mg
					(b) (4)
Suvorexant (MK-4305)	----	Active	(b) (4)	5.00	10.00
Polyvinylpyrrolidone/Vinyl Acetate Copolymer (Copovidone)	USP-NF, Ph. Eur., JPE				(b) (4)
Lactose Monohydrate	USP-NF, Ph. Eur., JP				
Microcrystalline Cellulose	USP-NF, Ph. Eur., JP				
Croscarmellose Sodium	USP-NF, Ph. Eur., JP				
Magnesium Stearate (b) (4) (b) (4)	USP-NF, Ph. Eur., JP				
					(b) (4)
Total Tablet Weight				66.4‖	130.9‖

Current NDA Resubmission

The current resubmission contains the following information supporting the approval of the 5 mg and 10 mg strengths:

1. (b) (4) [redacted] (b) (4)

Reviewer's Comments

This Reviewer agrees with the Applicant's statement (b) (4) [redacted]

2. Manufacturing processes

According to the Applicant, the manufacturing process for the 5 mg and 10 mg tablets is considered identical to the 15, 20, 30, and 40 mg strengths. (b) (4) [redacted] This information needs to be qualified by the CMC reviewer and it will be a review issue.

3. Dissolution Profile Comparisons

In response to the FDA's request submitted on Dec 18, 2013, dissolution profiles for two additional batches each of 5 mg and 10 mg potencies with the filed QC dissolution method were compared to dissolution profiles from 15 mg MK- 4305 tablets (WL00036691) used in pivotal clinical studies PN028/P029 (phase III studies) and 15 mg tablets (WL00041508) used in PN051 (comparative bioavailability study between 2x15 mg vs. 30 mg and 2x20 mg vs. 40 mg).

Figure 1 shows that the dissolution profiles of the proposed new 5 mg tablets of lots WL00053437 and WL00053438 in the QC release method were found to be identical to the 15 mg tablet dissolution for the batch tested in PN051 as all lots show dissolution (b) (4) [redacted] Similarly, Figure 2 shows the dissolution profiles of the proposed 10 mg tablets of lots WL00053282 and WL00053284 in the QC method were found to be similar to the dissolution profile of 15 mg tablet lot used in PN028/029. The f2 similarity factors were 89 and 92 respectively.

Figure 1. Average Dissolution Profile in QC Method: USP II, 0.4% SDS in USP Water, 75 rpm for 5 mg tablets WL00053437, WL00053438, WL00053439 and 15 mg tablet WL00041508.

Figure 2. Average Dissolution Profile in QC Method: USP II, 0.4% SDS in USP Water, 75 rpm for 10 mg tablets WL00053437, WL00053438, WL00053439 and 15 mg tablet WL00041508.

Conclusion

The dissolution data submitted on Oct 28, 2013 and additional information provided in the present submission support the approval of the 5 and 10 mg.

Dissolution Method and Acceptance Criterion for the New Strengths

The following method and acceptance criterion were originally proposed for QC purpose for the two 5 and 10 mg new strengths:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	75 rpm	900mL QLA sinker	37°C	0.4% SDS in water	Q = (b) (4) in 30 min

The dissolution method (b) (4) is acceptable. The method showed to have good discriminating ability towards several critical process parameters.

In a teleconference dated May 28, 2014, the FDA communicated the Applicant the need to tighten the acceptance criterion to Q= (b) (4) This original recommendation was based on data (b) (4) The Applicant proposed to consider the criterion to Q= (b) (4) in 30 min (b) (4) The FDA agreed with the proposal and requested the Applicant to submit their proposal in writing with supporting information. The data submitted on May 30, 2014, further support the implementation of the recommended dissolution acceptance criterion for both strengths. The data summarized on Table 2 shows that the 5 mg and 10 mg tablets were BE to the 20 mg tablet (b) (4) This criterion was also set based on data linking in vitro dissolution to in vivo PK data[1].

Table 2. Bioequivalence assessment for PN055/PN056.

	AUC 0-last	AUC 0-inf.	Cmax
4x5mg (n=24) vs 1x20mg (n=23)	96.13% (90.65% - 101.93%)	96.13% (90.53%- 102.08%)	106.83 % (99.14 – 115.12%)
2x10mg (n=35) vs 1x20mg (n=35)	95.71% (91.54% - 100.06%)	96.65% (92.23% - 101.29%)	102.28% (94.97%- 110.15%)

Figure 3. Dissolution Profile of 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg tablets from Registration Stability Batches and PK batches. Data taken from the Aug 13, 2013 correspondence.

Conclusion and Recommendation

The dissolution data and additional information provided in the present resubmission support the approval of 5 and 10 mg strengths. The resubmission of NDA 204-569 is recommended for approval from the Biopharmaceutics perspective.

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/s/

SANDRA SUAREZ
06/23/2014

ANGELICA DORANTES
06/23/2014

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 204569
End of Review Conference Type A
Sponsor: Merck & Co., Inc.
Drug: Suvorexant
Formulation: Tablets (15, 20, 30, 40 mg)
Indication: Insomnia
Submission Date: Aug 21, 2013
Internal Meeting Date: Sept 20, 2013
Sponsor Meeting Date: Sept 27, 2013
Reviewer: Hristina Dimova, Ph.D.
Team Leader: Angela Men, M.D., Ph.D.

1. Background

A New Drug Application (NDA) was submitted to the FDA on August 30, 2012 for treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. A review of the suvorexant efficacy and safety data was completed by the Peripheral and Central Nervous System (PCNS) Drug Advisory Committee Meeting (ACM) on May 22, 2013. On June 28, 2013, the FDA issued a Complete Response Letter, stating that the application cannot be approved in its present form and requested the following:

- 10 mg tablet must be available at time of approval as the starting dose and manufacturing data is need to support the application
- For patients expected to have significantly higher plasma levels of suvorexant (e.g. patients taking concomitant CYP3A4 inhibitors), a 5 mg tablet strength is needed.
- A safety update is required in the resubmission to include all data from nonclinical and clinical studies/trials under consideration, regardless of indication, dosage form, or dose level.

The objectives of the meeting are to obtain input and agreement on the Sponsor's plan to address the deficiencies in the Complete Response Letter.

2. Development Plans

The sponsor proposes a series of plans (not in question format) for the clinical and non-clinical sections of the re-submission.

[redacted]

Reviewer's Comments: Need to update [redacted] if available at the time of the NDA submission. Include [redacted] if available.

[redacted]

Reviewer's Comments: The sponsor needs to include [redacted] if available at the time of the NDA submission
ClinPharm has not been asked to review this protocol.

LIST OF QUESTIONS

Question 1:
Does the FDA confirm that the proposed development plan and data package including in vitro dissolution and stability are sufficient to support review and approval of the 5 mg and 10 mg tablets?

Internal Meeting Discussion:
According to sponsor, [redacted] no clinical BE studies are needed. However, the waiver for clinical BE studies needs to be supported by suvorexant dose proportionality in the approved dose range (5 mg -20 mg). While suvorexant pharmacokinetics are less than dose proportional over the 10 to 80-mg range (likely due to absorption limitations with increasing doses), this seems to apply to higher than 30 mg suvorexant doses. The relative bioavailability is predicted to be 83.9%, 98.4%, 69.9%, and 52.0% for 20-mg, 30-mg, 40-mg, and 60/80 in relation to a 10-mg suvorexant oral dose, which is set as a reference (100% BA). Therefore, it is unlikely that there could be any dose proportionality issues for the 5 -20 mg range.

FDA (CMC and ONDQA) Preliminary Response:
The proposed development plan and data package for 5 mg and 10 mg suvorexant tablets [redacted] is consistent with the proposal for 10 mg tablets discussed in the June 19, 2013, teleconference between Merck and FDA

representatives. We agree that our previous agreement regarding the development plan and data package for the 10 mg tablet will extend to [redacted] 5 mg tablet. The adequacy of the data to support approval will be a matter for review.

Clinical Pharmacology Related Meeting Discussion:
If an additional *in vivo* PK evaluation (at the doses of 5 and 10 mg) is needed, the dose proportionality of suvorexant in the dose range 5 to 20 mg can be assessed using a power model.

Question 2:
If development of a 5 mg tablet requires additional formulation development (incurring a significant delay compared to the 10 mg tablet) and differs from the other dose strengths (10 mg, 15 mg, and 20 mg), [redacted] then Merck would propose to provide a resubmission that would include data supporting only the new 10 mg tablet and appropriate precautionary labeling around use with moderate CYP3A inhibitors. Merck would also commit to a post approval submission of data supporting the 5 mg tablet.

a. Does FDA agree that suvorexant can be approved with the 10 mg dose strength with appropriate label restrictions (e.g. statement that moderate CYP3A inhibitors are not recommended, as with the strong CYP3A inhibitors) [see Section 5.1.2] until a 5 mg dose strength is available for those receiving concomitant moderate CYP3A inhibitors?

Clinical Pharmacology Preliminary Response:
This is acceptable.

b. Does FDA agree with Merck's proposal to commit to a subsequent post-approval submission of data supporting the 5 mg tablet together with revised labeling in support of approval of the 5 mg tablet?

Clinical Pharmacology Preliminary Response:
Yes, see response to 2a.

Question 3:
[redacted]

a. Does the Agency agree that [redacted] can be provided in the submission [redacted]?

Clinical Pharmacology Preliminary Response:
You will need to provide [redacted] if available at the time of the NDA submission and include [redacted] if available. No need to update the [redacted] information (summary tables, etc.) in CTD Module 2.7.2.

b. Does FDA agree that revisions to the clinical CTD sections (Module 2.5, 2.7.1-2.7.4 and integrated safety summaries) will not be required in the resubmission?

FDA Preliminary Response:
Yes.

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/s/

HRISTINA DIMOVA
10/17/2013

YUXIN MEN
01/02/2014

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 204569
Protocol and Quality Submissions
Sponsor: Merck & Co., Inc.
Drug: Suvorexant
Formulation: Tablets (15, 20, 30, 40 mg)
Indication: Insomnia
Submission Dates: Oct 22 and Oct 28, 2013
Internal Meeting Date: Dec 18, 2013
Reviewer: Hristina Dimova, Ph.D.
Team Leader: Angela Men, M.D., Ph.D.

Background
A New Drug Application (NDA 204569) was submitted to the U.S. FDA on August 30, 2012 for treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. FDA issued a Complete Response Letter on June 28, 2013. FDA stated that 10 mg tablet strength must be available at time of approval as the starting dose and that 5 mg tablet strength is needed for patients expected to have significantly higher plasma levels of suvorexant (e.g., patients taking concomitant CYP3A4 inhibitors).
An End of Review Conference Type A meeting with FDA was held on September 27, 2013 to discuss the suvorexant NDA resubmission plans. The Agency confirmed that the proposed quality development plan and data package for 5 mg and 10 mg suvorexant tablets (b) (4) is consistent with the proposal for 10 mg tablets discussed in the June 19, 2013, teleconference between Merck and FDA representatives. At the End of Review Conference, FDA also clarified that based on current CFR, f2 multimedia comparisons are needed to demonstrate dissolution similarity in multimedia for a biowaiver. However, if f2 testing fails, the sponsor may need to rely on in vivo data to justify/support the approval of the new strengths (5 mg and 10 mg). In addition, the agency clarified that the dose proportionality of suvorexant could be addressed by either applying the bioequivalence or the power model approaches.

Current Submissions:

Oct 22, 2013 Submission
PK protocol p055 "A Study to Evaluate the Relative Bioavailability of a Suvorexant Low Dose Formulation in Healthy Subjects under Fasting Conditions"
Objective: To evaluate the relative bioavailability of four suvorexant 5mg tablets and one suvorexant 20mg tablet after single dose administration in healthy subjects under fasting conditions
Study design: Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, relative bioavailability study
Study Population: Twenty-four healthy, non-smoking, male and female subjects, from 18 to 55 years of age
PK Sampling Schedule: Prior to dosing (0-hour) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 48 and 72 hours post-dose

Statistical Analysis
A linear mixed-effects model appropriate for this 2-period crossover design will be used to estimate the relative bioavailability of 20 mg suvorexant administered as four 5-mg tablets or one 20-mg tablet.
Individual AUCinf and Cmax values will be natural log transformed and analyzed separately in linear mixed effects models with fixed effects for treatment and period. Ninety percent (90%) confidence intervals (CI) will be constructed for the treatment differences in LS means for both endpoints. Exponentiating the log-scale 90% CIs will provide 90% CIs for the geometric mean ratios (four 5-mg tablets / one 20-mg tablet) for AUCinf and Cmax.
Comment: No criteria for comparison, e.g. (80%, 125%) bounds.

Clinical Pharmacology comment to Protocol p055:

If the sponsor chooses to use the power model approach, they need to obtain AUC and C_{max} after 5 mg and 10 mg to compare with the pooled data from their 15mg and 20mg tablets.

If the BE approach is used, the sponsor should define the criteria for comparison of the four 5mg tablets vs. one 20mg tablet, e.g:
Statistical Analysis
Log transformed AUC_{inf}, and C_{max} will be analyzed using a mixed effect model with sequence, day and treatment as fixed effects and patient within sequence as a random effect. BE will be concluded if the 90% confidence intervals for the true ratio of adjusted geometric means for both AUC_{inf}, and C_{max} fall within (80%, 125%).

In addition, the sponsor needs to have similar comparisons for the 10 mg tablet it the 10 mg is not granted bio-waiver per ONDQA (Pleases refer to their section).

Oct 28, 2013 Submission
Per the agency feedback received on 25-Sep-2013 and 16-Oct-2013, the sponsor has evaluated both in-vitro data for the 5 mg, 10 mg and 15 mg (reference) strength tablets and clinical experience. The sponsor believes there is sufficient justification to request a waiver of the CFR requirement to provide data from in vivo BA studies for the two lower strengths, 5 and 10 mg of suvorexant tablets and provides supportive information. Please refer to ONDQA review (Dr. Suarez) for detailed discussion on the supportive in vitro dissolution information. In summary, according to Dr. Suarez:
The dissolution data provided on 10/28/13 support the approval of the 5 and 10 mg strengths provided that the observed (b) (4) is not of clinical concern. Therefore, in vivo PK study may not be needed.

- The difference in dissolution profile among strengths is unlikely to results in differences in (dose adjusted) AUC since the extent of release is not being affected.

- It is likely that the C_{max} resulting from the 5 mg strength is similar to that of the 15 mg strength based on similar dissolution profiles. According to the sponsor, the administration of a moderate CYP3A inhibitor with suvorexant significantly increased suvorexant $AUC_{0-\infty}$ [GMR (90%CI): 2.05 (1.82, 2.30)]; by comparison, there was a less pronounced effect on C_{max} [1.22 (1.09, 1.36)]. Therefore, although 5 mg suvorexant co-administered with moderate CYP3A inhibitors is expected to provide a similar systemic exposure (AUC) to that following 10 mg suvorexant alone, the C_{max} would be less affected.

Clinical Pharmacology comments:
Agree with the second bullet point that C_{max} would be less affected with co-administration with moderate CYP3A inhibitors.
No in vivo PK study is needed as 1) the 5 mg tablet is being developed for dosing adjustment purpose only, and AUC is not expected to be affected (e.g. the AUC after 5 mg is expected to be ½ of that after 10 mg);
and 2) AUC correlates better with next day residual AEs (somnolence), while C_{max} correlated better with sleep induction, therefore the safety (next day somnolence) is unlikely to be affected even if C_{max} after 5 mg + moderate CYP3A inhibitor is somewhat higher than that after 10 mg suvorexant (with no CYP3A4 inhibitors).

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/s/

HRISTINA DIMOVA
12/12/2013

YUXIN MEN
12/31/2013

ONDQA BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-569	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DNP		
Applicant:	Merck Sharp & Dohme Corp.	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D	
Trade Name:	(b) (4) Tablets	**Acting Biopharmaceutics Supervisor:** Richard Lostritto, Ph.D	
Generic Name:	Suvorexant Film-Coated IR Tablets	**Date Assigned:**	Oct 28. 2013
Indication:	Treatment of Insomnia	**Date of Review:**	Dec 12, 2013
Formulation/strength	Immediate Release Tablet/5 mg, and 10 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**Desired Completion Date**
Oct 28, 2013	Oct 28, 2013	Nov 26, 2013
Type of Submission:	Correspondence	
Biopharmaceutics Review Focus:	• Dissolution data supporting the biowaiver request for the 5 mg and 10 mg tablets	

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Background

NDA 204-569 for suvorexant (MK-4305) was submitted on Aug 30, 2012. Suvorexant, an orexin receptor antagonist is being proposed for the treatment of insomnia. The original proposed dosing regimen for non-elderly adults is 40 mg once daily immediately before bed time and 30 mg once daily for elderly adults. The NDA was found acceptable from biopharmaceutics perspective[1]; however, a CR letter was issue on June 28, 2013 due to safety concerns. FDA stated that a 10 mg tablet strength must be available at time of approval as the starting dose and that a 5 mg tablet strength is needed for patients expected to have significantly higher plasma levels of suvorexant (e.g., patients taking concomitant CYP3A4 inhibitors).

Merck submitted a proposal to the Agency for development which was discussed on June 19, 2013. The Sponsor plans to develop two additional strength, 5 mg and 10 mg tablets (b) (4) and based on available CMC data on the 15 mg, 20 mg, 30 mg and 40 mg tablets, the sponsor anticipates that information pertaining to manufacture and control of the 5 mg and 10 mg strengths including in vitro dissolution and stability data will support review and approval of these lower dose strengths, without additional clinical data.

In response to the questions contained in a meeting package dated Aug 15, 2013, several comments related to the biopharmaceutics data needed to support the lower strengths were conveyed to the Sponsor on Sep 25, 2013.

On a teleconference dated Sep 27, 2013, the FDA clarified that the approved IVIVC cannot be used as a surrogate for BA/BE given that it was a Level C correlation which only took into consideration Cmax.

[1] Biopharmaceutics review for NDA 204569 original submission entered in DARRTS by Sandra Suarez on Sep 2012.

Under these conditions, the correlation could only be used to support the drug product specification ranges for some attributes (b) (4) Therefore, the approval of the lower strengths should be based on a dose- proportionally study. Alternatively, this study could be waived if the requirements stated in the submitted preliminary comments (as listed on the background section) are met. FDA suggested that if *f2* testing fails, the Applicant may consider relying on in vivo data to justify/support the approval of these strengths in such a way that if dissolution of the new strengths (5 mg and 10 mg) using the QC method is demonstrated to be within the bounds established from pivotal clinical studies (e.g. 15 mg data from Protocol 051), a new PK study may not be required.

Present Submission

In the present submission, the Applicant included dissolution profiles comparisons with similarity testing (*f2* and multivariate) in three different media as well as formulation information in support of the biowaiver of the BA/BE studies for the 5 mg and 10 mg strengths.

Review: This Biopharmaceutics review focuses on the evaluation of the acceptability of the data (dissolution profile comparisons, formulation composition proportionality) submitted to support the biowaiver of the BA/BE requirements for the 5 mg and 10 mg strengths.

Dissolution profile comparison in three different media between the 10 mg and 15 mg strengths met the *f2* similarity and multivariate criteria, (b) (4) It is noted that no statistical comparisons were provided between the 5 mg and 10 mg strengths. It is likely, based on dissolution data, that the profiles are not similar. However, the in vitro dissolution results are superseded by the results of the BE study PN051 in which BE was demonstrated between 2×15 mg vs. 30 mg and 2×20 mg vs. 40 mg tablets. Therefore, one can conclude that the 5 mg, 10 mg and 15 mg are dose proportional based on the following:

- Cmax and AUC were similar between the 15 mg vs. 30 mg and between the 20 mg vs. 40 mg strengths despite the pronounce difference in dissolution (e.g. f2 failed) suggesting that the QC dissolution method is over-discriminating.
- The dissolution profile for the 5 mg tablet is comparable to that for the 15 mg strength, which was shown to be BE to the 30 mg strength. The dissolution profile of the 10 mg strength is in between the profiles for the 15 mg and 30 mg strengths and the dissolution rate difference between the 5 mg and 10 mg strengths is smaller than that for the 15 mg vs. the 30 mg strengths, suggesting that the 5 mg and 10 mg strengths are likely to be BE.
- The difference in dissolution profile among strengths is unlikely to results in differences in AUC since the extend of release is not being affected.
- Based on similar dissolution profiles, it is likely that the Cmax resulting from the 5 mg strength is similar to that of the 15 mg strength. According to the Applicant this seems to be of no clinical relevance since although the administration of a moderate CYP3A inhibitor with suvorexant significantly increases suvorexant AUC0-∞ [GMR (90%CI): 2.05 (1.82, 2.30)]; by comparison, there is a less pronounced effect on Cmax [1.22 (1.09, 1.36)]. Therefore, the Applicant concludes that although 5 mg suvorexant co-administered with moderate CYP3A inhibitors is expected to provide a similar systemic exposure (AUC) to that following 10 mg suvorexant alone, the Cmax would be lower. During a telephone conversation, Dr. Hristina Dimova (Clinical Pharmacology Reviewer) confirmed the Applicant's statement in terms of the likelihood for lower Cmax following the administration of the 5 mg strength compared to that for the 10 mg strength.

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed the amendment to NDA 204-469 submitted on Oct 28, 2013. The dissolution data and additional information provided in the present submission support the biowaiver request for the in vivo BE studies for the 5 and 10 mg strength provided that the observed (b) (4)

(b) (4) which is highly likely to result in an increase in Cmax comparable to the 15 mg strength, is not of clinical concern.

The following responses should be conveyed to the Applicant:

Question 1: Does Agency agree that the similarity observed in the dissolution data for 10 mg and the available clinical experience supports a biowaiver of additional clinical characterization for the 10 mg strength?

Response:
Yes, we agree.

Question 2: Does Agency agree that the similarity observed in the dissolution data for 5 mg and the available clinical experience supports a biowaiver of additional clinical characterization for the 5 mg strength?

Response:
Yes, we agree.

Additional Comment to be conveyed to the Applicant:

1. Provide dissolution profile comparisons for two additional batches per strength at the time of NDA resubmission.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Richard Lostritto, Ph.D.
Secondary Signature
Office of New Drug Quality Assessment

cc. ADorantes

BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Suvorexant, also known as MK-4305 is a New Molecular Entity (NME). It is an orally active, potent, and reversible orexin receptor antagonist (ORA) and is anticipated to be the first in class ORA for the treatment of patients with insomnia. A CR letter was issue on June 28, 2013 due to safety concerns. FDA stated that a 10 mg tablet strength must be available at time of approval as the starting dose and that a 5 mg tablet strength is needed for patients expected to have significantly higher plasma levels of suvorexant (e.g., patients taking concomitant CYP3A4 inhibitors).

Merck submitted a proposal to the Agency for development which was discussed on June 19, 2013. The Sponsor plans to develop 5 mg and 10 mg tablets (b) (4) and based on available CMC data on the 15 mg, 20 mg, 30 mg and 40 mg tablets, the sponsor anticipates that information pertaining to manufacture and control of the 5 mg and 10 mg strengths including in vitro dissolution and stability data will support review and approval of these lower dose strengths, without additional clinical data.

In response to several biopharmaceutics related questions contained in a meeting package dated Aug 15, 2013, the following comments were conveyed to the Sponsor on Sep 25, 2013:

1. The approved dissolution method for the higher strengths is appropriate for the lower strengths provided that the following is met:
    - The dissolution profiles for the 5 mg and 10 mg strengths do not differ significantly from the higher strengths in such a way that the discriminating ability is lost.

      (b) (4)

    - The dissolution acceptance criterion for these strengths should be set based on the performance of the registration/commercial/ stability batches and may not be the same as that approved for higher strengths

2. We remind you that if you are not planning on doing any dose proportionality studies to support the approval of these strengths, a biowaiver request of the BA studies should be included in the NDA submission. The biowaiver will be granted if the following requirement are met:

    - The proposed lower and higher strengths of your product have the same dosage form;

      (b) (4)

    - The lower and highest strength products have the same manufacturing process; and
    - Dissolution profile comparisons between the higher and lower strengths in three different media meet the f2 similarity requirements.

On a teleconference dated Sep 27, 2013, the FDA clarified that the approved IVIVC cannot be used as a surrogate for BA/BE given that it was a Level C correlation which only took into consideration Cmax. Under these conditions, the correlation could only be used to support the drug product specification ranges for some attributes (b) (4) Therefore, the approval of the lower strengths should be based on a dose- proportionally study. Alternatively, this study could be waived if the requirements stated in the submitted preliminary comments (as listed on the background section) are met. FDA suggested that if *f2* testing fails, the Applicant may consider relying on in vivo data to justify/support the approval of these strengths in such a way that if dissolution of the new strengths (5 mg and 10 mg) using the QC method is demonstrated to be within the bounds established from pivotal clinical studies (e.g. 15 mg data from Protocol 051), a new PK study may not be required.

APPROVED DISSOLUTION METHOD AND ACCEPTANCE CRITERION

The following dissolution method and acceptance criterion was approved as a QC method for the 15 mg, 20 mg, 30 mg and 40 mg strengths of Suvorexant IR, tablets[1]:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	75 rpm	900mL QLA sinker	37°C	0.4% SDS in water	Q = (b) (4) in 30 min

DRUG PRODUCT

The components and composition of Suvorexant IR tablets are summarized in Table 1.

Table 1. SUVOREXANT TABLETS COMPOSITION

Components	Quality Reference	Function	(b) (4)	Amount per Tablet (mg) 5 mg	Amount per Tablet (mg) 10 mg
					(b) (4)
Suvorexant (MK-4305)	----	Active	(b) (4)	5.00	10.00
Polyvinylpyrrolidone/Vinyl Acetate Copolymer (Copovidone)	USP-NF, Ph. Eur., JPE				(b) (4)
Lactose Monohydrate	USP-NF, Ph. Eur., JP				
Microcrystalline Cellulose	USP-NF, Ph. Eur., JP				
Croscarmellose Sodium	USP-NF, Ph. Eur., JP				
Magnesium Stearate (non-bovine)	USP-NF, Ph. Eur., JP				
					(b) (4)
Total Tablet Weight				66.4‖	130.9‖

Present Submission

In the present submission, the Applicant included dissolution profiles comparisons with similarity testing (*f2* and multivariate) in three different media as well as formulation information in support of the biowaiver of the BA/BE studies for the 5 mg and 10 mg strengths.

Data Supporting the Biowaiver Request

As noted above, the biowaiver for the 5 mg and 10 mg strengths will be granted if the following requirements are met:

1. The proposed lower and higher strengths of your product have the same dosage form (b) (4)
2. The lower and highest strength products have the same manufacturing process; and;
3. Dissolution profile comparisons between the higher and lower strengths in three different media meet the *f2* similarity requirements;

1. (b) (4)

(b) (4)

Reviewer's Comments

The reviewer agrees with the Applicant's statement (b) (4)

2. Manufacturing processes

According to the Applicant, the manufacturing process for the 5 mg and 10 mg tablets is considered identical to the 15, 20, 30, and 40 mg strengths. (b) (4) This information needs to be qualified by the CMC reviewer and it will be a review issue.

3. Dissolution Profile Comparisons

Dissolution profiles comparisons were conducted in the following media:

- Approved QC media[1]: USP II at 75 rpm, 0.4% SDS in Water;

(b) (4)

The dissolution profiles were compared for one lot each of the 5 mg and 10 mg registration stability lots (WL00053439 and WL00053283, respectively) with 15 mg lots used in PN028/029 (WL00036691) and PN051 (WL00041508). According to the Applicant, both 15 mg lots were manufactured (b) (4) and exhibited dissolution profiles that based on PN051 data would be considered to result in bioequivalence.

Figures 1 to 4 show the dissolution profiles comparing the 5 mg, 10 mg, and 15 mg tablets in the different media tested. Table 1 summarizes the f2 values for the comparisons between the 10 mg vs. the 15 mg and the 5 mg and 15 mg strengths. Likewise, Table 3 summarizes the results of the multivariate analysis for these comparisons.

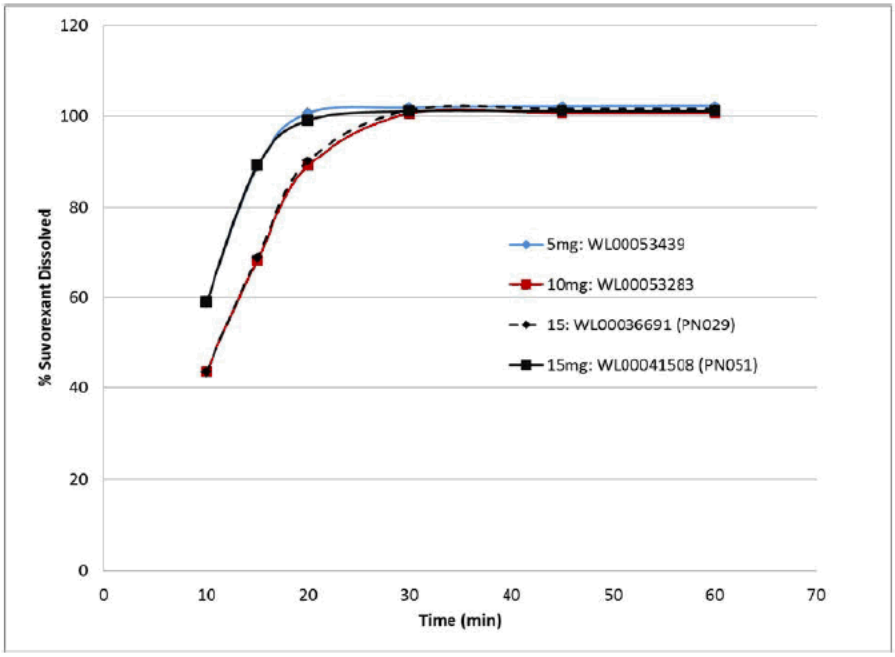

Figure 1. Average Dissolution Profile in QC Method: USP II, 0.4% SDS in USP Water, 75 rpm.

(b) (4)

Figure 2. Average Dissolution Profile (b) (4).

Figure 3. Average Dissolution Profile (b) (4)

Figure 4. Average Dissolution Profile (b) (4)

Table 2. Summary of Comparative Dissolution, F2 Values

(b) (4)

[redacted]

Table 3. Summary of Comparative Dissolution, Multivariate Analysis

(b) (4)

[redacted]

Reviewer's Comments

The results summarized on the data presented in Tables 2 and 3, suggest that, based on the dissolution testing conditions, it is likely that the 5 mg and the 10 mg are not dose-proportional to the 15 mg. In addition, it is likely that the 5 mg and the 10 mg strengths are not dose-proportional either. (b) (4) [redacted] *However, these results are superseded by the results of the BE study PN051 in which BE was demonstrated between 2×15 mg vs. 30 mg and 2×20 mg vs. 40 mg tablets. One can conclude then that the 5 mg, 10 mg and 15 mg are dose proportional based on the following:*

- *Cmax and AUC were similar between the 15 mg and 30 mg tablets (Table 4, Figure 5), despite the pronounce difference in dissolution (Table 5) suggesting that the QC dissolution method is over-discriminating.*
- *The profile of the 5 mg tablet is comparable to that for the 15 mg strength, which was shown to be BE to the 30 mg strength. The profile of the 10 mg strength is in between the profiles for the 15 mg and 30 mg strengths and the dissolution rate difference between the 5 mg and 10 mg strengths is smaller than that for the 15 mg vs. the 30 mg strengths (Figure 5), suggesting that the 5 mg and 10 mg strengths are likely to be BE.*
- *The difference in dissolution profile among strengths is unlikely to results in differences in AUC since the extend of release is not being affected.*
- *It is likely that the Cmax resulting from the 5mg strength is similar to that of the 15 mg strength based on similar dissolution profiles. According to the Applicant, the administration of a moderate CYP3A inhibitor with suvorexant significantly increases suvorexant $AUC_{0-\infty}$ [GMR (90%CI): 2.05 (1.82, 2.30)]; by comparison, there is a less pronounced effect on C_{max} [1.22 (1.09, 1.36)]. Therefore, although 5 mg suvorexant co-administered with moderate CYP3A inhibitors is expected to provide a similar systemic exposure (AUC) to that following 10 mg suvorexant alone, the C_{max} would be lower.*

Table 4. Bioequivalence assessment (AUC and Cmax, GMR with 94.12% CI in parenthesis) for PN051*.

	AUC0-t	AUC0-inf	Cmax
2x20 (n=59) vs 1x40 mg (n=60)	102.52% (99.08%-106.07%)	102.33% (98.80%-105.99%)	96.58% (90.96%-102.55%)
2x15 (n=60) vs 1x30 mg (n=59)	99.71% (96.66%-102.85%)	99.66% (96.52%-102.91%)	108.74%(101.10%-116.95%)

*Taken from reference number 1.

Table 5. Average (% RSD in parenthesis) Dissolution for Clinical Supplies used in PN051*

(b) (4)

[redacted]

Figure 5. Dissolution Profile of 5 mg and 10 mg Registration Stability Batch and Batches Used in PN051.

Conclusion

The dissolution data and additional information provided in the present submission support the approval of the 5 and 10 mg strength provided that the observed (b) (4) *is not of clinical concern.*

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/s/

SANDRA SUAREZ
12/12/2013

RICHARD T LOSTRITTO
12/12/2013

Clinical Pharmacology Individual Studies Review

PRODUCT (Generic Name):	Suvorexant (MK-4305)
PRODUCT (Brand Name):	Pending
NDA:	204569
DOSAGE FORM:	Tablets
DOSAGE STRENGTH:	15 mg, 20 mg, 30 mg and 40 mg
INDICATION:	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
NDA TYPE:	Standard
SUBMISSION DATE:	Aug 29, 2012
SPONSOR:	Merck Sharp & Dohme Corp.
PRIMARY REVIEWER:	Hristina Dimova, Ph.D.
REVIEWER (in vitro studies)	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

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1.1 PK and Initial Tolerability Studies

P001: A Randomized, Double-Blind, Placebo-Controlled, Alternating Panel, Single Rising Oral-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-4305 in Healthy Male Subjects

Objectives:
Part I: To evaluate the safety and tolerability of MK-4305 after administration of single rising oral doses to healthy young adult male subjects.
Part II: 1) To evaluate the safety and tolerability of MK-4305 after administration of single rising oral doses to healthy young adult male subjects. 2) To determine the effect of MK-4305 on power spectral density (e.g. delta band) of the waking electroencephalogram (EEG) in the eyes closed condition.
Part III: To investigate the potential effects of MK-4305 on QTc prolongation.

Study Design	This was a multi-part study. * Part I was a randomized, double- blind, placebo controlled, alternating panel, single oral rising dose study Part II was a randomized, double-blind, placebo-controlled, 4-period crossover study to evaluate the effects of single oral doses of MK-4305 on EEG Part III was a randomized, double-blind, placebo-controlled, 2-period crossover study
Study Population	40 healthy male subjects, 18-45 years old (16 in Part I, 12 in Part II and 12 in Part III)
Treatment Group	Part I consisted of Panels A and B, Part II consisted of Panel C, and Part III of Panel D *
Dosage and Administration	Part I, Panel A - single, oral doses of MK-4305 4 mg, 20 mg, 76 mg, 90 mg or matching placebo. Part I, Panel B –single, oral doses of MK-4305 10 mg, 50 mg, 76 mg, 120 mg or matching placebo. Part II, Panel C –single, oral doses of MK-4305 20 mg, 80 mg or matching placebo. Part III, Panel D -single, oral doses of MK-4305 120 mg or matching placebo.
PK Sampling: plasma	Plasma samples were collected prior to MK-4305 dosing and at various time points for 48 hours post-dose (Parts I and II) and up to 72 h in Part III**. For the 80 mg single night-time dose in Part II, only sparse samples were collected.
PK Sampling: urine	For Panel A and Panel B, Period 2 and Period 4, urine for MK-4305 was collected at pre-dose and 0 to 4, 4 to 8, 8 to 12 and 12 to 24 hours postdose. Only the urine from the highest dose of 90 mg Panel A /Period 4 was assayed using an exploratory urine assay.
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL Urine: exploratory urine assay for MK-4305

PK Assessment	Part I: C_{max}, t_{max}, AUC_{0-4}, AUC_{0-24}, AUC_{0-inf}, $t_{1/2}$ of MK-4305 Part II and III: C_{max}, t_{max}, AUC_{0-inf}, $t_{1/2}$ of MK-4305 (for the 80 mg single night-time dose in Part II, only $t_{1/2}$ of MK-4305)
PD Assessment	Part II: Power spectral density on frequency bands measured by awake electroencephalographic activity (qEEG) at pre-dose and up to 12 hr post dose Part III: 12-lead ECGs recorded by Holter device for 12 hours postdose All Parts: exploratory subjective measurements of the Bond and Lader Visual Analog Scale (VAS)
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* All doses were administered in the fasted state, except for Panel B, Period 4, where one panel of 8 subjects received a 10-mg dose of MK 4305 or matching placebo following a standard high-fat breakfast. All doses in Panels A and B were administered in the morning, except for Panel A, Period 5 and Panel C, Period 4, subjects were dosed in the evening (PM). There was at least a 7-day washout between treatment periods for any subject.
** 0 hr 0.5 hr 1 hr 1.5 hr 2 hr 4 hr 6 hr 7 hr 8 hr 10 hr 12hr 13 hr 16 hr 24 hr 48 hr 72 hr

Bioanalytical Assay:

Plasma samples were analyzed in accordance with protocol DM-909. The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR. Plasma samples were analyzed for MK-4305 using reversed phase HPLC and tandem mass spectrometry in the positive ion mode and Multiple Reaction Monitoring (MRM) mode after a liquid-liquid extraction of the drug from plasma. The lower limit of quantitation (LLOQ) was 1 ng/mL with a linear calibration range from 1 to 1000 ng/mL. Plasma concentrations were converted from units of ng/mL to μM using the molecular weight of MK-4305 (MW = 450.932 g/mol).
Selectivity was good, pre-dose plasma samples and control plasma samples did not contain detectable interferences at the retention times of MK-4305 or the IS.

Summary of the Validation Results for Suvorexant (MK-4305) Assay
Linear Range: 1.0 – 1000 ng/mL

	DM-909	
	n	Mean (%)
Intra-day Accuracy with Calibration Standards	6	95.6 – 105.0
Intra-day Precision (CV) with Calibration Standards	6	4.1 – 10.0
Intra-day Accuracy with Quality Control Samples	5	96.7 – 109.5
Intra-day Precision (CV) with Quality Control Samples	5	4.2 - 6.7
Inter-day Accuracy with Calibration Standards †	27	98.40 – 101.23
Inter-day Precision (CV) with Calibration Standards †	27	1.98 – 4.46
Inter-day Accuracy with Quality Control Samples †	54	97.61 – 103.82
Inter-day Precision (CV) with Quality Control Samples †	54	4.42 – 7.29
Extraction Recovery of Analyte	6	50.5 – 57.2

Urine samples were diluted 1:100 with control plasma to mimic plasma samples. The diluted urine samples were then extracted and detected using the plasma assay as described above. The lower limit of quantitation (LLOQ) for this method was 100 ng/mL with a linear range from 100 to 100,000 ng/mL, corresponding to a linear range 100 times higher than the plasma assay. The urine samples were analyzed for exploratory purpose only (the method was not validated).

Pharmacokinetic Results:

Part I: Following fasted AM administration of the single doses from 4 mg to 120 mg, MK-4305 was absorbed with a median T_{max} ranging from 1.0 – 2.0 hours and apparent terminal half life $t_{1/2}$ ranging from 8.5 to 15 hours.

Part II: Following fasted administration of single 20 and 80 mg AM doses, MK-4305 pharmacokinetics were consistent with those observed in Part I. Median T_{max} was 1.0 – 2.0 hours and apparent $t_{1/2}$ was 8.3 – 10 hours, while exposure and C_{max} were similar to those observed at the same or similar dose levels in Part I. An 80 mg single night-time dose was also administered in Part II, however only apparent $t_{1/2}$ is reported due to sparse PK sampling for this dose. The apparent $t_{1/2}$ for the 80 mg single night-time dose was also consistent with the half lives observed in Parts I and II.

In Part III, after administration of single fasted morning doses of 120 mg MK-4305, the PK of MK-4305 was also consistent with that observed at the 120 mg dose in Part I.

Urine was screened for MK-4305 in Panel A, 90 mg dose level only; the urine concentrations for MK-4305 were all below the limit of quantitation (BLOQ) for the subjects in this Panel.

Effect of food: A standard high-fat meal did not result in a meaningful change in MK-4305 $AUC_{0-\infty}$, however, the mean C_{max} was lower and median T_{max} was delayed by approximately 3 hours for this formulation (T1, see section 2.5.2 of QBR) of MK-4305. The geometric mean ratio GMR (fed/fasted) and for $AUC_{0-\infty}$ was 0.93 and 0.55 for C_{max}.

The effect of circadian time on MK-4305 pharmacokinetics was also explored. Night-time administration had no meaningful effect on $AUC_{0-\infty}$, while the mean C_{max} was decreased and median T_{max} was delayed by 1 hour. The GMR (PM/AM) for $AUC_{0-\infty}$ was 1.00 and 0.64 for C_{max}.

Panel A							
Parameter	4 mg † (N = 6)	20 mg † (N = 6)	76 mg † (N = 5)	76 mg (PM) † (N = 6)	90 mg † (N = 6)	GMR ‡ (90% CI) (PM/AM)	rMSE ##
$AUC_{0-\infty}$ § (µM•hr)	1.8 (1.4, 2.4)	7.7 (5.9, 10.0)	18.0 (13.7, 23.6)	17.9 (13.8, 23.3)	22.4 (17.3, 29.2)	1.00 (0.84, 1.18)	0.162
AUC_{0-4hr} § (µM•hr)	0.6 (0.5, 0.8)	2.3 (1.8, 2.9)	5.0 (3.8, 6.6)	3.4 (2.6, 4.4)	6.3 (4.8, 8.1)	0.68 (0.55, 0.85)	0.212
AUC_{0-24hr} § (µM•hr)	1.5 (1.3, 1.9)	6.4 (5.1, 7.9)	14.3 (11.4, 17.8)	13.3 (10.8, 16.5)	17.2 (14.0, 21.3)	0.93 (0.80, 1.10)	0.155
C_{max} § (µM)	0.236 (0.182, 0.307)	0.868 (0.667, 1.129)	2.026 (1.538, 2.669)	1.290 (0.991, 1.680)	2.253 (1.732, 2.931)	0.64 (0.52, 0.78)	0.198
C_{4hr} § (µM)	0.112 (0.086, 0.146)	0.516 (0.396, 0.672)	1.251 (0.943, 1.658)	0.958 (0.735, 1.248)	1.403 (1.078, 1.827)	0.77 (0.60, 0.98)	0.242
T_{max} ‖ (hr)	1.0 (0.5, 2.0)	2.0 (1.0, 4.0)	2.0 (0.5, 4.0)	3.0 (2.0, 6.0)	2.0 (1.0, 2.0)		.
Apparent terminal $t_{1/2}$ ¶ (hr)	8.5 (2.8)	9.4 (2.6)	9.0 (3.8)	10.7 (3.2)	10.9 (4.1)		.
Panel B							
Parameter	10 mg †† (N = 6)	10 mg (Fed) †† (N = 6)	50 mg †† (N = 6)	76 mg †† (N = 6)	120 mg †† (N = 6)	GMR ‡ (90% CI) (Fed/Fasted)	rMSE ##
$AUC_{0-\infty}$ § (µM•hr)	5.1 (3.9, 6.6)	4.7 (3.6, 6.2)	17.2 (13.2, 22.4)	23.5 (18.1, 30.6)	34.1 (26.2, 44.4)	0.93 (0.79, 1.09)	0.162
AUC_{0-4hr} § (µM•hr)	1.6 (1.2, 2.1)	0.6 (0.5, 0.8)	5.0 (3.9, 6.5)	6.3 (4.9, 8.2)	7.2 (5.6, 9.4)	0.38 (0.31, 0.47)	0.212
AUC_{0-24hr} § (µM•hr)	4.2 (3.4, 5.2)	3.6 (2.9, 4.5)	13.2 (10.7, 16.3)	17.4 (14.1, 21.5)	22.9 (18.5, 28.3)	0.87 (0.74, 1.01)	0.155
C_{max} § (µM)	0.605 (0.465, 0.788)	0.330 (0.254, 0.430)	1.999 (1.535, 2.603)	2.106 (1.619, 2.739)	2.507 (1.926, 3.264)	0.55 (0.45, 0.66)	0.198
C_{4hr} § (µM)	0.262 (0.201, 0.341)	0.332 (0.255, 0.433)	0.863 (0.662, 1.124)	1.378 (1.059, 1.794)	1.887 (1.448, 2.459)	1.27 (1.00, 1.61)	0.242
T_{max} ‖ (hr)	1.0 (1.0, 2.0)	4.0 (4.0, 6.0)	1.0 (0.5, 2.0)	2.0 (1.0, 4.0)	2.0 (1.0, 6.0)		.
Apparent terminal $t_{1/2}$ ¶ (hr)	9.4 (3.8)	10.0 (4.0)	11.2 (4.0)	10.7 (5.2)	15.0 (6.7)		.

† Subjects in Panel A were given single doses of 4 mg, 20 mg, 76 mg, 90 mg of MK-4305 or placebo in the fasted state; in Period 5, Panel A, subjects were given single dose of 76 mg or placebo in the evening (PM) in the fasted state.

†† Subjects in Panel B were given doses of 10 mg, 50 mg, 76 mg, 120 mg of MK-4305 or placebo in fasted state; in Period 4, Panel B, subjects were given single dose of 10 mg MK-4305 in the fed state.

‡ GMR = Geometric Mean Ratio

rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject CV on the raw scale for $AUC_{0-\infty}$, AUC_{0-4}, AUC_{0-24}, C_{max}, C_{4hr}.

Reviewer's note: The MK-4305 pharmacokinetic target value was 0.4 μM (based on preclinical data). This plasma target was sustained from 6.8 to 30.7 hours for 20 mg to 120 mg of MK-4305 including AM and the 76 mg PM doses.

Dose	Panel	N†	Time First Achieved (Hours Postdose)		Number of Hours Sustained	
			Mean	95% CI	Mean	95% CI
20 mg	Panel A	5	0.71	(0.47, 0.96)	6.85	(0.36, 13.35)
50 mg	Panel B	6	0.21	(-0.01, 0.43)	13.88	(7.95, 19.81)
76 mg	Panel A	5	0.31	(0.07, 0.56)	12.36	(5.87, 18.86)
76 mg PM	Panel A	6	0.78	(0.56, 1.00)	14.09	(8.16, 20.02)
76 mg	Panel B	6	0.26	(0.04, 0.48)	18.13	(12.20, 24.06)
90 mg	Panel A	6	0.22	(0.00, 0.45)	18.65	(12.72, 24.59)
120 mg	Panel B	6	0.22	(-0.01, 0.44)	30.68	(24.75, 36.61)

† N = number of subjects attaining target

Only includes treatments attaining target (0.4 uM)

Pharmacodynamic (PD) Results:

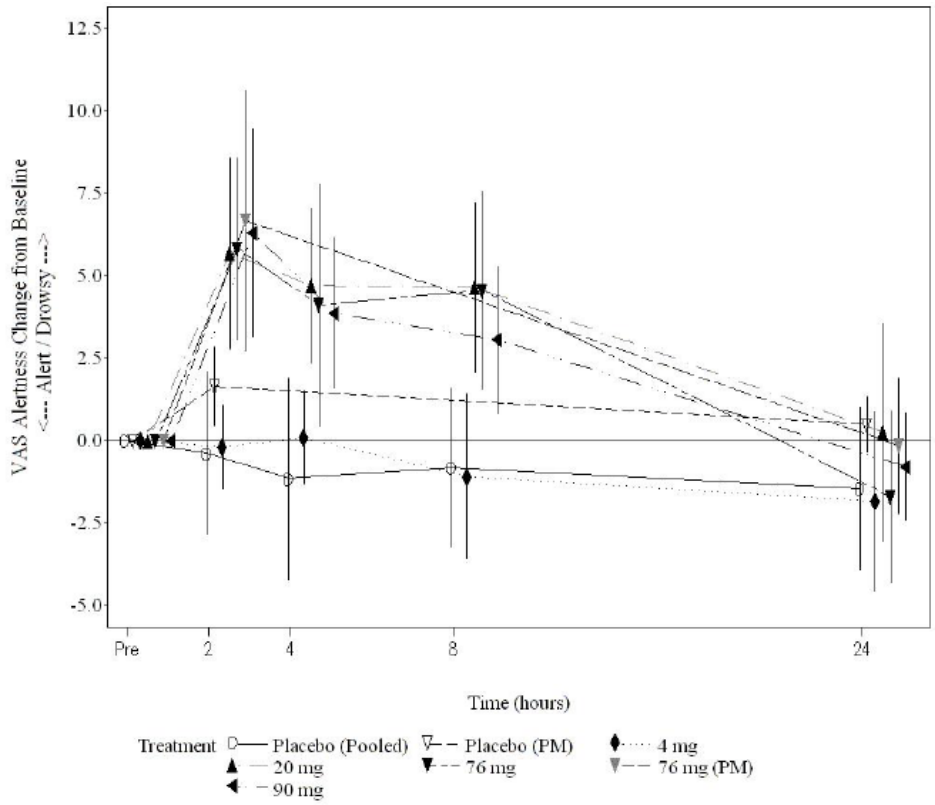
Part II examined the effect of MK-4305 on qEEG. Both 20 mg and 80 mg doses of MK-4305 produces an increase in power spectral density in the delta band, compared to placebo. There is a greater increase in delta power following 80 mg MK-4305 compared to 20 mg MK-4305.

Part III examined the effect of MK- 4305 on QTc. No meaningful changes in QTcF were observed. No subject on either MK-4305 or placebo had any QTcF change from baseline value of 30 msec or more. No subject on either MK-4305 or placebo had any QTcF value greater than 450 msec.

The PD effects of MK-4305 were also assessed using the exploratory subjective measurements of the Bond and Lader VAS. The scale was administered at 2, 4, 8 and 24 hr post AM administration in Part I, and at 1.5, 4.5, 8.5, 12.5 and 24 hr post AM and PM dosing in Part II.

The figure below displays the changes from baseline in alertness obtained in Part I. Following single oral doses of MK-4305 of 4 mg to 120 mg in Panels A and B there was increase in drowsiness (or alertness decreasing) at 2 hr post dose. Following 20 mg and 80 mg AM and PM in Part II, there was also increase in drowsiness at 1.5 hr post dose.

Change (Mean +/- SD) from baseline of Alertness for Panel A of Part I Following Single Oral Doses of MK-4305, 4 to 120 mg in Healthy Young Male Subjects (N=6 per active dose)



Reviewer's note: No effect on VAS at 4 mg, no dose-response after 20 mg.

Safety Results:

No serious clinical adverse experiences (AEs) were reported and no subject discontinued because of an adverse experience. The most frequently reported AE was somnolence (reported 1 or more times by 38 of 40 subjects). Five subjects reported inability to move (broader term Movement Disorder) for approximately 1 minute following single dose of MK-4305 at 80 or 120 mg, however the sponsor claims that these events should be differentiated from cataplexy.

P003: A Randomized, Double-Blind, Placebo-Controlled, Multiple Oral Rising-Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-4305 Administered to Healthy Male Subjects

Objectives:

Primary: To evaluate the safety and tolerability of rising multiple doses of MK-4305 administered to healthy young adult male subjects

Secondary: (1) To obtain preliminary plasma PK data of MK-4305 in the fasted state.
(2) To explore the time to attain the 0.4 μM plasma concentration target.

Exploratory: To explore the central PD effects of multiple doses of MK-4305 as evaluated by cognitive, psychomotor and arousal assessments.

Study Design	Randomized, double-blind, placebo-controlled, sequential panel, single and multiple oral rising-dose study in healthy male subjects. Subjects were assigned to one of five panels (Panels A, B, C, D or E). On Day 1, subjects were administered a single dose of MK-4305 or matching placebo. There was a 120 h washout period between Day 1 and Day 6. On Study Day 6 through Study Day 19 subjects received single oral doses of MK-4305 or placebo for 14 consecutive days.
Study Population	40 healthy male subjects, 18-45 years, BMI<31 kg/m^2, 8 per panel
Treatment Group	Five panels; each panel consisted of eight subjects (six subjects received MK-4305, 2 placebo)
Dosage and Administration	Subjects received study drug following a 4 hour fast at ~ 9 PM. Panel A: 10 mg MK-4305 or placebo Panel B: 20 mg MK-4305 or placebo Panel C: 40 mg MK-4305 or placebo Panel D: 80 mg MK-4305 or placebo Panel E: 100 mg MK-4305 or placebo
PK Sampling: plasma	Plasma samples were collected prior to MK-4305 dosing and at various time points for 72 hours post-dose and up to 96 h on Day 19*. PK trough concentration samples were collected on Days 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18.
Analysis	Plasma: LC-MS/MS method for MK-4305 and metabolite M9 Range: 1 to 1000 ng/mL for both analytes
PK Assessment	C_{max}, t_{max}, AUC_{0-4}, AUC_{0-24}, AUC_{0-inf}, $t_{1/2}$ of MK-4305 and metabolite M9
PD Assessment	Digit Symbol Substitute Test (DSST) Cognitive Drug Research (CDR) tasks of Immediate Word Recall - Accuracy, and Delayed Recall Karolinska Sleepiness Scale (KSS) Bond and Lader VAS
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* PK samples were collected at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72 h post-dose (and 96 h for Day 19)

Bioanalytical Assay:

Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using validated liquid chromatography-tandem mass spectrometric detection (LC-MS/MS) methods (method DM-909 for suvorexant and DM-928 for M9). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.

Summary of the Validation Results for M9 Assay (DM-928)
Linear Range: 1.0 – 1000 ng/mL

	DM-928	
	n	Mean (%)
Intra-day Accuracy with Calibration Standards	6	96.0 – 103.8
Intra-day Precision (CV) with Calibration Standards	6	3.6 – 10.0
Intra-day Accuracy with Quality Control Samples	5	96.0 – 103.1
Intra-day Precision (CV) with Quality Control Samples	5	3.9 – 4.6
Inter-day Accuracy with Calibration Standards †	21-24	98.00– 103.31
Inter-day Precision (CV) with Calibration Standards †	21-24	3.00 – 5.47
Inter-day Accuracy with Quality Control Samples †	48	100.33 – 103.79
Inter-day Precision (CV) with Quality Control Samples †	48	7.15 – 9.3
Extraction Recovery of Analyte	6	76.2 – 80.4

The assay performance during the analysis of the plasma samples was acceptable. MK-4305 and M9 plasma concentrations were converted from units of ng/mL to µM using the molecular weights of MK-4305 (MW = 450.932 g/mol) and M9 (MW = 466.931 g/mol).

There were quantifiable pre-dose concentrations for the multiple dosing portion of this study in 2 subjects at the 80 mg dose and 3 subjects at the 100 mg dose. Because the pre-dose concentrations were all less than 1% maximum plasma concentration observed in the subsequent concentration-time profile, PK parameters were calculated without correcting for the quantifiable pre-dose concentrations.

In addition, metabolite profiling for plasma samples was performed. Circulating metabolites at steady-state of MK-4305 were evaluated semi-quantitatively. Single dose, Day 3, and Day 14 plasma samples from the 40, 80, and 100 mg doses were evaluated. Plasma samples were pooled over the 0-24 hr collection period and the volumes of samples used for pooling from each time point were proportional to the time of collection so that the concentration of each component in the pooled sample is proportional to its AUC. Samples were analyzed using HPLC coupled with radioactivity detection and high resolution mass spectral detection (HPLC-HRMS) using electrospray ionization in positive ion mode.

Pharmacokinetic Results:

Following single- and multiple-dose PM administration, MK-4305 had a median T_{max} ranging from 1.5 – 4.0 h and apparent terminal half life $t_{1/2}$ ranging from 7.7 to 14.5 hours. Accumulation ratios for MK-4305 $AUC_{0\text{-}24hr}$ for the 10 mg to 100 mg doses ranged from 1.21 to 1.60 and were dose-independent.

An exploratory assessment of dose proportionality on multiple dose Day 14 for MK-4305 suggests that plasma $AUC_{0\text{-}24hr}$ and C_{max} both increased less than dose proportionally over the range of doses studied (10 mg to 100 mg). MK-4305 median time to (90% of) steady state ranged from 2 to 3 days; individual time to steady state ranged from 1 to 6 days.

Summary of PK Parameters of MK-4305 Following a Single Dose and then Multiple Dose Administration (Daily for 14 Days) of 10 mg to 100 mg in Healthy Male Subjects

Pharmacokinetic Parameter	10 mg	20 mg	40 mg	80 mg	100 mg
Single dose					
	N=6	N=6	N=5	N=6	N=6
$AUC_{0-\infty}$ † (µM*hr)	3.94 (2.85, 5.43)	5.97 (4.33, 8.24)	10.84 (7.62, 15.42)	15.57 (11.28, 21.48)	27.95 (20.25, 38.56)
AUC_{0-4hr} † (µM*hr)	1.01 (0.80, 1.28)	1.51 (1.19, 1.91)	2.18 (1.68, 2.82)	3.03 (2.39, 3.83)	2.42 (1.91, 3.07)
AUC_{0-24hr} † (µM*hr)	3.43 (2.62, 4.49)	5.03 (3.84, 6.58)	8.53 (6.45, 11.28)	11.48 (8.77, 15.01)	18.10 (13.83, 23.68)
C_{max} † (µM)	0.356 (0.288, 0.440)	0.572 (0.463, 0.708)	0.802 (0.640, 1.005)	1.329 (1.075, 1.644)	1.425 (1.152, 1.763)
C_{4hr} † (µM)	0.254 (0.201, 0.321)	0.347 (0.275, 0.439)	0.612 (0.479, 0.781)	0.879 (0.696, 1.111)	1.248 (0.988, 1.577)
C_{24hr} † (µM)	0.038 (0.024, 0.062)	0.068 (0.042, 0.110)	0.121 (0.073, 0.201)	0.163 (0.101, 0.264)	0.403 (0.249, 0.650)
T_{max} ‡ (hr)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (0.5, 4.0)	2.0 (2.0, 6.0)	4.0 (2.0, 6.0)
Apparent $t_{1/2}$ § (hr)	7.7 (1.7)	8.4 (1.7)	8.6 (1.1)	10.0 (5.2)	12.6 (7.0)
Multiple Dose Day 3					
	N=6	N=5	N=6	N=6	N=6
AUC_{0-24hr} † (µM*hr)	3.79 (2.90, 4.96)	6.11 (4.67, 7.99)	9.00 (6.88, 11.78)	14.97 (11.44, 19.58)	24.64 (18.83, 32.23)
AUC_{0-4hr} † (µM*hr)	1.11 (0.88, 1.41)	1.54 (1.22, 1.95)	3.01 (2.37, 3.81)	3.65 (2.88, 4.63)	5.44 (4.29, 6.90)
C_{max} † (µM)	0.428 (0.346, 0.530)	0.557 (0.450, 0.688)	1.091 (0.882, 1.350)	1.288 (1.041, 1.593)	2.109 (1.705, 2.609)
C_{4hr} † (µM)	0.272 (0.215, 0.343)	0.437 (0.346, 0.552)	0.564 (0.447, 0.713)	1.023 (0.810, 1.292)	1.671 (1.323, 2.111)
T_{max} ‡ (hr)	2.0 (1.0, 4.0)	3.0 (2.0, 4.0)	1.5 (1.0, 2.0)	2.0 (1.0, 8.0)	3.0 (1.0, 6.0)
Multiple Dose Day 14 (Last dose)					
	N=6	N=6	N=5	N=6	N=6
AUC_{0-24hr} † (µM*hr)	4.36 (3.33, 5.70)	6.08 (4.60, 8.04)	10.64 (8.13, 13.92)	18.32 (14.00, 23.97)	27.62 (21.11, 36.14)
AUC_{0-4hr} † (µM*hr)	1.09 (0.86, 1.38)	1.50 (1.16, 1.95)	3.13 (2.47, 3.97)	4.43 (3.49, 5.61)	5.49 (4.33, 6.96)
C_{max} † (µM)	0.414 (0.335, 0.512)	0.574 (0.458, 0.719)	1.080 (0.873, 1.336)	1.488 (1.203, 1.841)	2.085 (1.686, 2.579)
C_{4hr} † (µM)	0.329 (0.261, 0.416)	0.467 (0.366, 0.596)	0.691 (0.547, 0.872)	1.274 (1.009, 1.609)	1.788 (1.415, 2.258)
C_{24hr} † (µM)	0.063 (0.039, 0.102)	0.107 (0.064, 0.178)	0.192 (0.119, 0.310)	0.395 (0.245, 0.638)	0.644 (0.399, 1.040)
T_{max} ‡ (hr)	2.0 (1.0, 4.0)	4.0 (2.0, 4.0)	2.0 (1.0, 2.0)	2.0 (2.0, 4.0)	4.0 (2.0, 8.0)
Apparent $t_{1/2}$ § (hr)	8.1 (2.3)	9.2 (0.9)	9.4 (1.5)	11.2 (5.3)	14.5 (7.0)
Linearity with time: Multiple Dose Day 14 AUC_{0-24hr}/ Single Dose $AUC_{0-\infty}$ ‖					
AUC_{0-24hr} / $AUC_{0-\infty}$	1.11 (0.87, 1.41)	1.02 (0.79, 1.32)	1.02 (0.79, 1.32)	1.18 (0.93, 1.50)	0.99 (0.78, 1.26)

Pharmacokinetic Parameter	10 mg	20 mg	40 mg	80 mg	100 mg
Accumulation Ratio: Multiple Dose Day 14 / Single Dose ‖					
	N=6	N=5	N=6	N=6	N=6
$AUC_{0\text{-}24hr}$ (μM*hr)	1.27 (1.06, 1.52)	1.21 (1.00, 1.46)	1.25 (1.03, 1.51)	1.60 (1.33, 1.91)	1.53 (1.28, 1.83)
$AUC_{0\text{-}4hr}$ (μM*hr)	1.08 (0.83, 1.39)	1.00 (0.76, 1.31)	1.44 (1.10, 1.88)	1.46 (1.13, 1.89)	2.27 (1.76, 2.92)
C_{max} (μM)	1.16 (0.98, 1.39)	1.00 (0.83, 1.21)	1.35 (1.12, 1.62)	1.12 (0.94, 1.34)	1.46 (1.23, 1.75)
C_{4hr} (μM)	1.29 (1.10, 1.53)	1.34 (1.13, 1.60)	1.13 (0.95, 1.35)	1.45 (1.23, 1.71)	1.43 (1.21, 1.69)
C_{24hr} (μM)	1.65 (1.12, 2.43)	1.56 (1.03, 2.37)	1.59 (1.05, 2.41)	2.42 (1.64, 3.57)	1.60 (1.08, 2.36)

M9 exposure was similar to that observed for the parent compound MK-4305 after single PM dosing of MK-4305, with metabolite/parent $AUC_{0\text{-}24hr}$ ratios ranging from 1.03 – 1.17 and declined to 76 – 92% of MK-4305 exposure by Day 14 of multiple MK-4305 dosing. M9 C_{max} was generally lower than MK-4305 C_{max}.
Median T_{max} for M9, which ranged from 2.0 – 6.0 hours. The M9 mean $t_{1/2}$ of 8.7 – 17.5 h was similar to that for MK-4305. Accumulation ratios for M9 $AUC_{0\text{-}24hr}$ for the 10 mg to 100 mg doses of MK-4305 were independent of dose and ranged from 0.97 for the 40 mg treatment to 1.04 for the 100 mg treatment. Individual time to steady state ranged from 1 to 3 days.

Summary of PK Parameters of Metabolite M9 Following a Single Dose and then Multiple Dose Administration (Daily for 14 Days) of MK-4035 10 mg to 100 mg in Healthy Male Subjects

Pharmacokinetic Parameter	10 mg	20 mg	40 mg	80 mg	100 mg
Single dose					
	N=6	N=6	N=5	N=6	N=6
$AUC_{0\text{-}\infty}$ † (μM*hr)	4.45 (3.48, 5.69)	7.02 (5.49, 8.98)	12.56 (9.59, 16.45)	17.23 (13.47, 22.04)	30.53 (23.87, 39.05)
$AUC_{0\text{-}24hr}$ † (μM*hr)	3.52 (2.85, 4.34)	5.66 (4.59, 6.98)	9.90 (7.94, 12.35)	12.88 (10.44, 15.89)	21.15 (17.14, 26.09)
C_{max} † (μM)	0.251 (0.216, 0.293)	0.472 (0.405, 0.549)	0.737 (0.627, 0.867)	1.142 (0.982, 1.329)	1.585 (1.362, 1.844)
C_{24hr} † (μM)	0.060 (0.041, 0.089)	0.089 (0.060, 0.130)	0.161 (0.106, 0.243)	0.191 (0.130, 0.280)	0.398 (0.271, 0.584)
$AUC_{0\text{-}\infty}$ (M9 / MK-4305) †	1.13 (0.96, 1.33)	1.17 (1.00, 1.38)	1.16 (0.97, 1.39)	1.11 (0.94, 1.30)	1.09 (0.93, 1.28)
$AUC_{0\text{-}24hr}$ (M9 / MK-4305) †	1.03 (0.88, 1.20)	1.13 (0.96, 1.32)	1.16 (0.99, 1.37)	1.12 (0.96, 1.31)	1.17 (1.00, 1.37)
C_{max} (M9 / MK-4305) †	0.707 (0.551, 0.907)	0.824 (0.642, 1.058)	0.898 (0.684, 1.179)	0.859 (0.670, 1.103)	1.112 (0.867, 1.427)
T_{max} ‡ (hr)	5.0 (2.0, 8.0)	3.0 (2.0, 4.0)	4.0 (1.0, 6.0)	4.0 (2.0, 8.0)	6.0 (4.0, 8.0)
Apparent $t_{1/2}$ § (hr)	8.7 (1.9)	9.0 (2.0)	9.3 (1.1)	10.9 (4.7)	13.2 (5.1)

Summary of PK Parameters of Metabolite M9 (cont.)

Pharmacokinetic Parameter	10 mg	20 mg	40 mg	80 mg	100 mg
Multiple Dose Day 3					
	N=6	N=5	N=6	N=6	N=6
$AUC_{0\text{-}24hr}$ † (μM*hr)	3.71 (3.01, 4.58)	6.78 (5.50, 8.37)	9.34 (7.57, 11.52)	13.72 (11.12, 16.93)	24.30 (19.70, 29.99)
C_{max} † (μM)	0.284 (0.244, 0.330)	0.502 (0.432, 0.584)	0.913 (0.784, 1.062)	1.060 (0.911, 1.233)	1.719 (1.478, 2.001)
$AUC_{0\text{-}24hr}$ (M9 / MK-4305) †	0.98 (0.84, 1.14)	1.11 (0.95, 1.30)	1.04 (0.89, 1.21)	0.92 (0.79, 1.07)	0.99 (0.84, 1.15)
C_{max} (M9 / MK-4305) †	0.66 (0.52, 0.85)	0.90 (0.70, 1.16)	0.84 (0.65, 1.07)	0.82 (0.64, 1.06)	0.82 (0.64, 1.05)
T_{max} ‡ (hr)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	2.0 (2.0, 4.0)	4.0 (4.0, 12.0)	4.0 (2.0, 6.0)
Multiple Dose Day 14 (Last dose)					
	N=6	N=6	N=5	N=6	N=6
$AUC_{0\text{-}24hr}$ † (μM*hr)	3.53 (2.86, 4.36)	5.61 (4.50, 7.00)	9.55 (7.74, 11.78)	13.94 (11.30, 17.20)	21.94 (17.78, 27.07)
C_{max} † (μM)	0.253 (0.217, 0.294)	0.421 (0.358, 0.495)	0.856 (0.735, 0.996)	1.008 (0.866, 1.173)	1.513 (1.300, 1.760)
C_{24hr} † (μM)	0.063 (0.043, 0.093)	0.112 (0.074, 0.169)	0.166 (0.113, 0.244)	0.272 (0.185, 0.400)	0.482 (0.328, 0.708)
$AUC_{0\text{-}24hr}$ (M9 / MK-4305) †	0.81 (0.69, 0.95)	0.92 (0.79, 1.08)	0.90 (0.77, 1.05)	0.76 (0.65, 0.89)	0.79 (0.68, 0.93)
C_{max} (M9 / MK-4305) †	0.611 (0.476, 0.783)	1.160 (0.884, 1.523)	0.793 (0.618, 1.017)	0.677 (0.528, 0.869)	0.726 (0.566, 0.931)
T_{max} ‡ (hr)	4.0 (2.0, 8.0)	4.0 (2.0, 6.0)	2.0 (2.0, 4.0)	4.0 (4.0, 8.0)	6.0 (2.0, 8.0)
Apparent $t_{1/2}$ § (hr)	9.2 (2.4)	10.7 (1.2)	11.0 (2.0)	14.1 (6.9)	17.5 (7.3)
Accumulation Ratio: Multiple Dose Day 14 / Single Dose ‖					
	N=6	N=5	N=6	N=6	N=6
$AUC_{0\text{-}24hr}$ (μM*hr)	1.00 (0.86, 1.18)	0.99 (0.84, 1.18)	0.97 (0.81, 1.14)	1.08 (0.92, 1.27)	1.04 (0.88, 1.22)
C_{max} (μM)	1.01 (0.88, 1.15)	0.89 (0.77, 1.03)	1.16 (1.01, 1.34)	0.88 (0.77, 1.01)	0.95 (0.83, 1.09)
C_{24hr} (μM)	1.05 (0.74, 1.47)	1.26 (0.87, 1.81)	1.03 (0.72, 1.49)	1.43 (1.01, 2.01)	1.21 (0.86, 1.70)

The time to achieve the pharmacokinetic target concentration value of 0.4 μM (based on preclinical data) for MK-4305 was evaluated on multiple dose Day 14. The target concentration for C_{4hr} on day 14 was attained at doses ranging from 40 mg to 100 mg (attainment of the target is based on the lower bound of the CI) and the time to reach the target was observed to be 0.02 (for 100 mg) and 0.42 hours (for 40 mg). This target concentration was sustained for 12.16 hours (for 40 mg) to 45.23 hours (for 100 mg).

Reviewer's Comment: The above result suggesting that target suvorexant plasma levels are sustained for more than 8 hours argues against recommending doses >20mg.

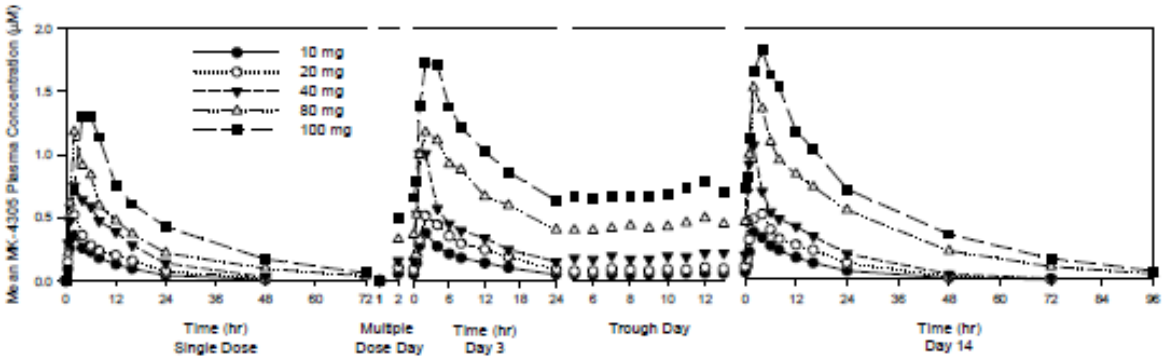
Multiple Dose Day 14 Geometric Means (GM) and 90% CIs for MK-4305 C_{4hr} (µM) Following Multiple Dose Administration (Daily for 14 Days) of 10 to 100 mg in Healthy Male Subjects

Dose (Panel)	N	GM † (90% CI)‡
10 mg (A)	6	0.329 (0.271, 0.400)
20 mg (B)	5	0.467 (0.381, 0.572)
40 mg (C)	6	0.691 (0.568, 0.839)
80 mg (D)	6	1.274 (1.049, 1.548)
100 mg (E)	6	1.788 (1.472, 2.172)

Dose (Panel)	N †	Mean Time (hr) First Achieved (95% CI)	Mean Number of Hours Sustained (95% CI)
40 mg (C)	6	0.42 (0.15, 0.68)	12.16 (-4.19, 28.51)
80 mg (D)	6	0.27 (0.00, 0.54)	32.10 (15.75, 48.45)
100 mg (E)	6	0.02 (-0.25, 0.28)	45.23 (28.88, 61.58)

† Number of subjects who attained target.

Mean MK-4305 Plasma Concentrations (µM) Versus Time (hr) Following a Single Dose then Multiple Dose Administration (Once Daily for 14 Days) of 10 mg to 100 mg in Healthy Young Male Subjects (N=6 per dose, N=5 for 40 mg Single Dose) (Linear Scale)



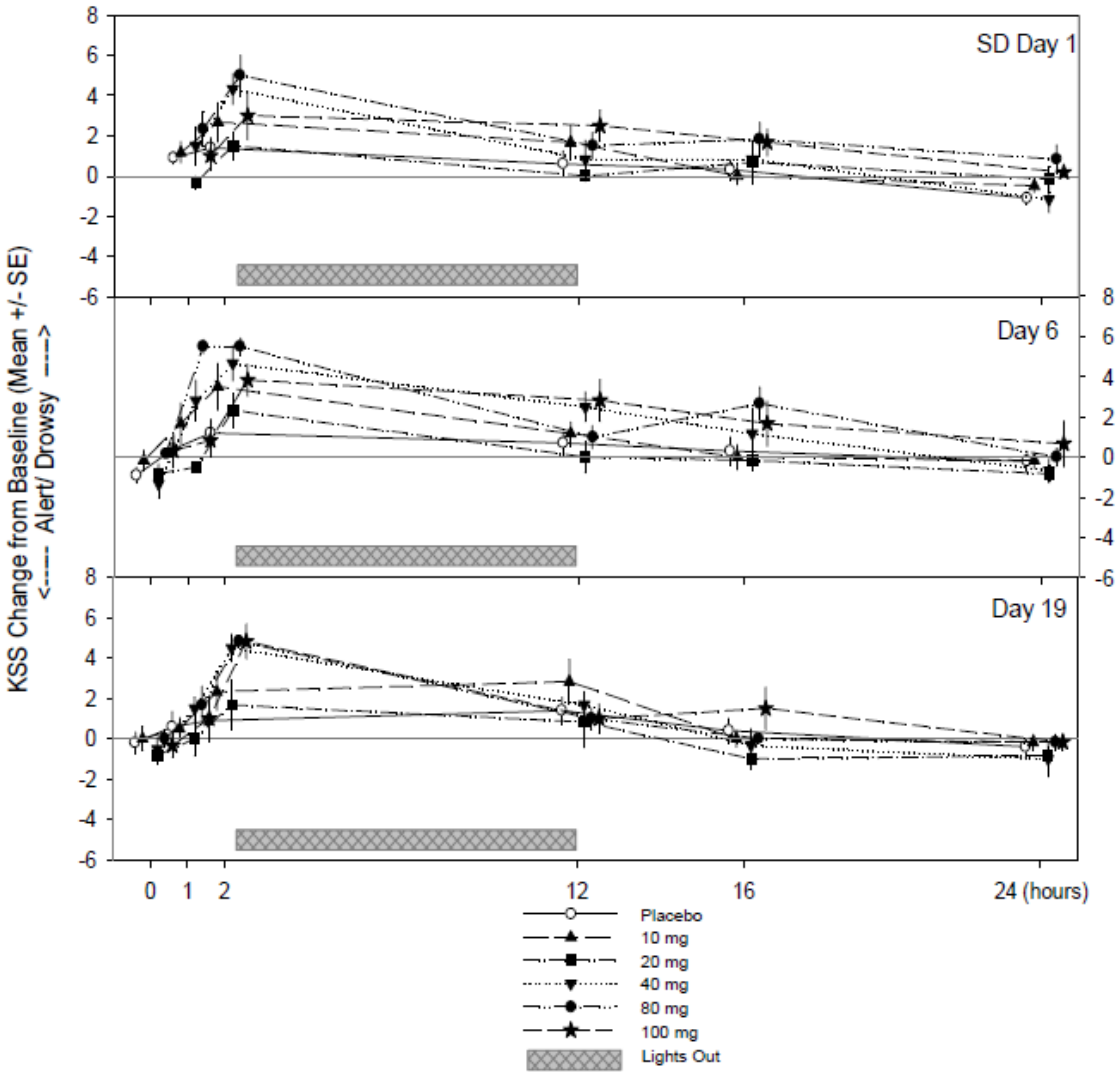
Metabolite Profiling Results

Single dose, Day 3, and Day 14 plasma samples (0-24 hr pooled) from the 40, 80, and 100 mg doses were evaluated. In addition to M9 and MK-4305, metabolite M17 became more prevalent in Day 3 and Day 14 plasma compared to single dose. The structure of M17 was determined to be a di-hydroxylated derivative of MK-4305 based on NMR analysis and comparison of HPLC retention time and MS patterns with a synthetic standard [For details, refer to the mass balance study report (P012)]. The concentration of M17 in Day 14 samples was estimated to be <10% of the total drug related material (ranging from 8.6– 9.8% for the three dose levels). In addition, based on the plasma concentration on Day 3 (M17 accounted for ~6%), M17 approached steady-state by Day 14 following multiple daily dosing of suvorexant in human. M17 also only represents <1% of the radioactive dose in human excreta.

Pharmacodynamic Results:

Visual Analog Scale (VAS) and Karolinska Sleepiness Scale (KSS) were assessed 1, 2, 11.5, 16 and 24 hours post PM suvorexant dosing. Digit Symbol Substitution Test (DSST) and Immediate and Delayed Word Recall (IDWR) both were assessed at pre-dose Day 1 and 12 hr post PM dosing and Day 8, 13 and Day 19 12 hr post PM dosing. The results for KSS (changes from baseline by dose and timepoint on day 1, 6 and 19) are displayed in the Figure below. MK-4305 showed a dose dependent increase in sleepiness/drowsiness as measured by the KSS. Following 12 hr post PM administration, values for sleepiness/drowsiness were gradually returning to baseline.

Change (Mean +/- SE) from baseline of Karolinska Sleepiness Scale (KSS) Following PM Single Dose (Study Day 1) and then Multiple Dose Administration (Daily for 14 Days; Study Days 6 to 19) of 10 mg to 100 mg MK-4305 in Healthy Male Subjects



Safety Results:

No serious adverse experiences AEs were reported in this study. All clinical AEs were transient in duration and were mild to moderate in intensity except for one subject (AN0026) in Panel D (80 mg) who reported a severe clinical AE of somnolence on five separate occasions starting on Day 6 (MD day 1). Note: this subject did not have higher MK-4305 plasma levels than the rest of the subjects in this group.

The most frequently reported clinical adverse experiences were somnolence (19 subjects reported 51 occurrences), fatigue, and headache.

One subject (AN0014) discontinued due to a clinical AE (maculo-papular rash) 15 hours following administration of 20 mg MK-4305 on Day 10 (MD day 5) in Panel B. This subject had no systemic or vital sign changes in association with the rash that lasted approximately nineteen days. Note: this subject had MK-4305 plasma levels lower than the mean values in this group.

P011: A Single Dose Extension Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Suvorexant (MK-4305)

Objectives:

Primary: To evaluate the safety and tolerability of single rising oral doses to healthy young adult male and female subjects.

Secondary: To obtain preliminary plasma PK data of MK-4305 in the fasted state.

Exploratory: To explore the central PD effects of single doses of MK-4305 as evaluated by cognitive, psychomotor and arousal assessments.

Study Design	Panel A: randomized, double-blind, placebo-controlled, single oral rising dose, 4-period study in healthy, young, male subjects. Panel B: randomized, double-blind, placebo-controlled, single oral rising-dose, 3-period study in healthy, young, female subjects. Panel A started and completed before Panel B.
Study Population	17 healthy subjects, 18-45 years, 8 males and 9 females*
Treatment Group	Two panels, 4 trt periods for panel A and 3 trt periods for panel B. For both panels, in each treatment period, 6 subjects received active drug and 2 subjects received placebo. There was a minimum 10-day washout between each treatment period for each subject.
Dosage and Administration	All doses were administered in the morning after a minimum 8-hr fast. Panel A: single doses of 150, 210, 240 and divided doses of 160 mg (80 mg at 0 hr and 80 mg at 1.5 hr) Panel B: single doses of 120, 180 and 240 mg
PK Sampling: plasma	Plasma samples were collected prior to MK-4305 dosing and at various time points for 144 hours post-dose. **
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL
PK Assessment	C_{max}, t_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$ of MK-4305
PD Assessment	Divided Attention Task (DAT) Choice Reaction Time Assessments (CRT) Karolinska Sleepiness Scale (KSS) Bond and Lader Visual Analog Scale (VAS)
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* One subject withdrew consent after Period 1 and was discontinued from the study. This subject was replaced by another subject who completed Periods 2 and 3 of the same treatment regimen.

** PK samples were collected at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144 h post-dose

Bioanalytical Assay:

Plasma samples were analyzed for suvorexant. M9 was not assayed. Plasma concentrations of suvorexant were determined using validated LC-MS/MS method (method DM-909). The assay performance during the validation was acceptable, details of the validation are presented in Section 2.6.1 in QBR.

The assay performance during the analysis of the plasma samples was acceptable. Representative chromatograms were provided by the sponsor.

Pharmacokinetic Results:

The doses originally proposed in this study were 150, 210, 270 and 330 mg suvorexant. Based on safety evaluation in Periods 1 and 2 (150 and 210 mg), the dose for Period 3 was lowered to 240 mg. A divided dose, 160 mg (80 mg at 0 hr and 80 mg at 1.5 hr), was evaluated in Period 4 to see whether higher C_{max} would be achieved.

The plasma PK parameters of suvorexant following single (fasted AM) rising oral dose administration to healthy young male subjects in Panel A and healthy young female subjects in Panel B are summarized in the table below. Suvorexant was absorbed with a median T_{max} ranging from 1.0 to 3.0 hours. The T_{max} observed in healthy young female subjects was similar to that observed in healthy young male subjects over a similar dose range. Mean apparent terminal half life ranged from 12.1 to 14.5 hours in healthy young male subjects, and from 14.4 to 15.8 hours in healthy young female subjects. $AUC_{0-\infty}$ and C_{max} appeared higher in females than in males.

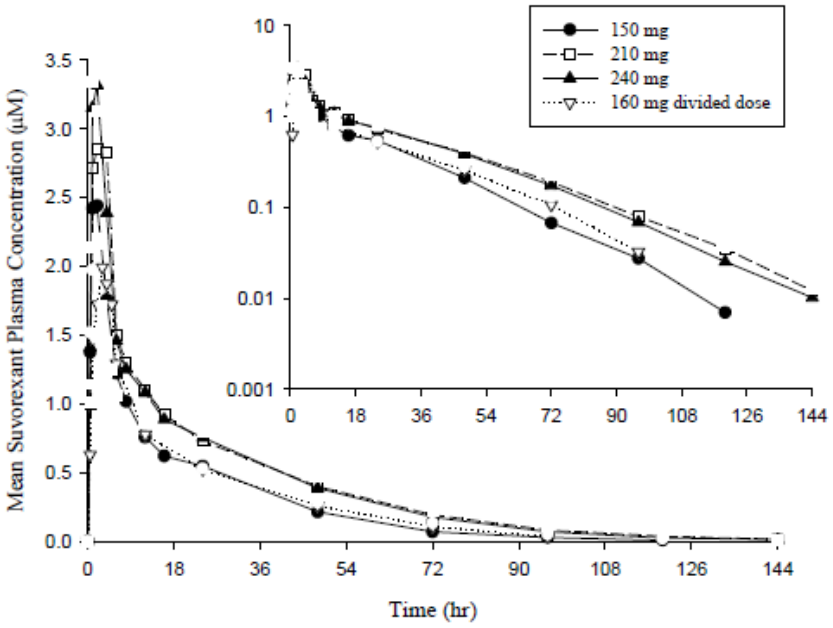
Healthy young male subjects in Panel A were also administered 160 mg as a divided dose of 80 mg at 0 hours and 80 mg at 1.5 hours. The median peak concentration occurred at 3.0 hours. The mean apparent terminal half life for this dose was 11.8 hours and is similar to the terminal half life observed at over the 150 to 240 mg single dose range in this study. The C_{max} and exposure achieved at the 160 mg divided dose were similar to the levels achieved with the single dose of 150 mg.

Summary Statistics of Suvorexant (MK-4305) PK Parameters Following Single Fasted AM Oral Doses of 150 mg, 210 mg, 240 mg and 160 mg Divided Dose Suvorexant in Young Healthy Male Subjects (Panel A) and Single Fasted AM Oral Doses of 120 mg, 180 mg and 240 mg Suvorexant (MK-4305) in Young Healthy Female Subjects (Panel B)

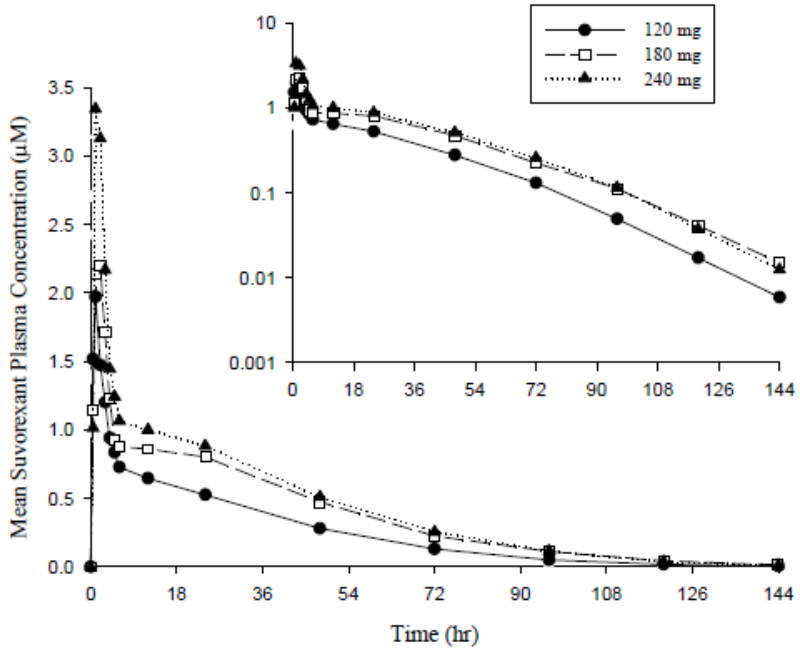
	Male †					Female ‡			
Parameter	150 mg (N = 6)	210 mg (N = 6)	240 mg (N = 6)	160 mg Divided Dose (N = 6)	rMSE #	120 mg (N = 6)	180 mg (N = 6)	240 mg (N = 5)	rMSE #
$AUC_{0-\infty}$ § (µM·hr)	37.01 (25.43, 53.88)	49.83 (34.23, 72.54)	44.42 (30.52, 64.67)	39.55 (27.16, 57.57)	0.125	30.64 (20.33, 46.16)	51.16 (33.95, 77.09)	62.43 (41.31, 94.34)	0.128
C_{max} § (µM)	2.469 (2.002, 3.044)	3.081 (2.498, 3.799)	3.160 (2.562, 3.897)	2.374 (1.925, 2.927)	0.117	1.829 (1.134, 2.952)	2.268 (1.406, 3.660)	3.102 (1.861, 5.169)	0.360
T_{max} ‖ (hr)	1.5 (0.5, 2.0)	3.0 (1.0, 4.0)	1.5 (1.0, 2.0)	3.0 (2.0, 5.0)		1.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.1 (1.0, 4.0)	
Apparent terminal $t_{1/2}$ ¶ (hr)	12.1 (1.6)	14.0 (2.3)	14.5 (2.0)	11.8 (1.3)		14.7 (1.5)	15.8 (1.7)	14.4 (1.6)	

rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject CV on the raw scale for $AUC_{0-\infty}$ and C_{max}

Mean Suvorexant (MK-4305) Plasma Concentrations (µM) Versus Time (hr) Following Administration of Single Fasted AM Oral Doses of 150 mg, 210 mg, 240 mg and 160 mg Divided Dose Suvorexant in Young Healthy Male Subjects (Panel A) (Inset: Semi-log Scale) (n=6 per dose)



Mean Suvorexant (MK-4305) Plasma Concentrations (µM) Versus Time Following Administration of Single Fasted AM Oral Doses of 120, 180 and 240 mg Suvorexant in Young Healthy Female Subjects (Panel B) N=6 per dose, N=5 for 240 mg



Pharmacodynamics:

Suvorexant at higher doses appeared to decrease alertness. There were no apparent effect of suvorexant on VAS calmness and contentedness. There was an increase in sleepiness as measured by KSS and decrease in alertness as measured by Bond and Lader VAS following AM dosing of suvorexant which is consistent with the desired PD effects.

Safety:

No serious clinical adverse experiences were reported, no subjects died and no subjects discontinued because of an adverse experience. The most frequently reported adverse experience was somnolence. An increased number of subjects reported somnolence with moderate intensity at higher doses.

Two female subjects reported sleep paralysis: AN 0012 reported sleep paralysis upon awakening lasting 5 min following placebo, AN 0114 reported sleep paralysis lasting 10 min following a single dose of 240 mg suvorexant. Note: Subject AN 0114 did not have higher MK-4305 plasma levels than the rest of the subjects in this group.

P012: An Open-Label Study to Investigate the Absorption, Metabolism, Excretion, and Mass Balance of a Single Oral Dose of [^{14}C] MK-4305 in Healthy Subjects

Objectives:

- To quantify total radioactivity and concentrations of MK-4305 and metabolite M9 in plasma after oral administration of a single dose of [^{14}C]-MK-4305.
- To examine the metabolism of MK-4305 in humans and to identify major metabolites in biological specimens.
- To investigate routes of elimination of MK-4305 in healthy subjects after oral administration of a single dose of [^{14}C]-MK-4305.

Study Design	Single-dose, open-label study to investigate the absorption, distribution, metabolism, and excretion (ADME) of [^{14}C]-MK-4305
Study Population *	6 healthy male subjects, 18-45 years, BMI $\leq$ 31 kg/m^2
Treatment Group	No trt groups, all subjects received [^{14}C]-MK-4305
Dosage and Administration	A single oral dose of 50 mg (~200 μCi) [^{14}C]-MK-4305 as five capsules each containing 10 mg (~40 μCi per capsule). The dose was administered orally with ~240 mL water, following an overnight fast.
PK Sampling: plasma, urine, fecal, CO_2 **	Sample collection for plasma, urine and fecal was planned up to a maximum period of 28 days post-dose. Radioactivity for plasma, urine and fecal sample collection was measurable out to 15 Days (336 hours) of post-dose. The CO_2 samples were not analyzed, as the recovery of radioactivity was acceptable.
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL
PK Assessment	C_{max}, t_{max}, $AUC_{0\text{-inf}}$, $t_{1/2}$ of MK-4305 $AUC_{0\text{-last}}$, C_{max}, and T_{max} of total radioactivity MK-4305 metabolite profiling and/or identification in plasma
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* One subject discontinued from study due to personal reason on Day 10 after his early post-study visit. The subject missed the last of 3 consecutive urine samples for radioactivity analysis per protocol. He was included in the pharmacokinetic and radioactivity analysis because he had two prior consecutive intervals with urine + feces recoveries <1% at his discontinuation.

** Blood, urine, fecal and CO_2 samples were collected until the majority of radioactivity was recovered to evaluate [^{14}C]-MK-4305 and metabolites up to a maximum period of 28 days post-dose. CO_2 samples were collected for archive. Urine and fecal samples were analyzed using real-time monitoring for radioactivity. Subjects were discharged when either one of these two criteria were satisfied: 1) total recovery $\geq$ 90% or 2) there was $\leq$ 1% radioactivity in each of 3 consecutive samples from combined 24-hr urine and fecal collections.

Blood collection times: Pre-dose, 30, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144 and 168 hours post-dose. If discharge criteria is not met at Day 8 (168 hours post-dose), blood at every 24-hour time-point up to Day 11 and on Days 14, 17, 23, and the final day of study duration will be collected until the discharge criteria is met, or a maximum stay of 28 days following study drug administration is reached.

Urine collection intervals: pre-dose (-2 to 0), 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144 and 144 to 168 hours post-dose.

Bioanalytical Assays:

Plasma samples were analyzed for suvorexant. M9 was not assayed. Plasma concentrations of suvorexant were determined using validated LC-MS/MS method (method DM-909). The assay performance during the validation was acceptable, details of the validation are presented in Section 2.6.1 in QBR.

Quantification of radioactivity for plasma, urine and feces was performed (b) (4) The concentration of radioactivity in plasma taken at predose, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, and 312 h postdose was determined by liquid scintillation counting (LSC).

Metabolite profiling and/or identification for plasma, urine and feces were performed by DMPK, MRL. Plasma samples were pooled over the 0-24 hr collection period and the volumes of samples used for pooling from each time point were proportional to the time of collection so that the concentration of each component in the pooled sample is proportional to its AUC. Samples were analyzed using HPLC coupled with radioactivity detection and high resolution mass spectral detection using electrospray ionization in positive ion mode. Plasma samples from a separate multiple dose study in human (P003) were also prepared for metabolite profiling. Day 1, 3, and 14 samples collected from 0-24 hr for the 100 mg dose group were pooled for each day across n=6 subjects. In addition, Day 14 samples from the 40 and 80 mg dose groups were also pooled from 0-24 hr for each dose group. All the samples were pooled using the "AUC" pooling method described above.

Quantitative estimation of metabolites was done by multiplying the percentage of radioactivity for a metabolite in a sample by the percentage of radioactive dose excreted in the sample.

Pharmacokinetic Results:

The summary statistics for MK-4305 and total radioactivity are presented in the table below. M9 was quantitated using metabolite profiling.

Median plasma concentration T_{max} of MK-4305 was 1.5 hr post dose and the mean apparent terminal $t_{1/2}$ was 12.3 hr.

The concentration of [^{14}C]MK-4305 derived radioactivity in plasma had a T_{max} of 1.5 hr.

Summary of MK-4305 Pharmacokinetics Compared to Total Radioactivity and Following a Single Dose Administration of [^{14}C] MK-4305 50 mg in Healthy Male Subjects (N=6)

	$AUC_{0-\infty}$ (µmol•hr/l or µmol eq•hr/l)	AUC_{0-last} (µmol•hr/l or µmol eq•hr/l)	AUC_{0-24hr} (µmol•hr/l or µmol eq•hr/l)	C_{max} (µmol/l or µmol eq/l)	T_{max}[a] (hr)	$t_{½}$[b] (hr)
MK-4305	16.09 ± 5.36	16.02 ± 5.37	11.55 ± 3.62	1.72 ± 0.72	1.5 (0.5, 2.0)	12.2 ± 1.8
Total Radioactivity	145.12 ± 57.19	132.27 ± 51.76	58.81 ± 27.15	4.98 ± 2.42	1.5 (1.0 , 2.0)	53.4 ± 18.6

The major route of elimination of MK-4305 was via metabolism.

The major route of excretion of MK-4305-derived radioactivity was via feces (66% of the dose recovered in the feces and 23% of the dose was excreted in urine). The overall mean recovery of radioactivity in urine and feces was 90% over the 336 hr study, with majority of the radioactivity excreted in the first 144 hr post dose (82%).

MK-4305 Plasma Pharmacokinetics Summary and Comparison to Total Radioactivity				
	MK-4305	Total Radioactivity	MK-4305/ Total Radioactivity	
Parameter	GM (95% CI)[†]	GM (95% CI)[†]	GMR (95% CI)[‡]	rMSE [§]
$AUC_{0\text{-last}}$ [#] (μM•hr)	15.38 (10.95, 21.58)	124.88 (88.96, 175.29)	0.12 (0.10, 0.14)	0.108
C_{max} (μM)	1.62 (1.09, 2.40)	4.58 (3.09, 6.77)	0.35 (0.27, 0.46)	0.173
$AUC_{0\text{-}\infty}$ (μM•hr)	15.45 (11.26, 21.21)	--	--	--
T_{max} (hr) [‖]	1.50 (0.50, 2.00)	1.50 (1.00, 2.00)	--	--
Half-life (hr) [††]	12.3 (1.8)	--	--	--
Proportion of The Total Radioactivity Dose Recovered				
	Urine	Feces	Toilet tissue	Total
Percentage of Total Radioactivity Dosage Recovery (%) 95% Confidence Interval	23.03 (16.38, 29.68)	66.37 (60.57, 72.16)	0.35 (-0.00, 0.70)	89.73 (83.48, 95.99)

[†] Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
[‡] GMR = Geometric mean ratio (MK-4305 / Total Radioactivity).
[§] rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. For log-transformed variables, rMSE*100% approximates the within-subject %CV on the raw scale.
[#] T_{last} = 72 – 120 hours for plasma MK-4305, T_{last} = 168 – 312 hours for plasma total radioactivity.
[‖] Median (min, max) for T_{max}.
[††] Harmonic mean (jack-knife SD) for half-life.

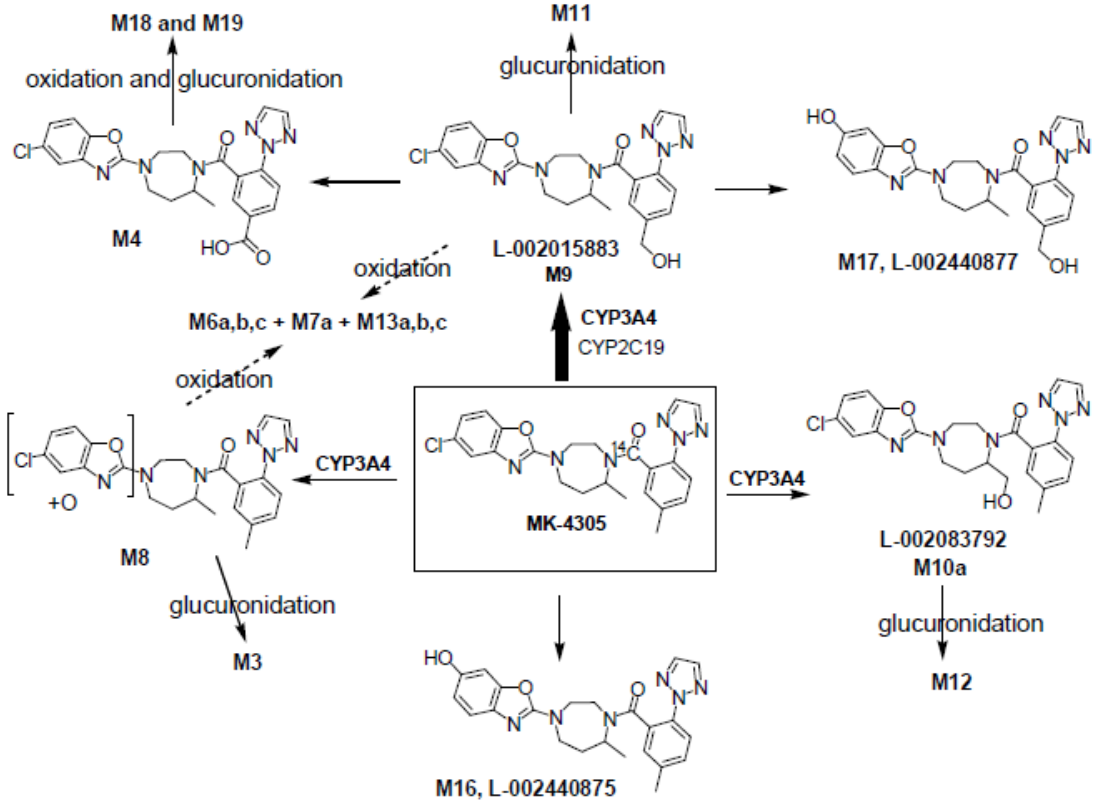
Comparison of the plasma $AUC_{0\text{-last}}$ values of unchanged MK-4305 and plasma radioactivity indicated that about 12% of the plasma radioactivity was accounted for by unchanged MK-4305.

MK-4305 and metabolite M9 were the predominant circulating entities following a single dose of MK-4305. Several minor metabolites including M4, M7a, M8, M10a, M12 and M17 were also detected in human plasma. All of the human circulating metabolites were also detected in the plasma of preclinical species including mouse, rat, rabbit, dog, and monkey, except for M17 which was not present in rat plasma.

The most prevalent components in urine samples were the carboxylic acid derivative (M4) and its glucuronides (M19), accounting for 4.1 and 5.2% of the dose, respectively. Glucuronides of oxidized metabolites, M3 and M12, were also observed and accounted for 3.8 and 2.7% of the dose, respectively. In addition, M11, a glucuronide of M9, was detected, accounting for about 1% of the dose.

The major component in feces was the carboxylic acid derivative, M4, accounting for 17.0% of the dose. M18, which results from further oxidation of M4, was also a major metabolite observed in the feces, representing 10.6% of the dose. The benzyl alcohol, M9, and a metabolite resulting from hydroxylation of the methyldiazapane moiety, M10a, each accounted for about 9% of the dose.

Proposed Structures and Metabolic Pathways of MK-4305 in Human



Distribution of Metabolites as Percent of Total MK-4305-Derived Circulating Material in Human Plasma (0-24 hr AUC Pool, Across n=6 Subjects)

Metabolite	Percent of Total[a]
MK-4305	30.1
M4	1.5
M7a	3.4
M8	6.0
M9	36.5
M10a	2.3
M12	12.2
M16	4.8
M17	3.3

[a] Estimated based on HPLC-radioactivity detection and MS analysis.

Reviewer's Comments:

1. M9 was a major circulating metabolite of suvorexant. However, M9 was found to be a P-gp substrate in human and is not expected to be active in vivo based on results from in vitro and EEG studies in dogs.

2. Circulating metabolites at steady-state of suvorexant were also evaluated semi-quantitatively using HPLC-HRMS. Day 3 and 14 plasma samples (0-24 hr pooled) from a multiple dose human study (PN003) were evaluated. Compared with the plasma profile after a single dose, in addition to M9 and suvorexant, metabolite M17 became prevalent in Day 3 and Day 14 plasma. The structure of M17 was determined to be a di-hydroxylated derivative of suvorexant based on NMR analysis. The level of M17 in Day 14 samples was estimated to be <10% of the total drug related material (ranging from 8.6 – 9.8% for the three dose levels). Circulating level of M17 approached steady-state by Day 14 following multiple daily dosing of suvorexant in human (based on the plasma total plasma radioactivity $t_{1/2}$ of 53 hr, M17 should have reached steady-state by Day 14), therefore its levels should not be expected to increase further. In addition, the in vitro potency of M17 was approximately 5-100-fold lower than that of suvorexant with Ki values of 355 and 46.5 nM for binding towards Orexin-1 and Orexin-2 receptors, respectively. Similar to M9, M17 was found to be a P-gp substrate in human. Based on the information above, M17 is unlikely to be present sufficiently in the CNS to contribute to the pharmacological activity of MK-4305 in humans. M17 did not show any activities in the Panlabs screen (secondary pharmacology). Since M17 in Day 14 samples was estimated to be less than 10% of the total drug related material and there were no notable findings in the primary and secondary pharmacology, M17 should not be considered a major human metabolite.
3. M12, a glucuronide derivative of an oxidation product of suvorexant, was another human circulating metabolite (accounting for 12.2% of the total circulating suvorexant-derived material). However, M12 is a glucuronide and is a much more polar compound; therefore, M12 is unlikely to have intrinsic pharmacological activity or to be brain penetrant.

Safety:
No serious clinical AEs were reported. No subjects discontinued the study due to an adverse experience. The most frequently reported clinical adverse experiences were somnolence (100% of subjects). No clinically significant abnormalities were noted in routine blood chemistry panels, hematology, ECG, or physical examinations including vital signs.

P018: A Study to Evaluate the Intravenous and Oral Dose Proportionality of Suvorexant (MK-4305) in Healthy Subjects

Objectives:

Part I: To determine the plasma pharmacokinetics of suvorexant and the dose proportionality of four, single, intravenous dose (IV) administrations of suvorexant.

Part II: To determine the dose proportionality of single, oral dose administrations of suvorexant (MK-4305) over the range of 10 mg to 80 mg.

Study Design	Open-label, randomized, two-part study in healthy subjects Part I: IV dose escalation study to assess the dose linearity of four IV doses of suvorexant. Part II: four-period cross over study to provide oral dose proportionality information using the final market image (FMI).
Study Population	48 healthy subjects, 18-60 years Part I: 32 (18 males and 14 females) Part II: 16 (8 males and 8 females)
Treatment Group	Two panels (IV and oral), 4 trt periods for each panel
Dosage and Administration	All doses were administered in the morning after a minimum 8-hr fast. Part I (IV dose): 5 mg, 10 mg, 20 mg, and 30 mg Part II (oral dose): 10 mg, 20 mg, 40 mg and 80 mg
PK Sampling: plasma	Part I : predose, 15; 30; and 45 minutes, and 1; 1.25; 1.5; 2; 3; 4; 6; 9; 12; 16; 24; 48; 72 and 96 hours following the initiation of IV infusion of study drug.* Part II : predose, 0.5; 1; 2; 4; 6; 9; 12; 16; 24; 48; 72 and 96 hours following oral dosing
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL
PK Assessment	Part I: The dose proportionality of suvorexant $AUC_{0-\infty}$ administered IV over the dose range of 5 to 30 mg was assessed by fitting a power-law model. ** Part II: The dose proportionality of suvorexant $AUC_{0-\infty}$ over the dose range of 10 to 80 mg was assessed by fitting a power-law model under a mixed-effect modeling approach. ***
PD Assessment	Bond and Lader Visual Analog Scale (VAS)
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* For Panel 4, Part I, suvorexant plasma samples were obtained at: predose; 15 and 30 minutes, and 1; 1.25; 1.5; 2; 2.5, 3; 4; 6; 9; 12; 16; 24; 48; 72 and 96 hours following the initiation of IV infusion of study drug.

** The power-law model had the following form: $\ln(AUCi) = \mu + \beta \ln[dosei] + \varepsilon i$, where μ was intercept, β the slope for the continuous covariate ln(dose) and εi was the random error. On the back-transformed scale, this model was: $AUCi = Ci\ dose^{\beta}$, where Ci was the proportionality constant. Assuming the power law model is an adequate fit to the data, $\beta = 1.00$ under perfect dose proportionality. The deviation of β from 1.00 reflects the degree of curvature in the dose-exposure relationship.

*** The power-law model had the following form: $\ln(AUCij) = Si + Pj + \beta \ln[dose] + \varepsilon ij$, where, Si was the random effect of subject i , pj the fixed effect of period j , β the slope for the continuous covariate ln(dose) and εij the random error. On the back-transformed scale, this model was: $AUCij = Cij\ dose^{\beta}$, where Cij was a function of the effect of subject, period and error. A check for the presence of a first-order carryover effect was conducted and found to be non-significant (hence, not included in the final model) . Assuming the power law model was an adequate fit to the data, $\beta = 1.00$ under perfect dose proportionality.

The deviation of β from 1.00 reflects the degree of curvature in the dose-exposure relationship. A 90% confidence interval (CI) based on a t-distribution, was generated from the above mixed effects model for β.

Bioanalytical Assay:

Plasma samples were analyzed for suvorexant. M9 was not assayed. Plasma concentrations of suvorexant were determined using validated LC-MS/MS) methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.

The assay performance during the analysis of the plasma samples was acceptable. Representative chromatograms were also provided.

Pharmacokinetic Results:

Part I - For the dose proportionality assessment of suvorexant following single dose IV administration of 5 mg to 30 mg, the slope (90%CI) from the power model was 0.84 (0.69, 0.99) for $AUC_{0-\infty}$. Since the confidence interval for the slope lies below 1.0, there is evidence that increases in $AUC_{0-\infty}$ are less than strictly dose proportional over the IV dose range in this study. According to the sponsor, this is driven largely by the exposures observed at the 30 mg IV dose, which were lower than expected based on the 5 – 20 mg IV dose exposures. In comparison, following IV administration of suvorexant over the range of 5 to 20 mg, dose-proportional increase in AUC was observed with CL unchanged, suggesting absorption-rate limitations following oral administration rather than other nonlinear mechanisms.

Summary of PK Parameters of Suvorexant (MK-4305) Following Administration of Single IV-Infusion Doses in Healthy Male and Female Subjects

PK Parameter	5 mg[†] N= 8	10 mg[†] N= 8	20 mg[†] N=8	30 mg[†§] N= 8
$AUC_{0-\infty}$ (μM•hr)	3.46 (2.78,4.32)	6.92 (5.54,8.63)	15.10 (12.11,18.84)	13.73 (11.00,17.13)
C_{eoi} (μM)	0.543 (0.470,0.627)	1.044 (0.904,1.206)	1.751 (1.516,2.023)	1.900 (1.645,2.194)
CL (mL/min)	52.28 (42.00,65.08)	52.72 (42.35,65.63)	48.60 (39.04,60.50)	80.62 (64.76,100.36)
V_{dss} (L)	36.51 (31.20,42.72)	42.46 (36.29,49.69)	57.12 (48.81,66.84)	57.33 (48.99,67.08)
Apparent terminal $t_{1/2}$[‡] (hr)	9.2 (3.4)	9.9 (5.2)	13.5 (5.0)	8.9 (1.7)

[†]Back-transformed least squares mean and 95% confidence interval from fixed effects model performed on natural log-transformed values.

[‡]Harmonic mean; jack-knife SD.

[§]Infusion time for 30 mg was 1.5 hours, compared to the 1 hour infusion time for 5, 10 and 20 mg.

Part II – Following suvorexant single oral dose administration of 10 mg to 80 mg, the slope and 90% CI from the power model was 0.78 and (0.70, 0.86) for $AUC_{0-\infty}$. As the confidence interval for the slope lies below 1.0, this suggests less than dose proportional PK over the 10 mg to 80 mg range in this study.

Summary of Pharmacokinetic Parameters of Suvorexant (MK-4305) Following Single Oral Dose Administration of 10 mg to 80 mg in Healthy Male and Female Subjects (Part II)

PK Parameter	10 mg[†] N= 16	20 mg[†] N= 16	40 mg[†] N=16	80 mg[†] N= 16
$AUC_{0-\infty}$ (μM•hr)	5.32 (4.55,6.23)	9.51 (8.12,11.14)	16.21 (13.85,18.98)	27.26 (23.28,31.91)
C_{max} (μM)	0.456(0.403,0.516)	0.646 (0.572,0.731)	0.956 (0.845,1.082)	1.518 (1.342,1.717)
T_{max}[‡] (hr)	1.5 (1.0,4.0)	1.0 (1.0,4.0)	2.0 (1.0,4.0)	2.0 (0.5,6.0)
Apparent terminal $t_{1/2}$[§] (hr)	12.1 (1.8)	12.5 (2.6)	12.6 (2.5)	13.6 (2.9)

Assessment of Dose Proportionality of Suvorexant (MK-4305) Following Single Oral Dose Administration of 10 mg to 80 mg in Healthy Male and Female Subjects (N=16) (Part II)

Parameter	Dose Range(mg)	Slope Estimate (90% CI)	Expected Fold-Change (90% CI)[†]	Expected Fold-Change with Perfect Dose-Proportionality
$AUC_{0-\infty}$	10-80	0.78 (0.70, 0.86)	5.10 (4.32, 6.03)	8
	10-40	0.80 (0.68, 0.93)	3.05 (2.57, 3.61)	4
	20-80	0.76 (0.63, 0.89)	2.87 (2.38, 3.45)	4
C_{max}	10-80	0.58 (0.51, 0.64)	3.32 (2.90, 3.80)	8
	10-40	0.53 (0.43, 0.64)	2.10 (1.82, 2.42)	4
	20-80	0.62 (0.51, 0.73)	2.35 (2.01, 2.73)	4

[†] Fold change for highest dose/ lowest dose based on results from the power model and assessment of dose proportionality over this dose range.

Absolute Bioavailability Estimate

A population PK model-based approach was used to estimate the absolute bioavailability of suvorexant 10, 20, 40, and 80 mg oral doses with the IV and PO dose proportionality data from P018. Due to the unusual exposures observed at the 30 mg IV dose, where exposures were similar to those observed at the 20 mg IV dose despite dose proportional increases in exposure over the 5 to 20 mg IV doses, the estimation of bioavailability values was done excluding and including the data from the 30 mg IV arm as a sensitivity analysis. For details, refer to the Pharmacometric Review, Section 3.1.2.

	Excluding 30 mg IV Arm		Including 30 mg IV Arm	
Dose (mg)	Bioavailability (5th and 95th Percentile)	Fractional Change Relative to 40 mg	Bioavailability (5th and 95th Percentile)	Fractional Change Relative to 40 mg
10	0.82 (0.74, 0.89)	0.74 Increase	0.88 (0.81, 0.94)	0.71 Increase
20	0.62 (0.55, 0.69)	0.33 Increase	0.68 (0.61, 0.74)	0.32 Increase
40	**0.47 (0.41, 0.53)**	**1**	**0.51 (0.46, 0.57)**	**1**
80	0.37 (0.31, 0.42)	0.21 Decrease	0.41 (0.36, 0.46)	0.21 Decrease

Safety:

Single oral and IV doses of suvorexant were generally well tolerated in healthy male and female subjects. No serious clinical or lab AEs were reported. The most frequently reported AE was somnolence. In Part I (IV administration), 100% of subjects receiving suvorexant 20 mg IV and 30 mg IV reported somnolence. 50% and 62.5% of the subjects, respectively reported somnolence after receiving 5 mg IV and 10 mg IV suvorexant. In Part II (oral administration), 56.3% and 75% of the subjects respectively reported somnolence after receiving 10 mg and 20 mg suvorexant and 87.5% of the subjects reported somnolence after receiving 40 mg and 80 mg suvorexant.

1.2 Intrinsic Factor PK Studies

P004: A Double-Blind, Randomized, Placebo-Controlled, Single-Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of MK-4305 in Healthy Elderly Male and Female Subjects

Objectives:

Primary: To evaluate the safety and tolerability of single doses of MK-4305 in healthy male and female elderly subjects following daytime administration of a single oral dose.
Secondary: To compare the single-dose pharmacokinetic parameters of MK-4305 in healthy elderly subjects to those obtained from healthy young male subjects (historical controls from Protocol 001).

Study Design	Double-blind, randomized, placebo-controlled, single-dose study in healthy, elderly, male and female subjects.
Study Population	10 male and 10 female, 65-77 years old
Treatment Group	2 panels, 1 treatment period in each panel Panel A: males, Panel B: females
Dosage and Administration	Eight subjects received active drug (a single 16 mg oral dose of MK-4305) and two (2) subjects received placebo, of each gender. All doses in Panels A and B were administered in the fasted state.
PK Sampling: plasma	Pre-dose, 0.5; 1; 2; 4; 6; 8; 12; 16; 24; 48; and 72 hours
Analysis	Plasma: LC-MS/MS method for MK-4305 and M9 Range: 1 to 1000 ng/mL
PK Assessment	$AUC_{0-\infty}$, C_{4hr}, C_{max}, T_{max}, and apparent t½ of MK-4305 and M9
PD Assessment*	CDR System composite scores for Power of Attention, Continuity of Attention, Quality of Episodic Secondary Memory (long-term memory), Quality of Working Memory and Speed of Memory Digit Symbol Substitution Test (DSST) Bond and Lader Visual Analog Scale (VAS) Karolinska Sleepiness Scale (KSS)
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* CDR Cognitive Tests and DSST were administered at pre-dose, and at 2 and 24 h post-dose. KSS and VAS were administered at pre-dose, and at 1, 2, 4, 6, 8 and 24 h post-dose

Bioanalytical Assay:

Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using validated LC-MS/MS methods (method DM-909 for suvorexant and DM-928 for M9). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:

The PK data from young male subjects (historical control from P001) were normalized to 16 mg after establishing dose proportionality in the dose range 4- 20 mg and pooled across the 4, 10, and 20 mg doses. Only data from healthy elderly male subjects was used for comparison to young male subjects.
The $AUC_{0-\infty}$ and C_{max} ratios of geometric means (GMs) for healthy elderly female subjects /healthy elderly male subjects were 1.55 and 1.29, respectively. The $AUC_{0-\infty}$ and C_{max} ratios of GMs for the comparison of healthy elderly male subjects with healthy young male subjects were 0.92 and 0.72, respectively.
The $AUC_{0-\infty}$ and C_{max} ratios of GMs for the comparison of M9 following 16 mg of MK-4305 in healthy elderly female subjects with healthy elderly male subjects were 1.38 and 1.05, respectively.

Summary Statistics for MK-4305 Pharmacokinetic Parameters Following Single Oral Dose Administration of MK-4305 16 mg in Healthy Elderly Male, Elderly Female, and Young Male Subjects

Population	N	$AUC_{0-\infty}$† (µM•hr) GM (95% CI)	C_{max}† (µM) GM (95% CI)	C_{4hr}† (µM) GM (95% CI)	T_{max}‡ (hr)	Apparent terminal $t_{1/2}$§ (hr)
Young Male#	26	6.30 (5.43, 7.31)	0.822 (0.724, 0.933)	0.389 (0.344, 0.439)	1.0 (0.5, 4.0)	8.6 (2.7)
Elderly Male	8	5.78 (4.53, 7.38)	0.590 (0.505, 0.690)	0.267 (0.212, 0.334)	1.0 (1.0, 2.0)	12.0 (2.3)
Elderly Female	8	8.99 (7.04, 11.47)	0.761 (0.652, 0.889)	0.293 (0.234, 0.367)	1.0 (0.5, 2.0)	15.0 (4.1)

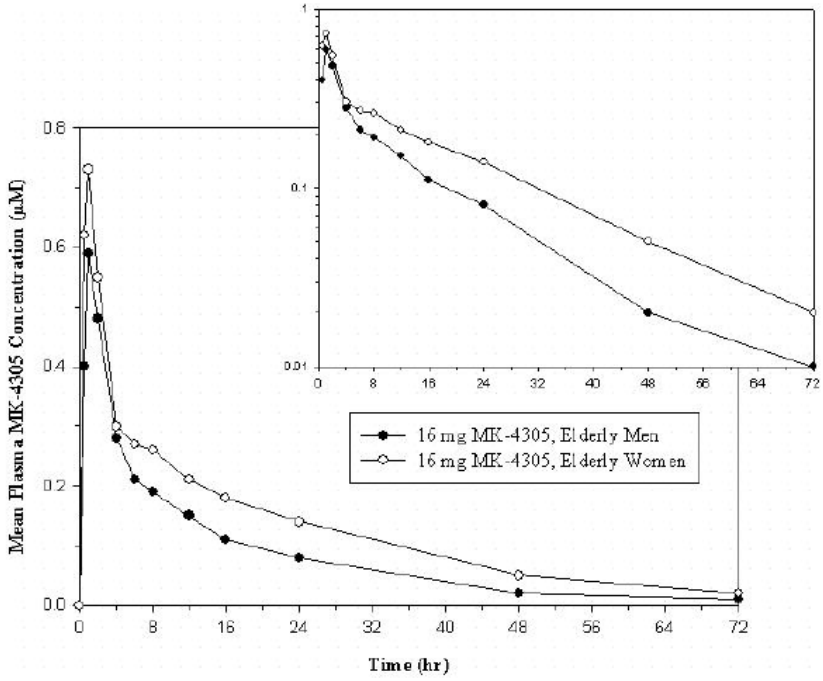
Comparison	$AUC_{0-\infty}$ (µM•hr) GMR (90% CI)	C_{max} (µM) GMR (90% CI)
Gender‖		
Elderly Female Vs. Elderly Male	1.55 (1.17, 2.06)	1.29 (1.08, 1.54)
Age‖		
Elderly Male Vs. Young Male	0.92 (0.71, 1.19)	0.72 (0.58, 0.89)

Summary Statistics for M9 Pharmacokinetic Parameters Following Single Oral Dose Administration of MK-4305 16 mg in Healthy Elderly Male and Elderly Female Subjects

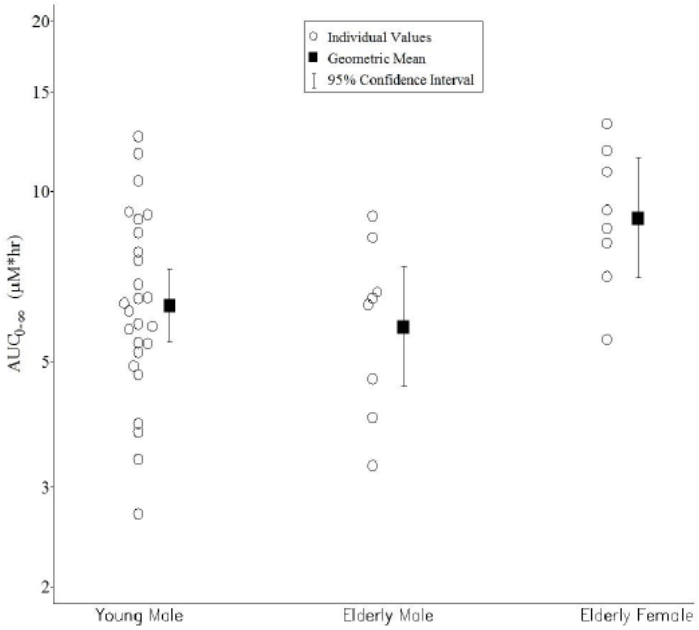
Population	N	$AUC_{0-\infty}$† (µM•hr) GM (95% CI)	C_{max}† (µM) GM (95% CI)	C_{4hr}† (µM) GM (95% CI)	T_{max}‡ (hr)	Apparent terminal $t_{1/2}$§ (hr)
Elderly Male	8	7.80 (6.16, 9.87)	0.504 (0.452, 0.562)	0.403 (0.357, 0.455)	2.0 (1.0, 6.0)	12.3 (3.0)
Elderly Female	8	10.74 (8.48, 13.60)	0.529 (0.474, 0.590)	0.421 (0.373, 0.475)	2.0 (1.0, 8.0)	15.6 (4.3)

Comparison	$AUC_{0-\infty}$ (µM•hr) GMR (90% CI)	C_{max} (µM) GMR (90% CI)
Gender‖		
Elderly Female vs. Elderly Male	1.38 (1.05, 1.81)	1.05 (0.92, 1.19)

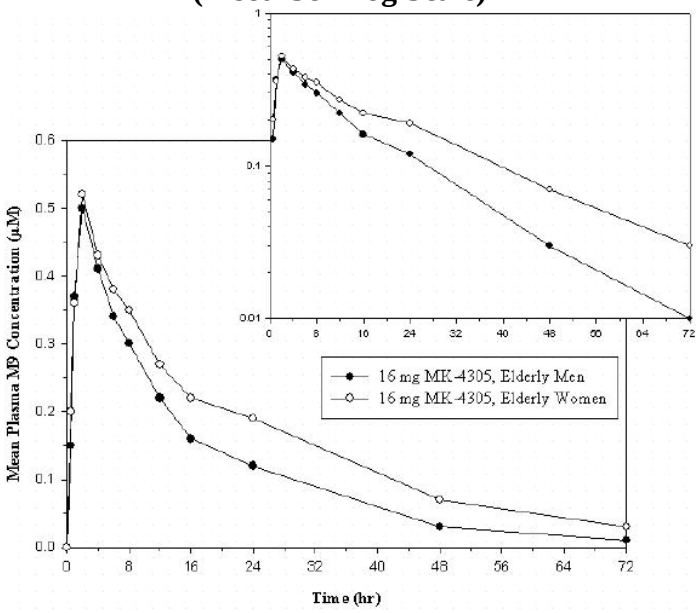
Arithmetic Mean MK-4305 Plasma Concentrations (µM) Following Single Oral Dose Administration of MK-4305 16 mg in Elderly Male, and Elderly Female Subjects (Inset=Semilog Scale)



Geometric Mean, 95% Confidence Intervals and Individual Plasma MK-4305 $AUC_{0-\infty}$ Values Following Single Oral Dose Administration of MK-4305 16 mg in Elderly Male (N=8), and Elderly Female (N=8) and Young Male Subjects (N=26 from P001 pooled across MK-4305 4, 10 and 20 mg, dose normalized to 16 mg)



Arithmetic Mean M9 Plasma Concentrations (µM) Following Single Oral Dose Administration of MK-4305 16 mg in Elderly Male and Elderly Female Subjects (Inset=Semilog Scale)



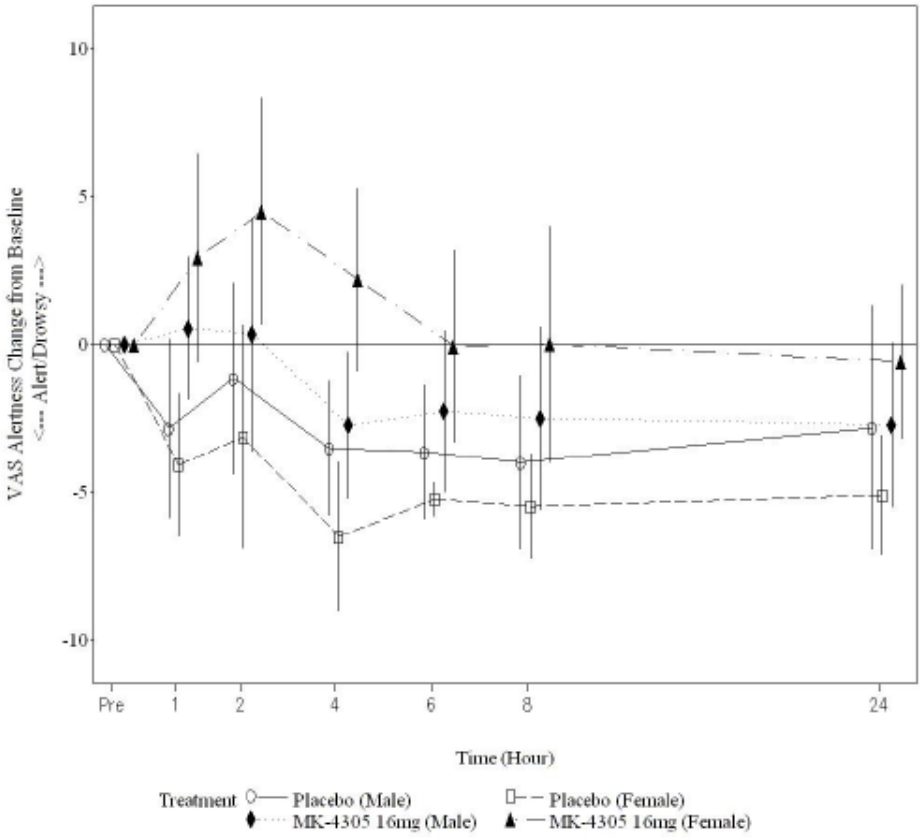
Reviewer's Comment: The results from this study suggest that elderly females have higher suvorexant exposure than elderly males: the $AUC_{0-\infty}$ in elderly females is approximately 55% higher than that observed in elderly males. Suvorexant exposure in healthy elderly men was similar to that in healthy young males through cross-study comparison.

Pharmacodynamic Results:

The PD effects of MK-4305 were assessed using the subjective measurements of the Bond and Lader VAS following single dose AM administration of MK-4305 16 mg in healthy elderly male and female subjects. The scale was administered at 1, 2, 4, 6, 8 and 24 hr post AM administration.

For the elderly females there appeared to be a decrease in alertness factor (or drowsiness increasing) at 2 hr post dose consistent with desired PD effect of MK- 4304. In elderly males there were minimal to no effects on alertness factor.

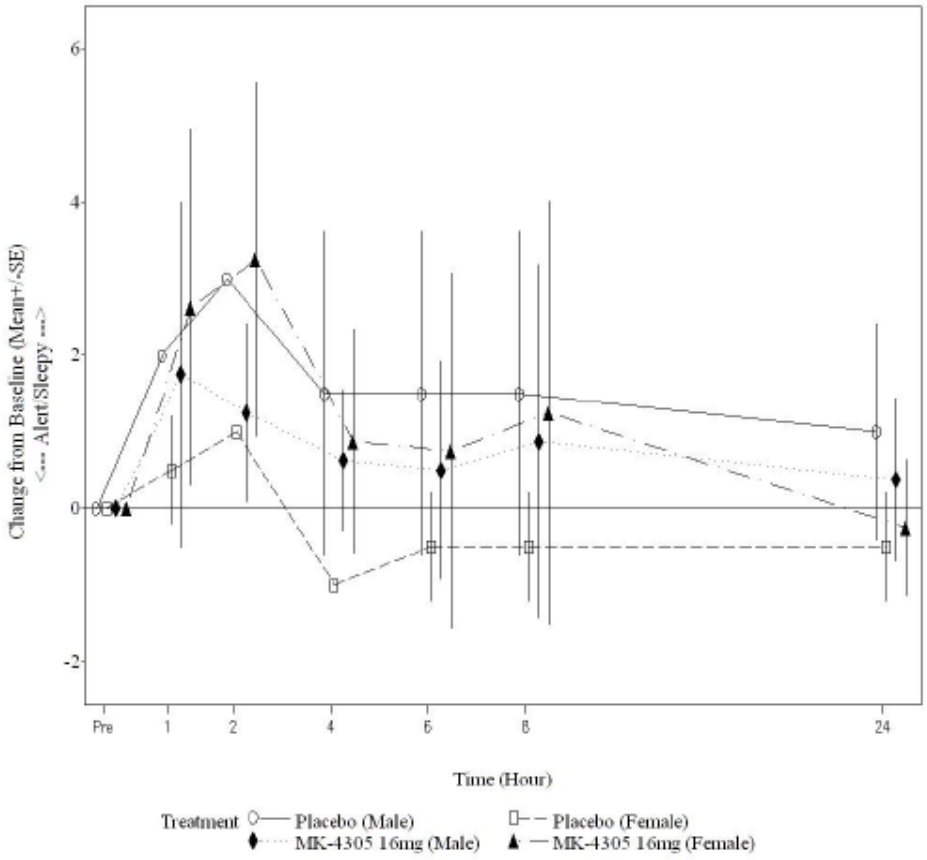
Mean Change from Baseline (+/- SE) for VAS Alertness Following Single Oral Dose Administration of MK-4305 16 mg or Placebo in Elderly Male (N=8 Active, N=2 Placebo) and Elderly Female (N=8 Active, N=2 Placebo) Subjects



The Karolinska Sleepiness Scale (KSS) was administered at 1, 2, 4, 6, 8 and 24 hr post AM administration.

Following an AM oral doses of 16 mg, elderly males and elderly females experienced a small effect of increased in sleepiness at 1 and 2 hr post dose respectively. Also, following AM oral doses of placebo (n=2), elderly males experienced a small effect of increased sleepiness. These findings suggest a small effect on alertness based on KSS consistent with the desired PD endpoints for MK-4305.

Mean Change from Baseline (+/- SE) for KSS Following Single Oral Dose Administration of MK-4305 16 mg or Placebo in Elderly Male (N=8 Active, N=2 Placebo) and Elderly Female (N=8 Active, N=2 Placebo) Subjects



Summary statistics for the DSST endpoints of number correct are provided in the table below. There were no decreases in the number correct which suggests no apparent impairment of 16 mg MK-4305 on DSST.

Summary Statistics for DSST (Number Correct) Following Single Oral Dose Administration of MK-4305 16 mg in Healthy Elderly Male and Elderly Female Subjects

Treatment	Time	Value			Change From Baseline†		
		N	Mean	SD	N	Mean	SD
Placebo (Male)	Predose	2	39.50	0.71	.	.	.
	2 Hours	2	37.00	2.83	2	-2.50	3.54
	24 Hours	2	39.50	3.54	2	0.00	2.83
Placebo (Female)	Predose	2	49.00	15.56	.	.	.
	2 Hours	2	50.50	12.02	2	1.50	3.54
	24 Hours	2	52.50	10.61	2	3.50	4.95
MK-4305 16mg (Male)	Predose	8	38.50	11.59	.	.	.
	2 Hours	8	40.75	12.65	8	2.25	2.92
	24 Hours	8	44.25	14.20	8	5.75	3.15
MK-4305 16mg (Female)	Predose	8	48.38	6.65	.	.	.
	2 Hours	8	49.38	5.55	8	1.00	3.25
	24 Hours	8	55.75	9.56	8	7.38	6.70

† Predose measurement serves as baseline, analysis performed on raw scale

Safety results:

No serious clinical adverse experiences (AEs) were reported. No subjects discontinued the study due to an AE. All clinical adverse experiences were mild in intensity. The most frequently reported clinical adverse experience was somnolence (40% of subjects). All subjects who reported somnolence received MK-4305; 6 females reported somnolence while 2 males reported somnolence.

P005: A Double-Blind, Randomized, Placebo-Controlled, Alternating Panel, Single Rising Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Suvorexant (MK-4305) in Healthy Japanese Male Subjects

Objectives:

Primary: To evaluate the safety and tolerability of suvorexant (MK-4305) after administration of single rising oral doses to healthy Japanese male subjects.

Secondary: To compare the effects of a standardized Japanese breakfast on the plasma PK of suvorexant to those in the fasted state after oral administration of single doses of suvorexant to healthy Japanese male subjects.

Exploratory: To compare plasma PK after oral administration of single doses of suvorexant in healthy Japanese male subjects and non-Japanese subjects using data from Protocol 001.

Study Design	Two-part, randomized, double-blind, placebo-controlled, alternating panel, single oral rising dose study
Study Population	32 healthy Japanese male subjects, 8 per panel, 20-45 years
Treatment Groups *	Two parts, 2 panels in each part, 4 trt periods for each panel. For all panels, in each treatment period, 6 subjects received active drug and 2 subjects received placebo. There was a minimum 10-day washout between each treatment period for each subject.
Dosage and Administration*	Part 1, panel A: 4 mg, 20 mg, 76 mg AM, 76 mg PM or matching placebo Part 1, panel B: 10 mg, 50 mg, 100 mg, 10 mg fed or matching placebo Part 2, Panel C: 4 mg, 20 mg, 76 mg AM, 76 mg PM or matching placebo Part 2, Panel D: 10 mg, 50 mg, 100 mg, 10 mg fed or matching placebo All doses were in the fasted state, except for 10 mg in panels B and D.
PK Sampling: plasma	Plasma samples were collected at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96 h post-dose
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL
PK Assessment	C_{max}, C_{4h}, t_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$ of MK-4305
PD Assessment	Karolinska Sleepiness Scale (KSS) Bond and Lader Visual Analog Scale (VAS)
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* Dosing was discontinued after Panel A, Period 3 and Panel B, period 2 based on preliminary evaluation of somnolence related AEs and the neurological exams in Part 1, which raised clinical concerns. Therefore, the protocol was amended to conduct Part 2. An additional 16 subjects were enrolled in two panels, Panel C (4 mg, 20 mg, 76 mg AM, 76 mg PM or matching placebo) and D (10 mg, 50 mg, 100 mg, 10 mg fed or matching placebo), each of which was to contain 4 treatment periods.

Bioanalytical Assay:

Plasma samples were analyzed for suvorexant. M9 was not assayed. Plasma concentrations of suvorexant were determined using a validated LC-MS/MS method (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.

The bioanalytical assay performance during analysis of the samples was acceptable.

Pharmacokinetic Results:

Suvorexant had a median T_{max} ranging from 1.0 – 4.0 hours and an apparent terminal half life ranging from 7.3 to 9.3 hours over the single dose range of 4 mg to 100 mg, following fasted AM administration based on Parts 1 and 2 combined.

Parts 1 and 2: Summary Statistics of Plasma Suvorexant (MK-4305) PK Parameters Following Single Oral AM Doses of 4 to 100 mg or Single Oral PM Dose of 76 mg Suvorexant (MK-4305) in Japanese Healthy Young Male Subjects

Panel A and C					
Parameter	4 mg† (N = 12)	20 mg† (N = 12)	76 mg† (N = 12)	76 mg (PM)† (N = 6)	rMSE‡
$AUC_{0-\infty}$§ (µM*hr)	1.68 (1.45, 1.94)	5.72 (4.94, 6.63)	14.18 (12.22, 16.44)	15.55 (12.98, 18.63)	0.153
AUC_{0-4hr}§ (µM*hr)	0.65 (0.56, 0.76)	1.97 (1.69, 2.30)	4.29 (3.68, 5.00)	2.71 (2.22, 3.32)	0.197
AUC_{0-24hr}§ (µM*hr)	1.53 (1.35, 1.73)	5.00 (4.42, 5.67)	11.99 (10.58, 13.59)	12.68 (10.80, 14.89)	0.149
C_{max}§ (µM)	0.244 (0.211, 0.282)	0.709 (0.613, 0.820)	1.595 (1.379, 1.845)	1.208 (0.995, 1.468)	0.192
C_{4hr}§ (µM)	0.130 (0.109, 0.156)	0.440 (0.367, 0.527)	1.168 (0.975, 1.398)	1.155 (0.881, 1.514)	0.317
C_{24hr}§ (µM)	0.013 (0.010, 0.016)	0.053 (0.041, 0.068)	0.156 (0.121, 0.201)	0.209 (0.154, 0.282)	0.242
T_{max}‖ (hr)	1.0 (0.5, 6.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.1)	4.0 (4.0, 6.0)	.
Apparent terminal $t_{1/2}$¶ (hr)	7.3 (1.7)	7.5 (1.7)	8.4 (1.7)	8.5 (2.2)	.
Panel B and D					
Parameter	10 mg# (N = 12)	10 mg (fed)# (N = 6)	50 mg# (N = 12)	100 mg# (N = 6)	rMSE‡
$AUC_{0-\infty}$§ (µM*hr)	2.92 (2.51, 3.39)	3.56 (2.96, 4.27)	10.41 (8.97, 12.08)	15.86 (13.19, 19.08)	0.153
AUC_{0-4hr}§ (µM*hr)	1.14 (0.98, 1.33)	0.85 (0.69, 1.04)	2.60 (2.23, 3.03)	4.37 (3.55, 5.37)	0.197
AUC_{0-24hr}§ (µM*hr)	2.63 (2.32, 2.98)	3.04 (2.58, 3.58)	8.61 (7.59, 9.77)	13.19 (11.19, 15.55)	0.149
C_{max}§ (µM)	0.408 (0.353, 0.473)	0.350 (0.287, 0.426)	1.029 (0.889, 1.191)	1.801 (1.476, 2.198)	0.192
C_{4hr}§ (µM)	0.228 (0.190, 0.273)	0.304 (0.232, 0.399)	0.790 (0.659, 0.946)	0.968 (0.738, 1.270)	0.317
C_{24hr}§ (µM)	0.023 (0.018, 0.030)	0.038 (0.028, 0.052)	0.126 (0.098, 0.163)	0.193 (0.142, 0.262)	0.242
T_{max}‖ (hr)	2.0 (0.5, 4.0)	3.0 (2.0, 4.0)	4.0 (2.0, 6.0)	2.0 (1.0, 6.0)	.
Apparent terminal $t_{1/2}$¶ (hr)	7.3 (1.5)	7.1 (1.4)	9.3 (2.0)	9.0 (2.1)	.

† Subjects in Panel A were given single doses of 4 mg, 20 mg, 76 mg or placebo in the fasted state; Subjects in Panel C were given single doses of 4 mg, 20 mg, 76 mg of suvorexant or placebo in the fasted state; in Period 4, Panel C, subjects were given single dose of 76 mg or placebo in the evening (PM) in the fasted state.

‡ rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject CV on the raw scale for $AUC_{0-\infty}$, AUC_{0-4hr}, AUC_{0-24hr}, C_{max}, C_{4hr} and C_{24hr}.

§ Back-transformed least squares mean and 95% CI from mixed effects model performed on natural log-transformed values.

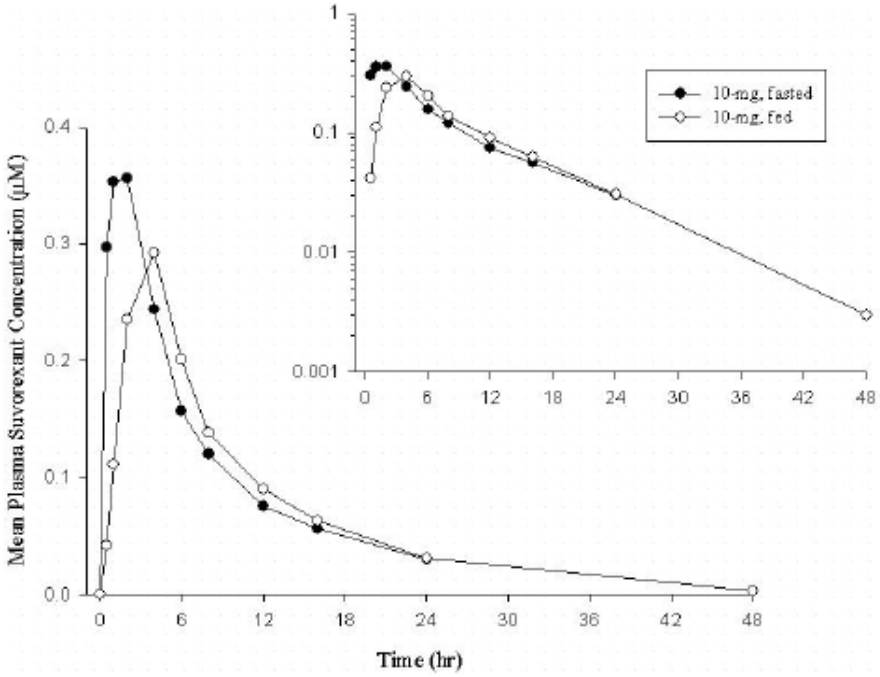
‖ Median (Minimum, Maximum).

¶ Harmonic mean (jack-knife SD).

Subjects in Panel B were given doses of 10 mg, 50 mg of suvorexant or placebo in fasted state; Subjects in Panel D were given doses of 10 mg, 50 mg, 100 mg of suvorexant or placebo in fasted state; in Period 4, Panel D, subjects were given single dose of 10 mg suvorexant in the fed state.

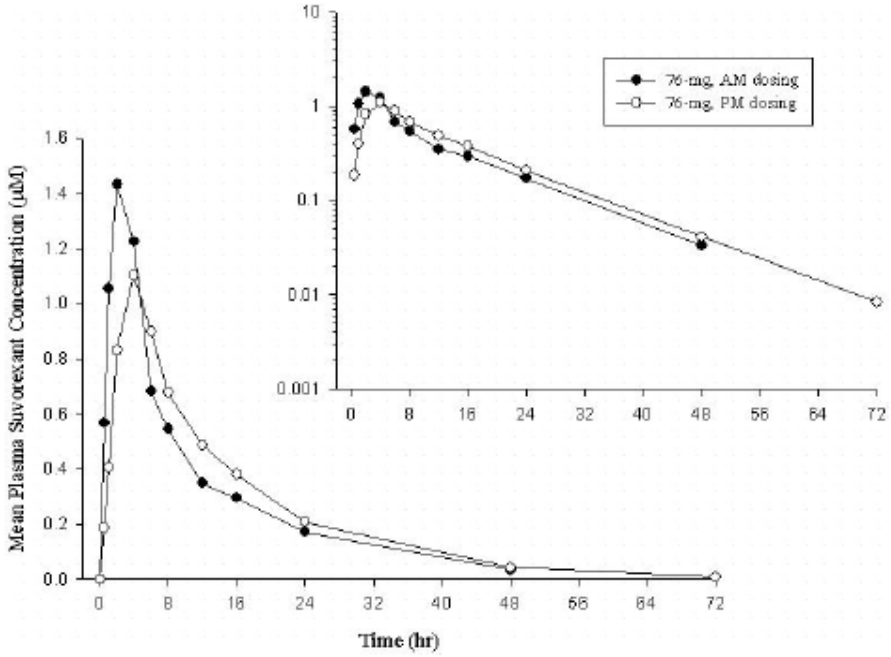
The effect of food on suvorexant pharmacokinetics was explored. A standard Japanese breakfast resulted in a similar C_{max}; however, the mean $AUC_{0-\infty}$ was higher and median T_{max} for suvorexant was delayed by approximately 1 hour. The GMR (fed/fasted) for $AUC_{0-\infty}$ and C_{max} were 1.34 and 0.88, respectively.

Mean Plasma Concentration-Time Profile Following Administration of a 10-mg Single Oral Dose of Suvorexant (MK-4305) to Japanese Healthy Young Male Subjects in the Fasted State and Following a Standard Japanese Breakfast (N=6, Inset: Semi-Log Scale)



The effect of circadian time on suvorexant pharmacokinetics was also explored. Night-time administration resulted in a similar $AUC_{0-\infty}$, while the mean C_{max} was decreased slightly and median T_{max} was delayed by approximately 2 hours. The GMR (PM/AM) for $AUC_{0-\infty}$ and C_{max} were 1.05 and 0.71, respectively.

Part 2: Mean Plasma Concentration-Time Profile Following Administration of a 76-mg Single Oral Dose of Suvorexant (MK-4305) in the PM and AM to Japanese Healthy Young Male Subjects in the Fasted State (N=6, Inset: Semi-Log Scale)



The dose to achieve pharmacokinetic target concentration, C_{4hr}, above 0.4 µM (based on preclinical EEG data) for suvorexant was evaluated after fasted morning administration, after fed morning administration and after night-time administration. All doses from 50 mg to 100 mg achieved C_{4hr} above 0.4 µM.

Parts 1 and 2: Geometric Mean (90% CI) of C4hr (µM) and Following Single Oral Doses of 4 to 100 mg Suvorexant (MK-4305) in Japanese Healthy Young Male Subjects

Dose	Panel	N	GM (90% CI)†
100 mg	D	6	0.968 (0.771, 1.215)
76 mg (PM)	C	6	1.155 (0.921, 1.449)
76 mg	A, C	12	1.168 (1.005, 1.357)
50 mg	B, D	12	0.790 (0.679, 0.918)
20 mg	A, C	12	0.440 (0.378, 0.512)
10 mg (fed)	D	6	0.304 (0.242, 0.381)
10 mg	B, D	12	0.228 (0.196, 0.265)
4 mg	A, C	12	0.968 (0.771, 1.215)

† Back-transformed least squares mean and 90% confidence interval from mixed effects model performed on natural log-transformed values.

An exploratory analysis suggested that dose proportionality could not be concluded for plasma $AUC_{0-\infty}$ and C_{max} over the range of doses studied (4 to 100 mg). Narrower dose ranges were further explored for $AUC_{0-\infty}$ and C_{max}. There were no dose ranges observed consistent with strict dose proportionality.

Parts 1 and 2: Assessment of Dose Proportionality of Suvorexant (MK-4305) Following Single Oral Fasted AM Doses of Suvorexant (MK-4305) 4 to 100 mg in Japanese Healthy Young Male Subjects (N=12 per dose, N=6 per dose at 100 mg)

Parameter	Slope Estimate (95% CI)	Predicted Fold-Change (95% CI)†	Expected Fold-Change with Perfect Dose-Proportionality
$AUC_{0-\infty}$ (µM*hr)	0.73 (0.69, 0.77)	10.52 (9.23, 11.98)	25
C_{max} (µM)	0.62 (0.57, 0.67)	7.46 (6.35, 8.76)	25

† Fold change for highest dose/lowest dose.

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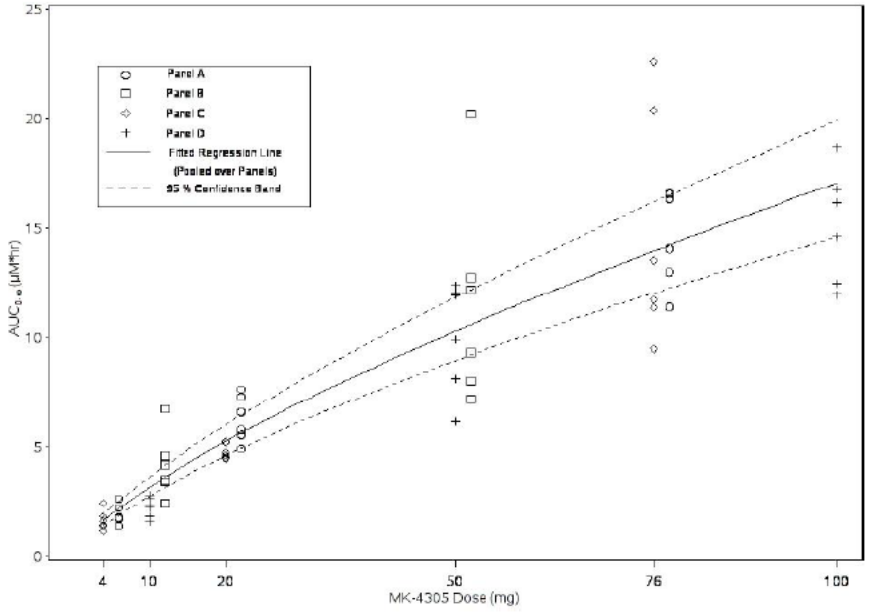


A comparison of pharmacokinetic parameters was conducted between Japanese and non-Japanese male subjects (from Protocol 001) administered suvorexant formulation T1. $AUC_{0-\infty}$ was approximately 28% lower and C_{max} was approximately 22% lower in Japanese subjects compared to non-Japanese subjects. T_{max} values in Japanese subjects were similarly distributed to those in non-Japanese subjects, while apparent terminal half lives in Japanese subjects were generally shorter than those in non-Japanese.

Parts 1 and 2: Assessment of Similarity of AUC0-∞ and C_{max} Following Single Oral Fasted AM Doses of Suvorexant (MK-4305) 4 to 120 mg between Japanese and non-Japanese Healthy Young Male Subjects

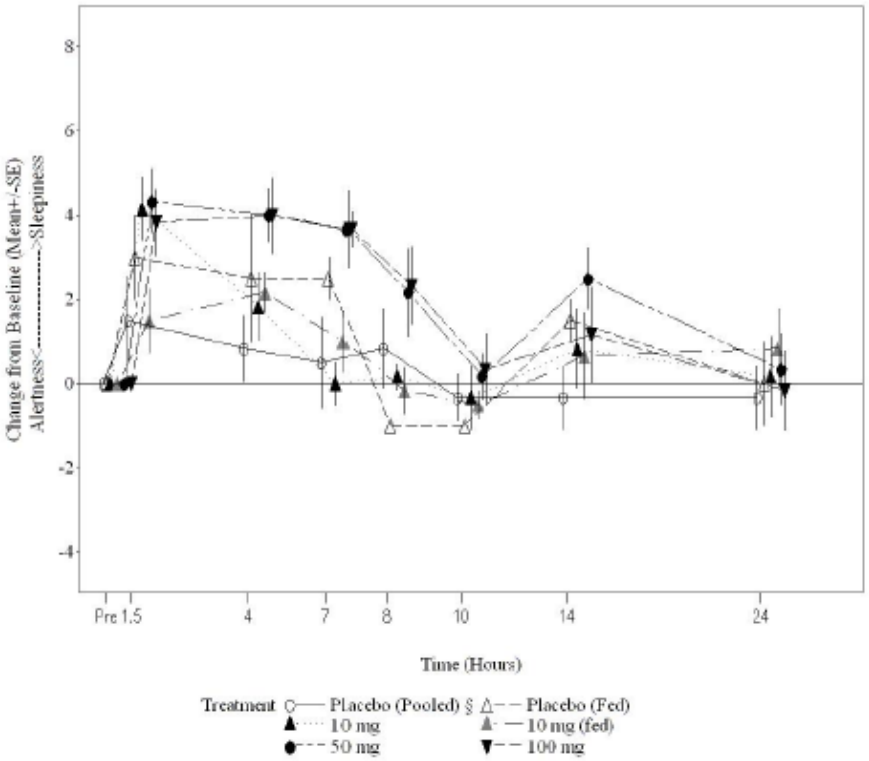
PK Parameter	Dose (mg)	Japanese N	Japanese GM‡	Japanese 95% CI‡	non-Japanese† N	non-Japanese GM‡	non-Japanese 95% CI‡	Ratio (Japanese/non-Japanese) GMR‡	Ratio (Japanese/non-Japanese) 90% CI‡	rMSE§
$AUC_{0-\infty}$ (µM*hr)	4	12	1.60	(1.41, 1.80)	6	2.23	(1.92, 2.59)	0.72	(0.65, 0.79)	0.257
	10	12	3.15	(2.84, 3.49)	6	4.39	(3.87, 4.99)	.		.
	20	12	5.27	(4.79, 5.79)	6	7.35	(6.54, 8.26)	.		.
	50	12	10.40	(9.40, 11.50)	6	14.51	(12.94, 16.26)	.		.
	76	12	14.19	(12.73, 15.80)	11	19.79	(17.59, 22.27)	.		.
	90	.			6	22.44	(19.90, 25.30)	.		.
	100	6	17.39	(15.51, 19.50)	.			.		.
	120	.			6	27.78	(24.52, 31.47)	.		.
C_{max} (µM)	4	12	0.232	(0.206, 0.261)	6	0.299	(0.259, 0.345)	0.78	(0.71, 0.85)	0.240
	10	12	0.416	(0.377, 0.460)	6	0.537	(0.475, 0.607)	.		.
	20	12	0.648	(0.591, 0.712)	6	0.836	(0.746, 0.936)	.		.
	50	12	1.164	(1.056, 1.284)	6	1.501	(1.343, 1.677)	.		.
	76	12	1.521	(1.370, 1.690)	11	1.961	(1.750, 2.198)	.		.
	90	.			6	2.185	(1.945, 2.454)	.		.
	100	6	1.813	(1.623, 2.025)	.			.		.
	120	.			6	2.626	(2.328, 2.962)	.		.

† Data from PN001.
‡ Back-transformed least squares mean and confidence interval estimated pooling across doses based on a linear mixed effects model with a fixed effect for ethnic-group, ln(dose) as a fixed covariate and a random effect for subject (reduced model) performed on natural log-transformed values.
§ rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model (reduced model). When multiplied by 100 approximates the within-subject % CV on the raw scale.
p-Values for testing ethnic-group-by-ln(dose) interaction= 0.121 and 0.194 for $AUC_{0-\infty}$ and C_{max}, respectively, based on a linear mixed effects (full model) performed on natural log-transformed values.

Pharmacodynamic Results:

Part 1 data, the VAS questionnaire had incomplete linguistic validation.
Summary statistics and changes from baseline were provided for Part 2 data only for the Bond and Lader derived factors of alertness, calmness and contentedness from the VAS as well as the Karolinska Sleepiness Scale (KSS measured from sleepy to alert).
Following single oral AM fasted doses of suvorexant 4 to 100 mg, the drowsiness generally peaked at 1.5 hours post-dose.
Plot of changes in KSS from baseline is provided below.

Change (Mean +/- SE) from Baseline for KSS Alertness for Panel D Following Single Oral Doses of Suvorexant (MK-4305) 10 to 100 mg in Japanese Healthy Young Male Subjects (N=6 per active dose, N=6 pooled placebo, N=2 Fed placebo)



Reviewer's Comment: The change in sleepiness was more pronounced after 10 mg suvorexant in the fasted state than after 10 mg suvorexant in the fed state and the peak occurred earlier in the fasted state.

Safety:

For Part 1, somnolence adverse experiences based on neurologic exams were not consistently recorded by the study site and this was considered an incomplete assessment of safety. The adverse experiences and assessment of laboratory, ECG and vital signs for Part 1 were recorded, there were no findings from Part 1 that were of clinical concern or precluded proceeding to Part 2.

In Part 2, no serious clinical AEs were reported and no subject discontinued because of an AE. The most frequently reported AEs was somnolence (reported 1 or more times by 16 of 16 subjects). It was reported by subjects following all doses of suvorexant, and also reported by all 12 subjects who received placebo. All AEs were rated mild or moderate in intensity. The duration of the somnolence events tended to be longer in the higher doses. Three subjects reported fatigue following a single dose of suvorexant 50 mg. One subject reported paralysis following a single dose of suvorexant a 100 mg. AN 0028 reported paralysis at a similar time as somnolence (at about 0.5 hr following suvorexant administration). The paralysis event occurred as the subject was falling in sleep which was consistent with "sleep paralysis"; and it was not preceded by any emotional trigger, and, according to the sponsor, should be differentiated from cataplexy.

P017: A Single Dose Study to Investigate the Pharmacokinetics of MK-4305 in Patients With Hepatic Insufficiency

Objectives:

Primary: To compare the plasma concentration-time profile and pharmacokinetics after administration of a single 20 mg dose of MK-4305 to patients with moderate hepatic insufficiency with that of the healthy matched (race, age, gender, body mass index) control subjects.

Secondary: To evaluate the safety and tolerability of MK-4305 in patients with hepatic insufficiency, and in healthy subjects, after administration of a 20 mg single oral dose.

Exploratory: To evaluate plasma protein binding of MK-4305 and determine the unbound area under the curve for each individual and compare with healthy matched controls.

Study Design	Open-label, 2-part study*
Study Population	8 healthy (5 male and 3 female) and 8 subjects with moderate hepatic impairment, 51-65 years
Treatment Groups	2 groups, 1 treatment /group
Dosage and Administration	20 mg suvorexant in the fasted state (fasted at least 8 h prior to dosing)
PK Sampling: plasma	Plasma samples were collected at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144 h post-dose** Blood samples were collected at pre-dose for the in vitro determination of total protein binding and unbound fraction of MK-4305
Analysis	Plasma: LC-MS/MS method for MK-4305 and M9 Range: 1 to 1000 ng/mL for both analytes
PK Assessment	C_{max}, C_{4h}, t_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$ of MK-4305 and M9 $AUC_{0\text{-}\infty(unbound)}$ and $C_{max(unbound)}$ for MK-4305
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* In Part I, patients with moderate hepatic insufficiency (Child-Pugh scores of 7 to 9) were enrolled. If the pharmacokinetics of MK-4305 in healthy matched control subjects and patients with moderate hepatic insufficiency were similar as defined by a true ratio of the geometric mean AUC (moderate hepatic insufficiency patients / healthy matched control subjects) of no more than 2.00, then the study was complete. Part II was to be conducted to evaluate the pharmacokinetics of MK-4305 in patients with mild hepatic insufficiency based on the safety, tolerability, and pharmacokinetics from Part I. Part II was not conducted.

** 96, 120, 144 h for hepatic patients only

Bioanalytical Assay:

Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using validated LC-MS/MS methods (method DM-909 for suvorexant and DM-928 for M9). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.

The assay performance during the analysis of the plasma samples was acceptable. Representative chromatograms were also provided.

MK-4305 plasma protein binding analysis was performed on pre-dose blood samples taken from each patient/subject using an ultracentrifugation method. Each sample was spiked with 2 μM [^{14}C]MK-4305 by adding 5.0 μL of a 0.4 mM [^{14}C]MK-4305 stock solution (50% acetonitrile:water) to 3.0 mL polyallomer Microfuge® tubes containing 1.0 mL of plasma. The samples were centrifuged at approximately 4°C and 3000 rpm (1500 x g) for 15 minutes. The plasma was then removed and placed into polypropylene tubes (2 aliquots per subject) and frozen at -70 °C until shipped (on dry ice) at the end of the study. Blood samples were also collected at 2 and 24 hours post MK-4305 dose for possible determination of the in vivo protein binding of MK-4305. Plasma samples for in vivo binding were not assayed, as the percent of MK-4305 bound to plasma proteins did not appear to change over the MK-4305 concentration range observed in the clinical studies.

Pharmacokinetic Results:

For patients with hepatic insufficiency, certain prescription medications used to treat manifestations of hepatic disease (e.g., diuretics, lactulose, etc.) were allowed during the study, but the patient was required to be on a steady dose, drug, and regimen for ~1 month prior to study drug administration. However, subjects could not use any medication known to be an inducer or inhibitor of the cytochrome P-450 CYP3A enzyme system, which cannot be discontinued at least 2 weeks prior to the study start and throughout the study. Generally, any concomitant medication was prohibited on the day of dosing. If medically necessary, thiazide and other diuretics could be administered 4 to 6 hours postdose; however, loop diuretics (e.g., furosemide) were not permitted the day of dosing.

Note: Upon enrollment, Subject AN (allocation number) 0003 was taking 20 mg Lasix® (furosemide) twice daily for high blood pressure and ascites. Subject AN 0003's Lasix® doses were held on Day 1 due to MK-4305 administration on Day 1; the Lasix® therapy resumed on Day 2 and was recorded as a concomitant medication. Given the short half-life of furosemide, this concomitant medication was not expected to affect the assessment of the study objectives.

In patients with moderate hepatic insufficiency MK-4305 exposure ($AUC_{0-\infty}$) was similar to that observed in healthy matched control subjects following a single 20 mg oral dose of MK-4305. The $AUC_{0-\infty}$ ratio of geometric means (patients with moderate hepatic insufficiency / healthy matched control subjects) and corresponding 90% CI were 1.03 and (0.74, 1.43). Since the upper limit of the 90% CI was less than 2.00, the primary hypothesis, that $AUC_{0-\infty}$ of MK-4305 in patients with moderate hepatic insufficiency is similar to that observed in healthy matched control subjects, was supported and Part II (patients with mild hepatic insufficiency) was not conducted.

The GMR for C_{max} (patients with moderate hepatic insufficiency / healthy matched control subjects) was 0.94. Median T_{max} remained unchanged while the apparent terminal $t_{1/2}$ was increased from 14.7 to 19.1 hours in healthy subjects versus patients with moderate hepatic insufficiency.

There were insufficient data to make any inference between the Child-Pugh scores and MK-4305 $AUC_{0-\infty}$ values.

MK-4305 plasma protein binding was approximately 99%, with individual %fu ranging from 0.61% to 1.14% in patients with moderate hepatic insufficiency, and from 0.66% to 1.94% in the healthy matched control subjects. The GMR (patients with moderate hepatic insufficiency / healthy matched control subjects) was 0.90 for $AUC_{0-\infty(unbound)}$ and 0.82 for $C_{max(unbound)}$.

Summary of Pharmacokinetic Parameters of MK-4305 Following a Single Dose of 20 mg MK-4305 Administered to Patients With Moderate Hepatic Insufficiency and to Healthy Matched Control Subjects

	MK-4305 in Patients With Moderate Hepatic Insufficiency			MK-4305 in Healthy Matched Control Subjects			MK-4305 in Patients With Moderate Hepatic Insufficiency / MK-4305 in Healthy Matched Control Subjects		
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE[†]
$AUC_{0-\infty}$ [‡] (µM•hr)	8	14.09	(10.48, 18.93)	8	13.73	(10.09, 18.69)	1.03	(0.74, 1.43)	0.330
C_{max} [‡] (µM)	8	0.800	(0.603, 1.062)	8	0.854	(0.636, 1.147)	0.94	(0.68, 1.29)	0.316
$AUC_{0-\infty(unbound)}$ [‡] (nM•hr)	8	118.19	(78.68, 177.52)	8	131.27	(85.91, 200.57)	0.90	(0.57, 1.42)	0.454
$C_{max(unbound)}$ [‡] (nM)	8	6.710	(4.320, 10.422)	8	8.161	(5.157, 12.912)	0.82	(0.50, 1.35)	0.492
T_{max} [§] (hr)	8	1.0	(1.0, 2.1)	8	1.0	(1.0, 2.0)			
Apparent terminal $t_{½}$ [‖] (hr)	8	19.1	10.6	8	14.7	3.9			

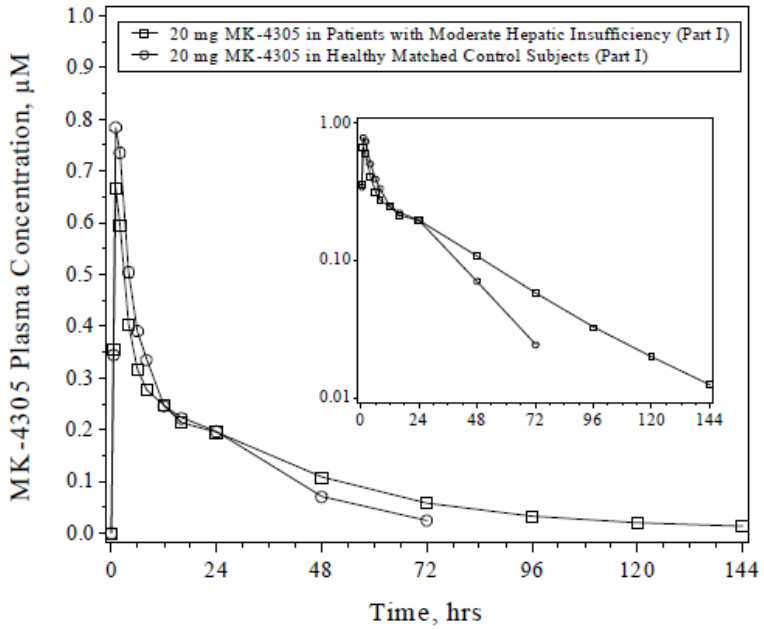
[†]rMSE: Square root of conditional mean squared error (residual error) from the ANCOVA model. rMSE×100% approximates the %CV on the raw scale.

[‡]Back-transformed least squares mean and confidence interval from linear effect model performed on natural log-transformed values.

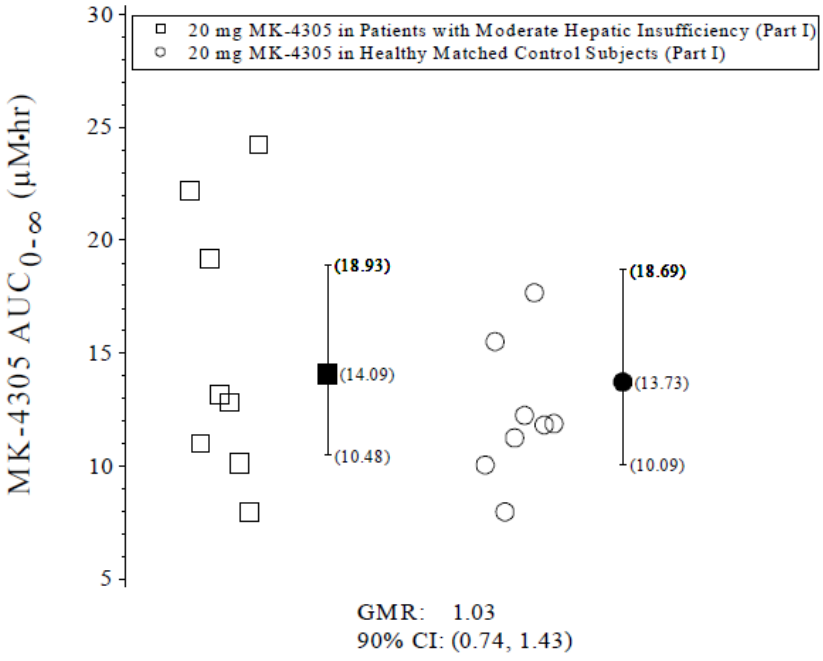
[§]Median (Min, Max) reported for T_{max}.

[‖]Harmonic mean, jack-knife SD reported for apparent terminal $t_{½}$.

Mean Plasma Concentration-Time Profiles of MK-4305 Following a Single Dose of 20 mg MK-4305 Administered to Patients With Moderate Hepatic Insufficiency and to Healthy Matched Control Subjects (inset=semilog scale)



Individual MK-4305 $AUC_{0-\infty}$ (µM•hr) Values, Geometric Means and 95% CIs Following a Single Dose of 20 mg MK-4305 Administered to Patients With Moderate Hepatic Insufficiency and Healthy Matched Control Subjects



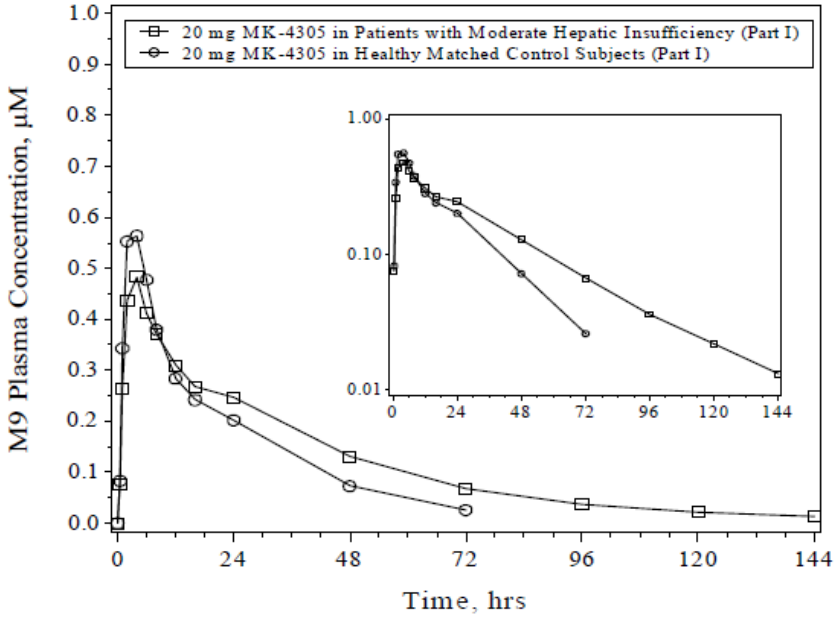
Reviewer's Comment: higher variability in patients with moderate hepatic impairment.

Metabolite M9:
Following a single 20 mg MK-4305 dose, the M9 GMR (patients with moderate hepatic insufficiency / healthy matched control subjects) for $AUC_{0-\infty}$ and C_{max} were 1.32 and 0.95, respectively.

Summary of PK Parameters of M9 Following a Single Dose of 20 mg MK-4305 Administered to Patients With Moderate Hepatic Insufficiency and to Healthy Matched Control Subjects

	M9 in Patients With Moderate Hepatic Insufficiency			M9 in Healthy Matched Control Subjects			M9 in Patients With Moderate Hepatic Insufficiency / M9 in Healthy Matched Control Subjects		
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE[†]
$AUC_{0-\infty}$[‡] (µM•hr)	8	16.94	(12.80, 22.41)	8	12.80	(9.56, 17.13)	1.32	(0.97, 1.81)	0.312
C_{max}[‡] (µM)	8	0.531	(0.389, 0.726)	8	0.558	(0.403, 0.773)	0.95	(0.67, 1.35)	0.349
T_{max}[§] (hr)	8	4.0	(2.0, 4.0)	8	4.0	(2.0, 6.0)			
Apparent terminal $t_{½}$[‖] (hr)	8	20.8	9.9	8	15.8	4.0			

Mean Plasma Concentration-Time Profiles of M9 Following a Single Dose of 20 mg MK-4305 Administered to Patients With Moderate Hepatic Insufficiency and Healthy Matched Control Subjects



Reviewer's Comments: The apparent terminal $t_{1/2}$ of both suvorexant and M9 were increased in patients with moderate hepatic insufficiency compared to healthy subjects. In addition, even though the GMR for $AUC_{0-\infty}$ (patients with moderate hepatic insufficiency / healthy matched control subjects) was 1.03, the variability in patients with moderate hepatic impairment was higher.

In order to assess the effect of moderate hepatic impairment on the steady state suvorexant exposure, simulations based on nonparametric superposition were performed by the pharmacometrics reviewer Dr. Brar.
The ratios for the main PK parameters at steady state for moderate hepatic impairment vs. healthy subjects are provided below:

Steady state	Ratio
AUC(tau)	1.17
C_{9hr}	1.12
C_{max}	1.02

Conclusion: Based on these simulations, no dose adjustment is needed in subjects with moderate hepatic impairment.

Safety results:
No serious adverse experiences were reported in this study and no subject or patient discontinued because of an AE. All AEs were mild in intensity. Somnolence, reported by 6 of the 8 patients with moderate hepatic insufficiency and 5 of the 8 healthy matched control subjects, was the most common AE in this study.
No laboratory adverse experiences were reported. Patients with hepatic insufficiency had some abnormalities in laboratory safety parameters at pre-study that were consistent with their disease state (e.g., AST and/or ALT, PT, platelets) and a single 20 mg dose of MK-4305 did not appear to have any impact on these laboratory parameters.

P023: A Single Dose Study to Investigate the Pharmacokinetics of Suvorexant (MK-4305) in Patients with Impaired Renal Function

Objectives:

Primary: To compare the plasma concentration-time profile and pharmacokinetics after administration of a single 20 mg dose of MK-4305 to patients renal impairment with that of healthy matched (race, age, gender, body mass index) control subjects.

Secondary: To evaluate the safety and tolerability of suvorexant after administration of a single oral dose of suvorexant (MK-4305) to patients with impaired renal function and to healthy subjects.

Study Design	Open-label, 2-part study*
Study Population	8 subjects with severe renal impairment **, 6 male and 2 female, 29-66 years and 8 matched healthy subjects
Treatment Groups	2 groups, 1 treatment /group
Dosage and Administration	20 mg suvorexant in the fasted state (fasted at least 8 h prior to dosing)
PK Sampling: plasma	Plasma samples were collected at pre-dose and at 0.5, 1, 2, 4, 6, 9, 12, 16, 24, 48, 72, 96, 120 h post-dose Blood samples were collected at pre-dose for the in vitro determination of total protein binding and unbound fraction of MK-4305 and at 2 h and 24 h post-dose for in vivo protein binding of MK-4305.
Analysis	Plasma: LC-MS/MS method for MK-4305 and M9 Range: 1 to 1000 ng/mL for both analytes
PK Assessment	C_{max}, C_{4h}, t_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$ of MK-4305 and M9 $AUC_{0\text{-}\infty(unbound)}$ and $C_{max(unbound)}$ for MK-4305
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* Part II (Panels C, D, E, F) consisting of 8 patients with moderate renal impairment and 8 patients with mild renal impairment and the same number of healthy matched control subjects was planned but not conducted. Part II was contingent on the results from Part I.

** A 24-hour urinary CrCL <30 mL/min was the inclusion criteria for patients with severe renal impairment.

Bioanalytical Assay:

Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using validated LC-MS/MS methods (method DM-909 for suvorexant and DM-928 for M9). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Plasma for In Vitro and In Vivo Protein Binding

Whole blood for in vitro (drawn before drug administration) and in vivo protein binding analysis (drawn at time points indicated above), were collected in plastic tubes containing K2EDTA as the anticoagulant and placed on ice until plasma was separated. Blood samples were centrifuged at 3000 rpm for 15 minutes at 4°C. Plasma was transferred to polypropylene tubes (2 aliquots per patient/subject) and stored at -70°C until transferred

to Merck. Only the in vitro samples were assayed. The in vivo samples for protein binding were archived.
Suvorexant plasma protein binding analysis was performed using an ultracentrifugation method. Each sample was prepared at a concentration of 2 μM [^{14}C] suvorexant by adding 5.0 μL of a 0.4 mM [^{14}C] suvorexant stock solution (50% acetonitrile:water) to 3.0 mL polyallomer Microfuge® tubes (Beckman) containing 1.0 mL of plasma.

Pharmacokinetic Results:

A total of 16 subjects/patients, 8 patients with severe renal impairment and 8 healthy matched control subjects were enrolled; all 16 subjects/patients completed the study. Patients with severe renal impairment were allowed the use of various concomitant therapies (e.g., ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics) provided the patients were on a stable regimen for at least 1 month prior to study drug administration and if these agents were not strong inhibitors of CYP3A4. As per protocol, diuretics were held for 4 hours prior to dosing.
No prior therapies were reported by matched healthy subjects. Three matched healthy subjects reported concomitant therapies for the treatment of headache (acetaminophen) during the study.

Following single dose administration, suvorexant had a median T_{max} of 2.0 hours in patients with severe renal impairment and 1.0 hour in matched healthy control subjects. The mean apparent terminal half life was 13.5 hours for both populations.
The ratio of geometric means GMR (severe renal impairment patients/matched healthy control subjects) for the unbound $AUC_{0-\infty}$ and C_{max} were 1.18 and 1.10, respectively.
Suvorexant plasma protein binding was similar in severe renal impairment patients and matched healthy control subjects (ranged from 0.9 to 1.3% in severe renal impairment patients and 0.9 to 1.5% in matched healthy control subjects).

Summary of the Plasma Pharmacokinetic Parameters of Suvorexant (MK-4305) Following a Single Dose of 20-mg Suvorexant (MK-4305) Administered to Patients with Severe Renal Impairment and to Healthy Matched Control Subjects

	Severe Renal Impairment			Healthy Matched Control			Severe Renal Impairment / Healthy Matched Control		
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE‡
$AUC_{0-\infty}$† (μM•hr)	8	11.98	(9.45, 15.20)	8	9.81	(7.72, 12.47)	1.22	(0.93, 1.60)	0.7178
C_{max}† (μM)	8	0.830	(0.723, 0.952)	8	0.724	(0.630, 0.832)	1.15	(0.98, 1.34)	0.1706
$AUC_{0-\infty(unbound)}$† (μM•hr)	8	0.13	(0.10, 0.18)	8	0.11	(0.08, 0.15)	1.18	(0.83, 1.67)	0.3580
$C_{max(unbound)}$† (μM)	8	0.009	(0.008, 0.011)	8	0.008	(0.007, 0.010)	1.10	(0.91, 1.34)	0.2087
T_{max}§ (hr)	8	2.0	(1.0, 2.0)	8	1.0	(0.5, 2.0)			.
Apparent Terminal $t_{1/2}$‖ (hr)	8	13.5	6.2	8	13.5	2.7			.

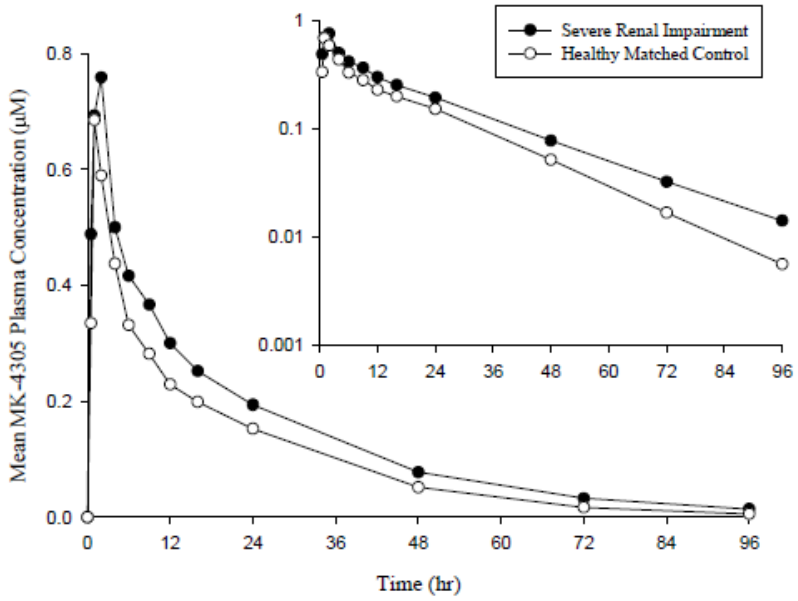
† Geometric mean computed from least squares estimate from an ANCOVA performed on the natural-log transformed values.
‡ rMSE: Square root of conditional mean squared error (residual error) from the linear fixed effect model. For log-transformed variables, rMSE*100% approximates the between-subject %CV on the raw scale.
§ Median [Min, Max] reported for T_{max}.
‖ Harmonic mean, jack-knife standard deviation (SD) reported for $t_{½}$.

The GMR for $AUC_{0-\infty}$ and C_{max} of metabolite M9 were 0.88 and 0.77, respectively.
The statistical analysis output for pharmacokinetic data is provided below.

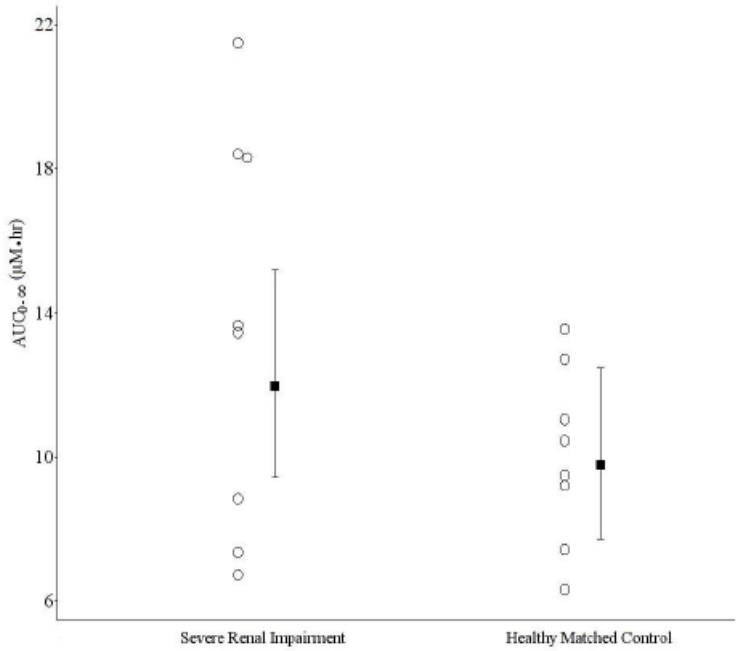
Summary of the Plasma Pharmacokinetic Parameters of Metabolite M9 Following a Single Dose of 20-mg Suvorexant (MK-4305) Administered to Patients with Severe Renal Impairment and to Healthy Matched Control Subjects

	Severe Renal Impairment			Healthy Matched Control			Severe Renal Impairment / Healthy Matched Control		
M9 Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE‡
$AUC_{0-\infty}$† (μM•hr)	8	11.80	(9.77, 14.23)	8	13.42	(11.10, 16.22)	0.88	(0.71, 1.09)	0.5263
C_{max}† (μM)	8	0.440	(0.387, 0.501)	8	0.572	(0.502, 0.651)	0.77	(0.66, 0.89)	0.1600
T_{max}§ (hr)	8	2.0	(2.0, 16.0)	8	4.0	(2.0, 6.0)			.
Apparent Terminal $t_{1/2}$‖ (hr)	8	14.8	5.2	8	14.4	2.8			.

Mean Plasma Concentration-Time Profiles for Suvorexant (MK-4305) Following a Single Dose of 20-mg Suvorexant (MK-4305) Administered to Patients with Severe Renal Impairment and to Healthy Matched Control Subjects (Inset: Semi-log Scale) (N = 8 per Group)

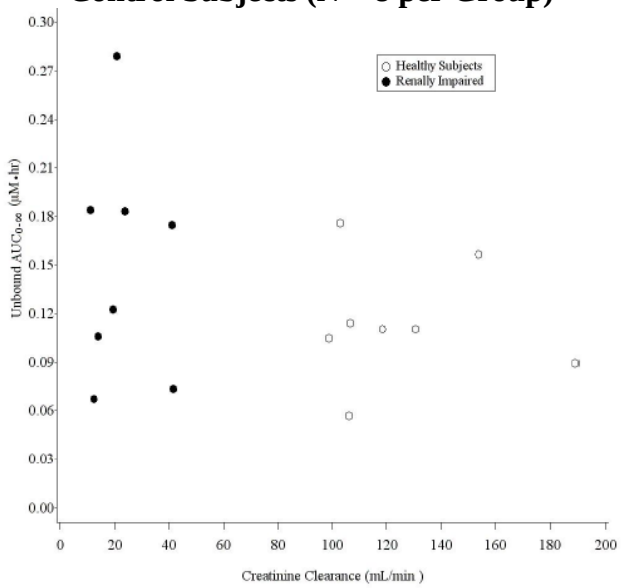


Individual Suvorexant (MK-4305) Plasma AUC0-∞ Values Following a Single Dose of 20-mg Suvorexant Administered to Patients with Severe Renal Impairment and to Healthy Matched Control Subjects (N = 8 per Group)

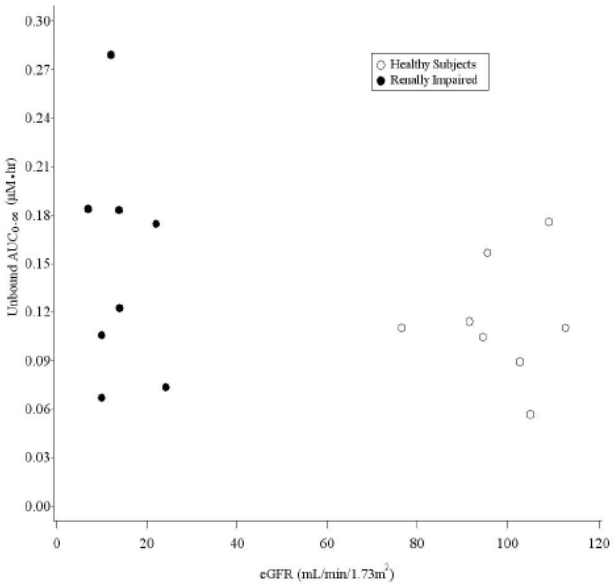


The relationship between suvorexant pharmacokinetics and renal insufficiency were visually assessed by scatter plots of the unbound $AUC_{0-\infty}$ and C_{max} versus estimated CrCL by Cockcroft-Gault (and versus eGFR by MDRD) for the patients with severe renal impairment and for the healthy matched controls. The unbound $AUC_{0-\infty}$ and C_{max} versus the estimated CrCL, either by Cockcroft-Gault or by MDRD, indicated no relevant difference in the PK between the two populations.
Formal modeling of the relationship between the estimated values of CrCL/ eGFR and PK was not performed, as only Part I of the study was conducted. Therefore, no data are available for the estimated CrCL/ eGFR values in the moderate renal impairment range. Higher variability of PK observed in severe renal impairment.

Scatter Plot of Individual Unbound $AUC_{0-\infty}$ Values versus estimated CrCL by Cockcroft-Gault (mL/min) Values Following a Single Dose of 20-mg Suvorexant Administered to Patients with Severe Renal Impairment and to Healthy Matched Control Subjects (N = 8 per Group)



Scatter Plot of Individual Unbound $AUC_{0-\infty}$ Values versus eGFR by MDRD ($mL/min/1.73m^2$)



Safety:
No serious adverse experiences were reported and no subjects discontinued due to an AE. Four healthy subjects reported 5 AEs (headache n=3 and dry mouth n=2). Two patients with severe renal impairment reported a total of 2 AE (somnolence and oligomenorrhoea). No laboratory AEs were reported.

Conclusion: No dose adjustment is needed for patients with renal impairment.

P027: A Multiple Dose Study of MK-4305 in Elderly Subjects

Objectives:

Primary: Panels A and B: To evaluate the safety and tolerability of multiple oral doses of suvorexant (MK-4305) for seven consecutive days in healthy elderly subjects.

Panel A only (Panel B had limited PK sampling): To obtain preliminary PK data (AUC_{0-24h}, etc. and accumulation ratio) of suvorexant in the fasted state

Panel D: To evaluate the safety and tolerability of single oral doses of suvorexant QD for twenty-one consecutive days in healthy elderly subjects and obtain preliminary PK data (accumulation ratio [Day 21 AUC_{0-24h}/ Day 1 AUC_{0-24h}]) of suvorexant

There were no secondary objectives.

Exploratory: To explore the PD effects of multiple doses of suvorexant in elderly subjects as evaluated by cognitive, psychomotor and subjective/somnolence assessments.

Study Design *	Double-blind, randomized, placebo-controlled, sequential panel, multiple dose study
Study Population: elderly (65-77 years old) BMI $\leq$ 33 kg/m^2	Panel A: 22 (eight subjects of each gender received 40 mg suvorexant and three subjects of each gender received matching placebo) Panel B: 22 (eight subjects of each gender received 40 mg suvorexant and three subjects of each gender received matching placebo) Panel D: 30 subjects (10 of each gender received 30 mg suvorexant and five of each gender matching placebo)
Treatment Groups	3 panels, 1 treatment /panel
Dosage and Administration	Suvorexant in the fasted state (fasted at least 4 h prior to dosing): Panels A and B: 40 mg suvorexant or matching placebo QD for 7 days. Panel C was not conducted; was replaced by Panel D. Panel D: 30 mg suvorexant or matching placebo QD for 21 days.
PK Sampling: plasma	Plasma samples were collected at pre-dose and at 0.5, 1, 2, 4, 6, 10, 16, 24 (48, 72, 96, 120, 144 h post-dose) **
Analysis	Plasma: LC-MS/MS method for MK-4305 and M9 Range: 1 to 1000 ng/mL for both analytes
PK Assessment	C_{max}, C_{4h}, t_{max}, AUC_{0-inf}, $t_{1/2}$ of MK-4305 and M9 Panel A: Suvorexant accumulation ratio [Day 7 AUC_{0-24h}/ Day 1 AUC_{0-24h}]) Accumulation ratio [Day 21 AUC_{0-24h}/ Day 1 AUC_{0-24h}]) of suvorexant (panel D)
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* In Panel A subjects received 40 mg suvorexant/ matching placebo at approximately 9:30 PM in a fasted state (4 hours) and went to bed approximately 120 minutes after dosing. In Panel B subjects received 40 mg suvorexant /placebo at 9:30 PM in a fasted state and went to bed approximately 30 minutes after dosing. In Panel D subjects received 30 mg suvorexant/placebo at 9:30 PM in a fasted state and went to bed approximately 30 minutes after dosing.

** Up to 24 h. On the last dosing day only up to 144 hours post-dose in Panels A and B and up to 132 hours post-dose in Panel D.

Note: No medications, including prescription and non-prescription drugs or herbal remedies were allowed in this study.
Subjects with CrCL of ≤60 mL/min (based on the Cockcroft-Gault equation) were excluded.

Bioanalytical Assay:
Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using validated LC-MS/MS methods (method DM-909 for suvorexant and DM-928 for M9). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results
Four subjects discontinued this study; 2 subjects from Panel B and 2 subjects from Panel D. For Panel A, all subjects completed.
For Panel B, AN 0028 discontinued due to personal reasons, after receiving 4 daily doses of suvorexant 40 mg. AN 0028 was replaced by AN 0128 who completed the study.
AN 0024 discontinued due to possible sleep apnea which was not disclosed at screening, after receiving 4 daily doses of suvorexant 40 mg. Note: This subject did not have high suvorexant levels on Day 4.
For Panel D, two subjects, AN 0417 and AN 0421 discontinued due to laboratory AEs, elevated amylase and lipase after receiving 20 daily doses of suvorexant 30 mg.
Note: These subjects did not have high suvorexant levels on Day 21.
The PK data of two subjects in Panel D, AN 0408 and AN 0425, did not match the dose prescribed by the allocation schedule, due to a likely protocol deviation (AN 0425 was to receive placebo but had detectable concentrations of suvorexant in all plasma samples; AN 0408 was to receive 30 mg suvorexant but had no detectable levels of suvorexant in all plasma samples). These two subjects in Panel D were excluded from the PK and PD analysis but not from the safety analysis.

Following multiple dose PM administration of 30 and 40 mg suvorexant (Panels A and D), suvorexant had median T_{max} values of 2.0 hours and mean apparent terminal half-life ranging from 16.4 to 18.4 hours for the combined gender population. The mean accumulation ratios for suvorexant $AUC_{0\text{-}24hr}$ for the 30 to 40 mg doses ranged from 1.34 to 1.45 for the combined genders.
Note: Females had higher AUC and longer $t_{1/2}$ than males in Panels A and B but not in Panel D.

Summary of PK Parameters of Suvorexant Following Multiple Dose PM Administration of 40 mg, Once Daily for 7 Days in Panel A, or 30 mg, Once Daily for 21 Days in Panel D in Healthy Elderly Male and Female Subjects

Dose	Gender	N	$AUC_{0\text{-}24\,hr}$ † (μM·hr)	C_{max} (μM) †	C_{24hr} (μM) †	C_{4hr} (μM) †	T_{max} (hr) ††	Apparent terminal $t_{1/2}$(hr) §
First Day (1st Day)								
Panel A 40 mg	C	16	13.36 (11.40, 15.66)	1.139 (0.965, 1.343)	0.356 (0.283, 0.446)	0.733 (0.645, 0.832)	2.0 (0.5, 6.0)	--
	M	8	11.83 (9.79, 14.29)	1.033 (0.831, 1.285)	0.283 (0.220, 0.363)	0.686 (0.582, 0.808)	2.0 (1.0, 6.0)	--
	F	8	15.09 (12.49, 18.23)	1.255 (1.009, 1.560)	0.447 (0.348, 0.575)	0.783 (0.665, 0.922)	2.0 (0.5, 4.0)	--
	F/M	8	1.28 (1.02, 1.59)	1.21 (0.94, 1.57)	1.58 (1.18, 2.12)	1.14 (0.94, 1.38)	--	--
Last Day (7th Day)								
Panel A 40 mg	C	16	17.88 (15.25, 20.96)	1.336 (1.132, 1.575)	0.567 (0.452, 0.711)	0.835 (0.735, 0.948)	2.0 (1.0, 10.1)	18.4 (4.4)
	M	8	14.48 (11.98, 17.49)	1.134 (0.912, 1.410)	0.416 (0.323, 0.534)	0.720 (0.611, 0.847)	1.5 (1.0, 6.0)	16.8 (3.7)
	F	8	22.07 (18.27, 26.66)	1.573 (1.266, 1.956)	0.772 (0.601, 0.993)	0.968 (0.822, 1.140)	2.0 (1.0, 10.1)	20.3 (4.6)
	F/M	8	1.52 (1.22, 1.90)	1.39 (1.08, 1.79)	1.86 (1.39, 2.49)	1.35 (1.11, 1.63)	--	--
Accumulation (7th Day / 1st Day)								
Panel A 40 mg	C	16	1.34 (1.26, 1.42)	1.17 (1.04, 1.32)	1.59 (1.51, 1.68)	1.14 (1.07, 1.21)	--	--
	M	8	1.22 (1.15, 1.30)	1.10 (0.93, 1.30)	1.47 (1.39, 1.55)	1.05 (0.98, 1.13)	--	--
	F	8	1.46 (1.37, 1.56)	1.25 (1.06, 1.49)	1.73 (1.64, 1.82)	1.24 (1.15, 1.33)	--	--
First Day (1st Day)								
Panel D 30 mg	C	19	10.30 (8.95, 11.85)	0.940 (0.800, 1.105)	0.272 (0.228, 0.323)	0.586 (0.505, 0.680)	2.0 (1.0,6.0)	--
	M	9	10.27 (8.32, 12.67)	0.874 (0.687, 1.110)	0.245 (0.190, 0.315)	0.653 (0.526, 0.811)	2.0 (1.0,4.0)	--
	F	10	10.32 (8.46, 12.60)	1.004 (0.800, 1.260)	0.298 (0.234, 0.378)	0.531 (0.433, 0.652)	1.0 (1.0,6.0)	--
	F/M	9	1.00 (0.79, 1.28)	1.15 (0.87, 1.51)	1.22 (0.91, 1.62)	0.81 (0.64, 1.04)	--	--
Last Day (21st Day)								
Panel D 30 mg	C	17	14.93 (12.94, 17.21)	1.133 (0.960, 1.337)	0.431 (0.362, 0.514)	0.861 (0.738, 1.004)	2.0 (1.0,6.0)	16.4 (3.7)
	M	9	14.54 (11.79, 17.95)	1.097 (0.864, 1.395)	0.404 (0.314, 0.520)	0.906 (0.730, 1.125)	2.0 (1.0,6.0)	15.7 (7.2)
	F	8	15.36 (12.51, 18.87)	1.161 (0.913, 1.475)	0.456 (0.356, 0.584)	0.826 (0.664, 1.027)	1.5 (1.0,4.0)	17.1 (4.1)
	F/M	8	1.06 (0.83, 1.35)	1.06 (0.80, 1.40)	1.13 (0.84, 1.51)	0.91 (0.71, 1.18)	--	--
Accumulation (21st Day / 1st Day)								
Panel D 30 mg	C	17	1.45 (1.35, 1.56)	1.21 (1.08, 1.35)	1.59 (1.44, 1.75)	1.47 (1.32, 1.64)	--	--
	M	9	1.42 (1.28, 1.57)	1.26 (1.07, 1.47)	1.65 (1.44, 1.89)	1.39 (1.19, 1.62)	--	--
	F	8	1.49 (1.33, 1.66)	1.16 (0.98, 1.36)	1.53 (1.33, 1.76)	1.55 (1.32, 1.82)	--	--

†Back-transformed least squares mean and 95% confidence interval (90% confidence interval for accumulation) from mixed effects model performed on natural log-transformed values.

††Median; minimum, maximum.

§Harmonic mean; jack-knife SD

C=Combined genders; M=Males; F=Females; F/M = Ratio of Females/Males

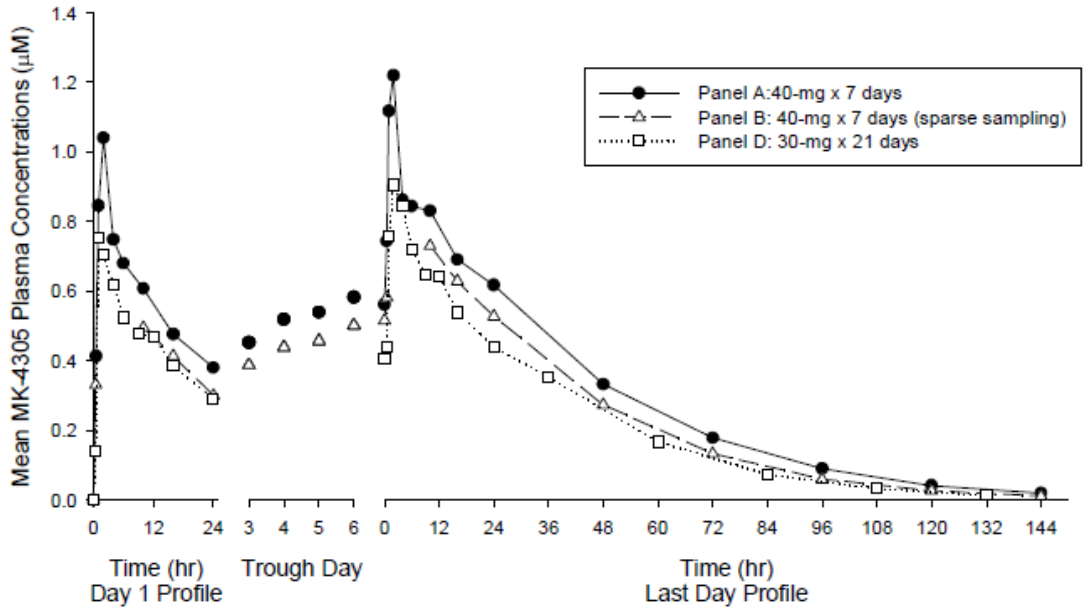
For Panel D, AN 408 pharmacokinetic data is excluded from analysis due to a probable protocol deviation.

Summary of PK Parameters of Suvorexant Following Multiple Dose PM Administration of 40 mg, Once Daily for 7 Days in Panel B, Healthy Elderly Male and Female Subjects

Dose	Gender	N	C_{24hr} (μM) †	Apparent terminal $t_{1/2}$(hr) ‡
First Day (1st Day)				
Panel B 40 mg	C	17	0.274 (0.219,0.343)	--
	M	9	0.218 (0.171,0.279)	--
	F	8	0.354 (0.273,0.460)	--
	F/M	8	1.62 (1.21,2.18)	--
Last Day (7th Day)				
Panel B 40 mg	C	15	0.467 (0.373,0.584)	16.1 (4.5)
	M	7	0.350 (0.273,0.449)	13.5 (2.5)
	F	8	0.633 (0.488,0.821)	18.7 (5.4)
	F/M	8	1.81 (1.34,2.43)	
Accumulation (7th Day / 1st Day)				
Panel B 40 mg	C	15	1.70 (1.60,1.81)	--
	M	7	1.60 (1.47,1.75)	--
	F	8	1.79 (1.64,1.94)	--

†Back-transformed least squares mean and 95% confidence interval (90% confidence interval for accumulation ratios) from mixed effects model performed on natural log-transformed values.
‡Harmonic mean; jack-knife SD
C=Combined genders; M=Males; F=Females; F/M = Ratio of Females/Males

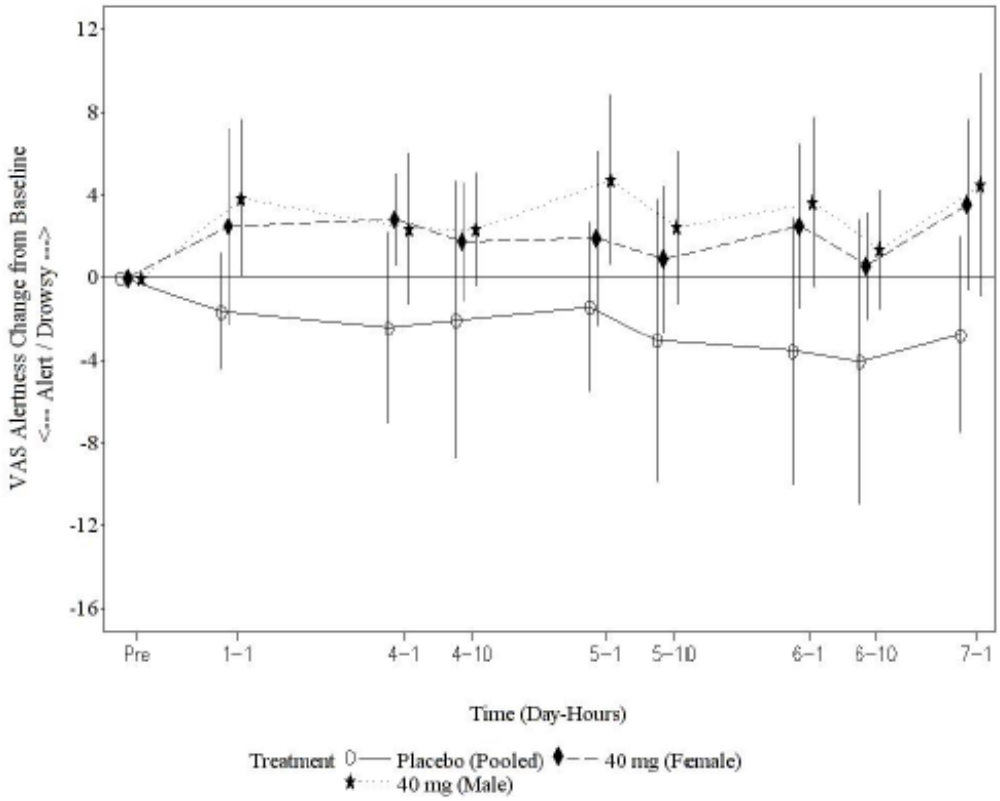
Mean Suvorexant Plasma Concentrations (μM) Versus Time (hr) Following Multiple PM Dose Administration of 40 mg, Once Daily for 7 Days (Panel A-B), or 30 mg, Once Daily for 21 Days (Panel D) in Healthy Elderly Male and Female Subjects (N=16/Panel A, N=17/Panel B, N=19/Panel D) (Linear Scale)



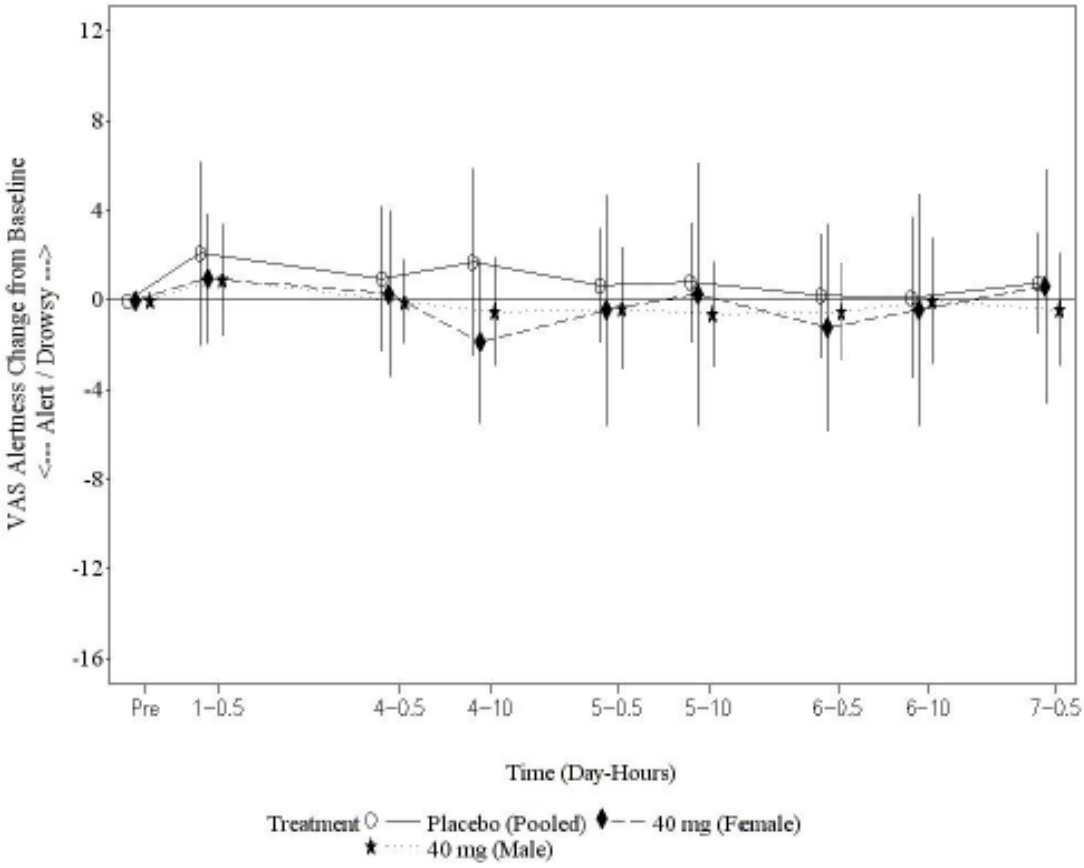
Pharmacodynamic Results:

For Panel A (lights out 2 hr after dosing), the scale was administered predose on day 1, at 1 hr postdose on days 1, 4, 5, 6 and 7, 10 hrs postdose on days 4, 5 and 6. In Panel A, 40 mg suvorexant given in the PM (lights-out 2 hr after dosing) for 7 days appeared to decrease alertness and increase sleepiness at 1 hr after dosing as measured by VAS and KSS. This decrease in alertness and increase sleepiness appeared to diminish at 10 hr post dose.
For Panel B and D (lights out 30 min after dosing), the scale was administered predose on day 1, at 0.5 hr (just prior to lights out) postdose on days 1, 4, 5, 6, and 7 (or 21, panel D) and 10 hrs postdose on days 4, 5 and 6 (or 21, panel D).
In Panels B and D, suvorexant given in the PM (lights-out 0.5 hr after dosing) for 7 and 21 days, respectively did not appear to result in a decreased alertness or increased sleepiness as measured by VAS and KSS at any time point postdose.
Note: The effect of suvorexant appears to occur about 1 h post dose.

Change (Mean ± SD) from Baseline for Alertness in Panel A Following Multiple Dose PM Administration of 40 mg once daily for 7 days (lights out 2 hours post dose) in Healthy Elderly Male and Female Subjects
(N=8 per each gender, N=6 pooled placebo)



Change (Mean ± SD) from Baseline for Alertness in Panel B Following Multiple Dose PM Administration of 40 mg once daily for 7 days (lights out 30 minutes postdose) in Healthy Elderly Male and Female Subjects (N=8 females, N=9 males with only N=7 males Days 5 to 7, N=6 pooled placebo)



Safety:

The most frequently reported clinical adverse experience was somnolence, reported by a total of 25 subjects: 100% (16 subjects) on 40 mg suvorexant in Panel A (with lights out at 2 hr after dosing), 0% or no subjects who received 40 mg suvorexant in Panel B (with lights out at 30 min after dosing), 20% (4 subjects) on 30 mg suvorexant with lights out at 30 min, and 22.7 % (5 subjects) who received placebo (all panels combined). The duration of somnolence was generally 7 hours.

Note: This argues against taking the drug immediately before going to bed.

Five subjects experienced laboratory AEs: three had elevated amylase and lipase. Upon retesting (two days later), the serum amylase declined to within normal limits, but lipase remained slightly elevated. Two subjects: AN 0042 (40 mg suvorexant) and AN 0041 (placebo) had glomerular filtration rate decreased (as estimated by Cockcroft and Gault) and both AEs were considered not drug related.

1.3 Extrinsic Factor PK Studies

P010: A Study to Evaluate the Effect of Alcohol on the Single Dose Pharmacokinetics and Pharmacodynamics of MK-4305

Objectives:

Primary: (1) To investigate the safety and tolerability of single dose of 40 mg MK-4305 alone and in combination with alcohol. (2) To investigate the effect of alcohol (0.7 g/kg) on psychomotor/cognitive performance of MK-4305 as measured by CDR cognitive testing battery.

Secondary: To evaluate the PK parameters of a single dose of 40 mg MK-4305 when administered in the presence and absence of alcohol.

Exploratory: (1) To explore the PD effects of MK-4305 alone or in combination with alcohol on other cognitive tests (e.g. CRT, IDWR, numeric working memory). (2) To investigate the effect of a single dose of 40 mg MK-4305 alone and in combination with alcohol (0.7 g/kg) on postural stability.

Study Design	Randomized, double-blind, double-dummy, placebo-controlled, four period crossover study
Study Population	31 healthy male (19) and female (12) subjects, 19-43 years, 29 completed the study
Treatment Group	4 treatments in a cross-over manner, see below
Dosage and Administration*	Treatment A: MK-4305 placebo and oral placebo alcohol solution Treatment B: 40 mg MK-4305 and oral placebo alcohol solution Treatment C: MK-4305 placebo and oral solution of alcohol (0.7 g/kg) Treatment D: 40 mg MK-4305 and an oral solution of alcohol. There was at least 5 days of washout between each treatment period.
PK Sampling: plasma	Plasma samples for MK-4305 ** Serum samples for Alcohol concentrations **
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL Whole blood alcohol concentrations per the local standard operating procedures
PK Assessment	C_{max}, t_{max}, AUC_{0-24}, AUC_{0-inf}, $t_{1/2}$ of MK-4305
PD Assessment	Digit Vigilance Test (DVT) Digit Symbol Substitute Test (DSST) Bond and Lader Visual Analog Scale (VAS) Postural stability assessed using Accusway
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* The dose of alcohol administered in this study (0.7 g/kg body weight) has reliably demonstrated impairment on cognitive testing battery and postural stability in other alcohol interaction studies with CNS depressants

** PK samples were collected at pre-dose and at 0.5, 1, 2, 3, 5, 9, 16, 24, 48, 72 h post-dose (and 96 h for Day 19)

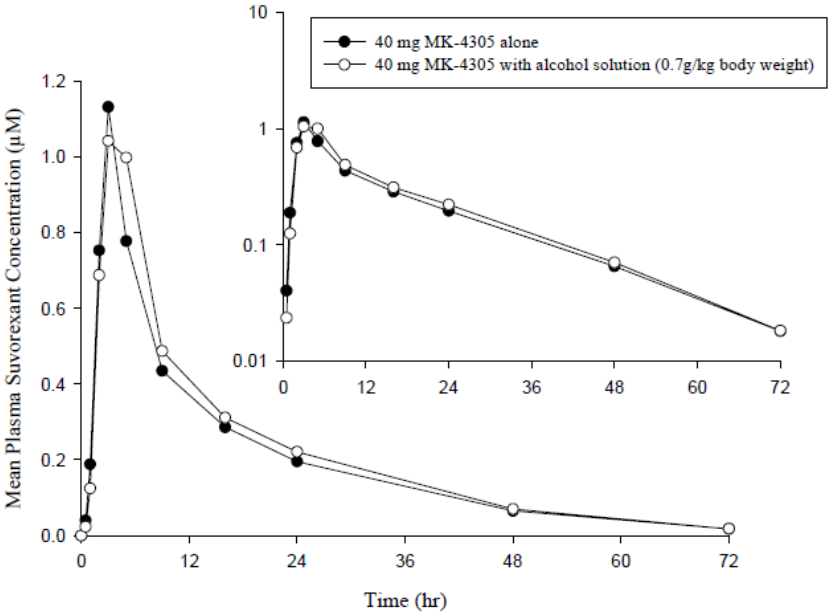
Bioanalytical Assay:
Plasma concentrations of suvorexant were determined using validated LC-MS/MS method (method DM-909). The assay performance during the validation was acceptable, details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Whole Blood for Alcohol Assay
Whole blood samples were collected into plastic vacutainers containing potassium EDTA (K_2EDTA) and processed for the analysis of whole blood alcohol concentrations by the laboratory at the Clinical Research Unit as per the local standard operating procedures.
Note: No details of the assay were provided in the report, only alcohol concentrations were provided in Appendix 16.1.11.1.

Suvorexant Pharmacokinetic Results

There was no PK interaction between alcohol and suvorexant. The mean plasma concentration profile of suvorexant when administered with or without alcohol is provided below.

Arithmetic Mean Plasma Concentration-Time Profile of Suvorexant Following AM Administration of a Single Dose of 40 mg Suvorexant (MK-4305) when Co-administered With and Without Alcohol in Healthy Young Subjects (Inset: Semi-log Scale) (N=30)



Statistical Summary for Pharmacokinetic Parameters of Suvorexant (MK-4305) Following AM Administration of a Single Dose of 40 mg Suvorexant When Co-administered With and Without Alcohol in Healthy Young Subjects

	MK-4305 with Alcohol			MK-4305 Alone			MK-4305 with Alcohol / MK-4305 Alone	
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (µM.hr)†	28	15.06	(13.31, 17.05)	28	13.76	(12.15, 15.57)	1.09	(1.04, 1.16)
C_{max} (µM)†	30	1.258	(1.158, 1.366)	30	1.200	(1.105, 1.304)	1.05	(0.98, 1.12)
T_{max} (hr)‡	30	3.0	[2.0, 5.1]	30	3.0	[1.0, 5.0]	-	-
Apparent terminal $t_{1/2}$ (hr)§	28	12.1	3.2	28	12.1	3.4	-	-

Alcohol PK Results

Statistical Summary for Pharmacokinetic Parameters of Alcohol Following AM Administration of Alcohol when Co-administered With and Without Suvorexant (MK-4305) in Healthy Young Subjects

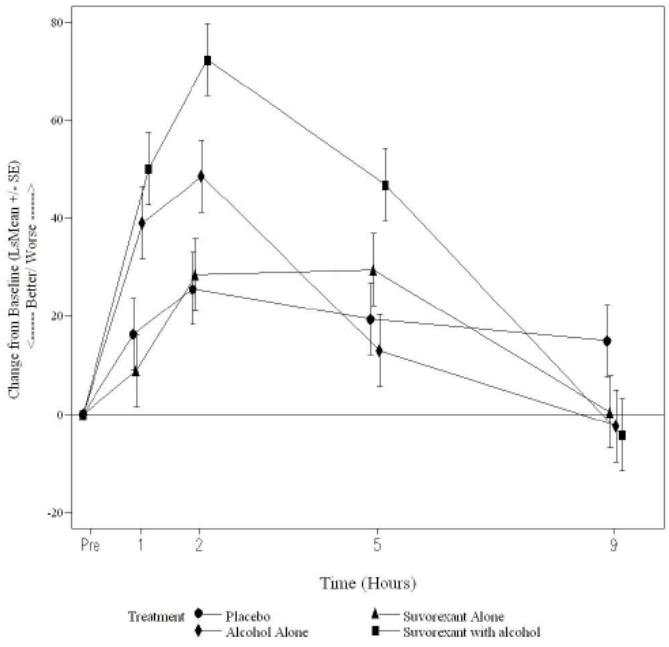
	MK-4305 with Alcohol			Alcohol Alone			MK-4305 with Alcohol / Alcohol Alone	
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0\text{-last}}$ (g/dL•hr)†	30	0.282	(0.265, 0.300)	30	0.285	(0.268, 0.304)	0.99	(0.95, 1.03)
C_{max} (g/dL)†	30	0.081	(0.077, 0.086)	30	0.082	(0.078, 0.087)	0.99	(0.95, 1.03)
T_{max} (hr)‡	30	2.0	[0.5, 3.0]	30	2.0	[0.5, 3.0]	-	-

Pharmacodynamic Results

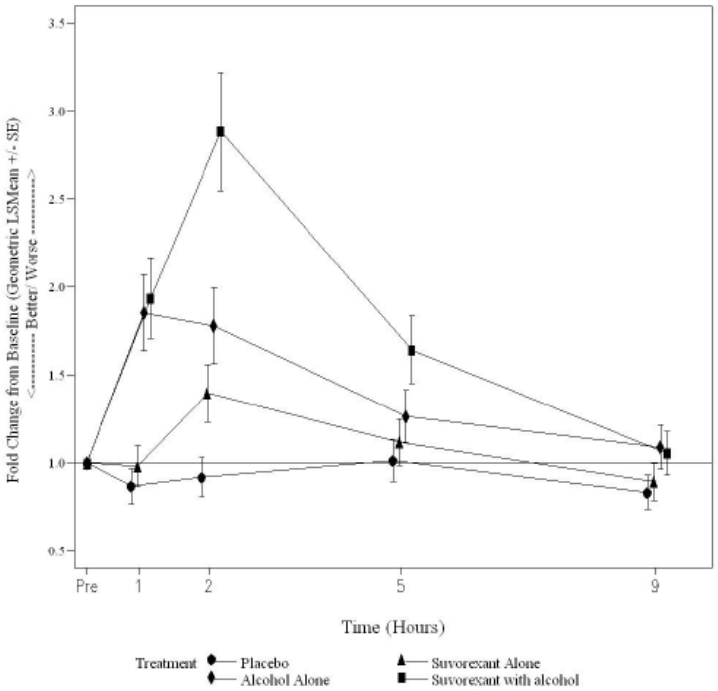
When suvorexant 40 mg was co-administered with alcohol (0.7 mg/kg), an additive effect on psychomotor performance alcohol and suvorexant was demonstrated. Alcohol

impaired sustained attention/vigilance as assessed by DVT, whereas suvorexant alone did not produce impairment on DVT. Co-administration of suvorexant and alcohol produced additive impairment as compared to suvorexant alone or alcohol alone on sustained attention/vigilance as assessed by DVT (speed) at 2 hours post-dose. The co-administration of suvorexant with alcohol also produced additive impairment on working memory as assessed by numeric working memory tests.
For body sway tests, there was statistically significant impairment observed with suvorexant alone versus placebo, and with alcohol alone versus placebo at 1 h and 2 h post-dose. There was also statistically significant impairment observed for suvorexant with alcohol versus suvorexant alone comparison, and suvorexant with alcohol versus alcohol alone comparison at 2 hours postdose. These data suggests there was an additive impairment on balance when suvorexant is co-administered with alcohol.
For DSST number correct, there were statistically significant decreases in number correct for alcohol at 1 hour postdose compared to placebo, for suvorexant alone versus placebo and for suvorexant with alcohol compared to alcohol alone at 5 hour postdose. Decreases in the number of correct digit substitutions are indicative of impairment.

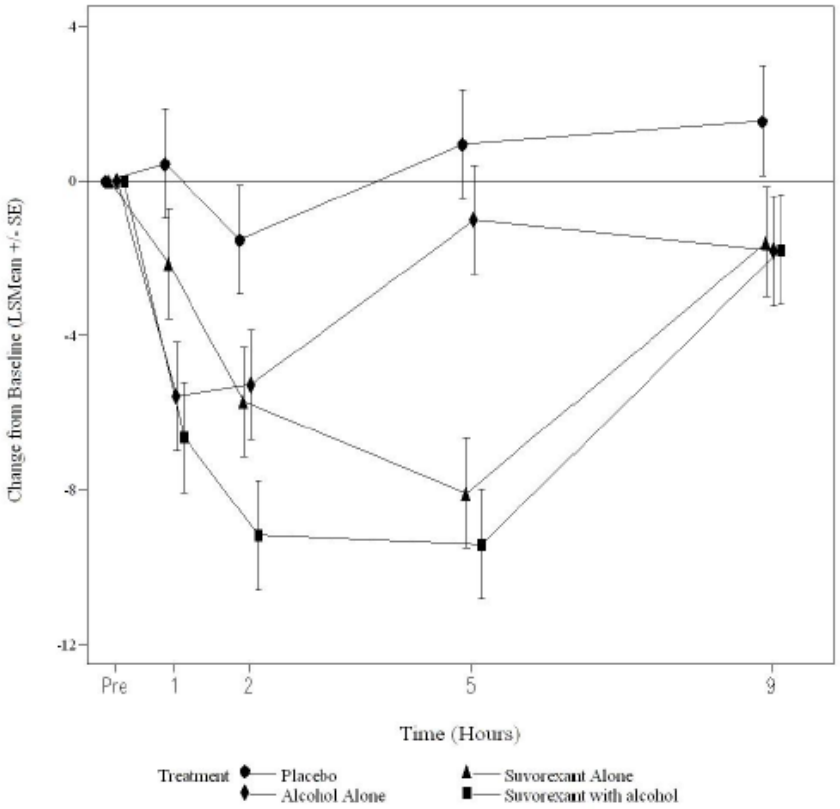
Mean ± SE for Digit Vigilance Reaction Time (msec) Change from Baseline after Administration of a Single Dose of 40 mg Suvorexant (MK-4305) When Coadministered With and Without Alcohol in Healthy Young Subjects (N=30)



Mean ± SE for Body Sway A95 Eyes Closed Fold-Change from Baseline after AM Administration of a Single Dose of 40 mg Suvorexant (MK-4305) When Coadministered With and Without Alcohol in Healthy Young Subjects (N=30)



Mean ± SE for Digit Symbol Substitution Test Number Correct Change from Baseline after Administration of a Single Dose of 40 mg Suvorexant (MK-4305) When Coadministered With and Without Alcohol in Healthy Young Subjects (N=30)



Summary of Statistically Significant Impairment for Between-Treatment Comparisons for Pharmacodynamic Tests Following AM Administration of a Single Dose of 40 mg Suvorexant (MK-4305) When Co-administered With and Without Alcohol in Healthy Young Subjects

PD Test/Endpoint	Direction of Change Indicating Impairment	MK-4305 alone v.s. Placebo	Alcohol alone v.s. Placebo	MK-4305 with Alcohol v.s. MK-4305 alone	MK-4305 with Alcohol v.s. Alcohol alone
Digit Vigilance Test (DVT)					
Reaction time speed (msec)	↑	N.S.	↑ hour 1, 2	↑ hour 1, 2	↑ hour 2, 5
Targets detected correctly (%)	↓	N.S.	N.S.	↓ hour 5	↓ hour 5
Choice Reaction Time (CRT)					
Reaction time-speed (msec)	↑	N.S.	N.S.	N.S.	↑ hour 2
Immediate Word Recall					
Words correctly recalled (%)	↓	N.S.	N.S.	N.S.	N.S.
Delayed Word Recall					
Words correctly recalled (%)	↓	N.S.	↓ hour 1, 2	↓ hour 1, 2	N.S.
Numeric Working Memory					
Speed (msec)	↑	↑ hour 2	N.S.	N.S.	↑ hour 2, 5
Sensitivity index (SI)	↑	↑ hour 2	N.S.	↑ hour 2	↑ hour 2
Body Sway					
A95 Eyes closed (area of the 95% confidence ellipse enclosing the center of pressure) (cm2)	↑	↑ hour 2	↑ hour 1, 2	↑ hour 1, 2, 5	↑ hour 2
A95 Eyes Open (area of the 95% confidence ellipse enclosing the center of pressure) (cm2)	↑	↑ hour 2	↑ hour 2	↑ hour 1	N.S.
Digit Symbol Substitution Test (DSST)					
number symbols correct (#)	↓	↓ hour 5	↓ hour 1	N.S	↓ hour 5
Bond and Lader Visual Analog Scale (VAS)					
Alertness	↑	N.S.	↑ hour 1, 2, 5, 9 (all)	↑ hour 1	N.S
Calmness	↑	N.S	N.S	N.S	N.S
Contentedness	↑	N.S	N.S	N.S	N.S

↑ hour *t1, t2*… indicates statistically significant impairment (increase) at these time points;
↓ hour *t1, t2*… indicates statistically significant impairment (decrease) at these time points;
N.S. indicates comparison not statistically significant at any time point.

Safety:

MK-4305 alone and in combination with alcohol was generally safe well tolerated in healthy young male and female subjects. There were no serious adverse experiences (SAE) or laboratory adverse experiences reported. One subject (AN 0026) discontinued on Day 2 in Period 3 (approximately 16 hours following 40 mg MK-4305) due to a clinical adverse experience of upper abdominal pain. This subject had a history of gastric ulcers. The investigator determined the event to be moderate in intensity and not related to study drug. This subject also reported clinical experiences of chest pain and dyspnea around the same time on Day 2 in Period 3, and both of the events were considered not related to study drug by the investigator.

The majority of the clinical AEs (67 reported by 18 subjects) reported were considered to be possibly or definitely drug-related by the principal investigator. The most frequently reported AEs were headache, somnolence, nausea, dizziness and feeling drunk.

Conclusions:

There was no PK interaction between alcohol and suvorexant, however co-administration of alcohol with suvorexant produced additive impairment as compared to suvorexant alone on sustained attention/vigilance as assessed by Digit Vigilance Test (DVT), on balance as assessed by body sway and on working memory.
Suvorexant should not be co-administered with alcohol.

P008: A Study to Evaluate the Effect of Multiple Doses of Ketoconazole on the Single Dose Pharmacokinetics of MK-4305

Objectives:

(1) To assess the effect of multiple doses of ketoconazole, a strong CYP3A4 inhibitor, on the single-dose pharmacokinetic profile of MK-4305 ($AUC_{0-\infty,}$ C_{max}, T_{max}, and apparent terminal t½);
(2) To evaluate safety and tolerability of a single oral dose of MK-4305 when co-administered with multiple oral doses of ketoconazole.

Study Design	Open-label, 2-period, fixed-sequence study
Study Population	10 healthy male subjects, 22-45 years
Treatment Group	1 group, 2 periods. Subjects received all treatments.
Dosage and Administration	Period 1: 4 mg MK-4305 Period 2: ketoconazole 400 mg for 11 days and a single dose of 4 mg MK-4305 on Day 2. There was at least a 5-day washout between the MK-4305 dose in Period 1 and the first dose of ketoconazole in Period 2.
PK Sampling: plasma	Plasma samples for MK-4305 and M9 *
Analysis	Plasma: LC-MS/MS method for MK-4305 and M9 Range: 1 to 1000 ng/mL for both analytes
PK Assessment	C_{max}, t_{max}, AUC_{0-24}, AUC_{0-inf}, $t_{1/2}$ of MK-4305 and M9 after suvorexant administration with and without ketoconazole
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* PK samples were collected at pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 (and 96, 120, 144, 168, 192, 216 and 240 h post-dose in period 2)

Bioanalytical Assay:

Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using validated LC-MS/MS methods (method DM-909 for suvorexant and DM-928 for M9). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in the QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Study Design Rationale

According to the literature reference[1] provided by the sponsor, the duration of ketoconazole dosing was long enough to ensure maximal CYP3A4 inhibition: co-administration of midazolam with ketoconazole on Day 2 of multiple dose ketoconazole administration increased the midazolam AUC and Cmax 13.14- and 5.2-fold respectively, which were indistinguishable from that observed with co-administration on Day 5 (AUC increase 13.96-fold and Cmax increase 5.0-fold).

Therefore, two days of dosing with ketoconazole would be sufficient to achieve CYP3A4 inhibition prior to dosing with MK-4305 for characterization of the potential drug-drug interaction pharmacokinetic data. Due to the 240-hour PK sampling for characterization of MK-4305, and the need to ensure continued ketoconazole-mediated CYP3A4 inhibition throughout the sample duration, ketoconazole was dosed for an additional 9 days past the dosing of MK-4305. CYP3A4 activity returns to baseline within 7 days of discontinuing ketoconazole dosing.

Note: Agree with this DDI study design.

Pharmacokinetic Results

Ketoconazole significantly increased suvorexant systemic exposure ($AUC_{0-\infty}$) and $t_{1/2}$. Only a 23% increase in suvorexant C_{max} was observed with prolongation in mean T_{max}. The increase in suvorexant AUC, with minimal increases in C_{max}, suggests that ketoconazole inhibits systemic clearance of suvorexant.

Summary of Pharmacokinetic Parameters of MK-4305 Following a Single Oral 4 mg Dose of MK-4305 Administered With and Without Multiple 400 mg Ketoconazole Doses to Healthy Subjects

	MK-4305 alone			MK-4305 with Ketoconazole			MK-4305 with Ketoconazole / MK-4305 alone	
PK Parameter	N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI
$AUC_{0-\infty}$ (μM•hr) †	10	2.61	(1.84, 3.71)	10	7.28	(5.13, 10.32)	2.79	(2.35, 3.31)
C_{max} (μM) †	10	0.277	(0.222, 0.347)	10	0.342	(0.274, 0.428)	1.23	(1.05, 1.44)
T_{max} (hr) §	10	1.0	0.5, 2.0	10	2.0	1.0, 4.0		
Apparent $t_{1/2}$ (hr) ‖	10	11.2	4.2	10	19.4	6.9		

Following co-administration of suvorexant with ketoconazole, M9 exposure (AUC) increased 1.80 while C_{max} slightly decreased (0.71). Similar increases in $t_{1/2}$ and T_{max} of M9 to those reported for the parent were observed. However, the metabolite/parent ratio decreased from 0.88 to 0.57 with ketoconazole coadministration.

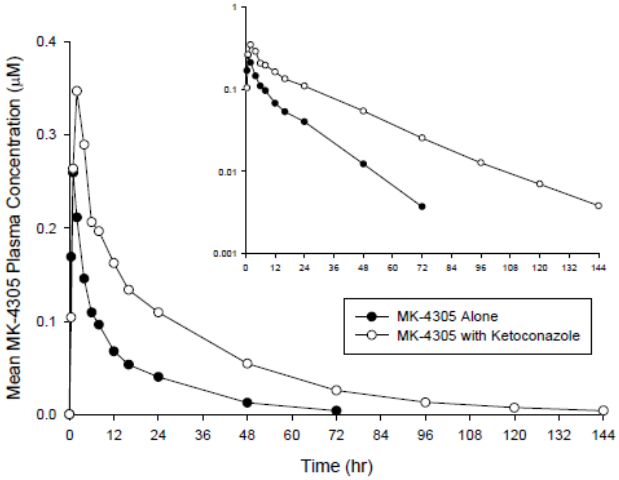
The decreased M9/MK-4305 ratio and the increased M9 $t_{1/2}$, indicates that both the formation and metabolism of M9 are inhibited by ketoconazole.

[1] *Bjornsson TD, Callaghan JT, Einolf HJ, Fischer V, Gan L, Grimm S, et al. The conduct of in vitro and in vivo drug-drug interaction studies: a PhRMA perspective. J Clin Pharmacol 2003;43:443-69.*

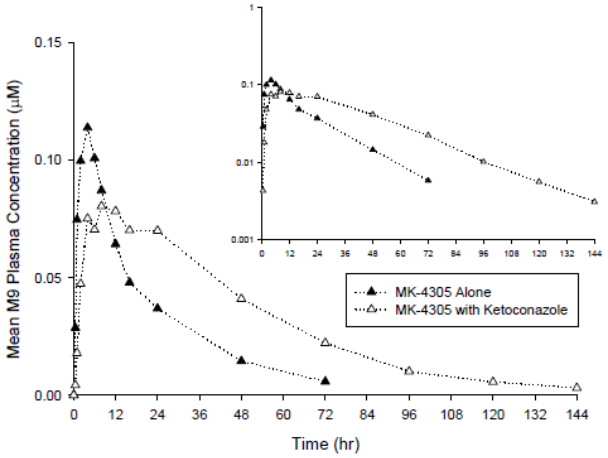
Summary of Pharmacokinetic Parameters of M9 Following a Single Oral 4 mg Dose of MK-4305 Administered With and Without Multiple 400 mg Ketoconazole Doses to Healthy Subjects

	MK-4305 alone			MK-4305 with Ketoconazole			MK-4305 with Ketoconazole / MK-4305 alone		
M9 PK Parameter	N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI	rMSE ‡
$AUC_{0-\infty}$ (μM•hr) †	10	2.30	(1.66, 3.20)	10	4.15	(2.99, 5.77)	1.80	(1.64, 1.98)	0.1143
C_{max} (μM) †	10	0.123	(0.110, 0.137)	10	0.088	(0.078, 0.098)	0.71	(0.64, 0.80)	0.1334
T_{max} (hr) §	10	4.0	1.0, 6.0	10	8.0	4.0, 24.0			
Apparent $t_{1/2}$ (hr) ‖	10	11.7	7.0	10	21.4	8.1			

Mean Plasma Concentration-Time Profile of MK-4305 Following a Single Oral 4 mg Dose of MK-4305 Administered With and Without Multiple 400 mg Ketoconazole Doses to Healthy Subjects (Inset: Semi-log Scale) (N=10)



Mean Plasma Concentration-Time Profile of M9 Following a Single Oral 4 mg Dose of MK-4305 Administered With and Without Multiple 400 mg Ketoconazole Doses to Healthy Subjects (Inset: Semi-log Scale) (N=10)



Safety:
There were no serious adverse experiences and no subjects discontinued due to an AE in this study. A total of 14 AEs were reported in 7 subjects. The most common adverse experience was somnolence. There were no laboratory adverse experiences.

Recommendations: Suvorexant exposure was significantly (3-fold) increased with concomitant administration of a strong CYP3A inhibitor. Suvorexant should not be co-administered with strong CYP3A inhibitors.

P013: A Study to Evaluate the Effect of Multiple-Doses of MK-4305 on the Pharmacokinetics of Oral Contraceptives in Healthy Female Subjects

Objectives:

Primary: To evaluate the effect of multiple-dose administration of suvorexant (MK-4305) on the PK of oral contraceptive components, ethinyl estradiol (EE) and norelgestromin (NGMN) the active metabolite of norgestimate, after co-administration of Ortho Cyclen

Secondary: To assess the safety and tolerability of the co-administration of suvorexant (MK-4305) and oral contraceptives in healthy adult female subjects.

(2) To assess the pharmacodynamic effects of suvorexant (MK-4305) on the level of alertness/somnolence by subjective evaluations on the KSS and Bond-Lader VAS scales.

Study Design	Open-label, randomized, 2-period, crossover study
Study Population	20 healthy female subjects, 24-44 years
Treatment Group	Each subject received two different treatments, Treatment A: a single oral dose of Ortho Cyclen on Day 1 and Treatment B: daily oral doses of 40 mg suvorexant on Days 1-18 with Ortho Cyclen co-administered with suvorexant on Day 14.
Dosage and Administration	Treatment A: a single oral dose of Ortho Cyclen on Day 1 Treatment B: daily oral doses of 40 mg suvorexant for 18 days with Ortho Cyclen co-administered with suvorexant on Day 14. Ortho Cyclen tablets: EE (0.035 mg) and norgestimate (0.250 mg, NGT) In each treatment period, study drug was administered at approximately 9:00 pm, following a ~4 hour fast. There was a minimum 10-day washout between each treatment period.
PK Sampling: plasma	EE and NGMN: Plasma was collected for the analysis of EE and NGMN pre-dose in Treatments A and B and at specified time points through 96 hours post Day 1 dosing in Treatment A and Day 14 dosing in Treatment B. * Plasma was collected for analysis of suvorexant at pre-dose in Treatments A or B and at specified time points through 96 hours post Day 18 dosing in Treatment B. ** Trough Levels ***
Analysis: plasma	LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL LC-MS/MS method for EE Range: 2 to 500 pg/mL LC-MS/MS method for NGMN Range: 0.02 to 10 ng/mL
PK Assessment	C_{max}, t_{max}, AUC_{0-24}, AUC_{0-inf}, $t_{1/2}$ of suvorexant C_{max}, t_{max}, AUC_{0-inf}, $t_{1/2}$ of ethinyl estradiol (EE) and norelgestromin (NGMN)
PD Assessment	Bond and Lader Visual Analogue Scale (VAS) Karolinska Sleepiness Scale (KSS)
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* PK samples for EE and NGMN were collected at pre-dose and at 0.25 and 0.75 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 and 96 post-dose

** PK samples for suvorexant were collected at pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 and 96 h post-dose
*** Suvorexant Plasma Collection for Trough Levels: Days 2, 3, 4, 5, 7, 9, 11, 13, 14, 15, 16, and 17
EE and NGMN Plasma Collection for Trough Levels: Days 15, 16, 17, and 18 only

Bioanalytical Assays:

Suvorexant:

Plasma concentrations of suvorexant were determined using validated LC-MS/MS method (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in the QBR.

The assay performance during the analysis of the plasma samples was acceptable.

EE and NGMN Assays:

Whole blood samples were collected in vacutainer tubes containing 15.0 mg sodium fluoride and 12.0 mg potassium oxalate and centrifuged at 2000-3000 rpms for 10-15 minutes. Plasma was stored at -70°C and processed for the analysis of EE and NGMN plasma concentrations (b) (4)

The analytical methods for the determination of concentration of EE and NGMN were based on a liquid-liquid extraction, separation by reversed phase HPLC and detection by tandem mass spectrometry in Multiple Reaction Monitoring (MRM) mode. Both methods were validated. The lower limit of quantitation (LLOQ) for the ethinyl estradiol method was 2 pg/mL with a linear calibration range from 2 to 500 pg/mL; the LLOQ for the norelgestromin method was 0.02 ng/mL with a linear calibration range from 0.02 to 10 ng/mL. The performance assays during the analysis of the plasma samples was acceptable.

One subject (AN0013) was excluded from all PK analyses because of a non-zero pre-dose EE plasma concentration in Period 1 prior to administration of any treatment and fluctuations in plasma concentration beyond 10 hrs postdose.

Study Design Rationale

This study was designed to evaluate the potential for a drug interaction effect of suvorexant on EE and NGMN (the primary active metabolite of the norgestimate component of Ortho Cyclen) following co-administration of suvorexant with Ortho Cyclen.

Based on in vitro data, suvorexant had the potential to be an inducer of Phase II metabolic enzymes. Based on a prior drug interaction study (P017), suvorexant dosed once daily for fourteen days was a weak inhibitor of CYP3A. Therefore, the duration of suvorexant dosing in the present study was fourteen days prior to co-administration of Ortho Cyclen to ensure that any potential time dependent effects of suvorexant on metabolic enzyme activity involved in the biotransformation of Ortho Cyclen components can be evaluated. This design is appropriate.

Pharmacokinetic Results:

No subject reported prior drug therapy usage within 14 days prior to the start of the study. Administration of acetaminophen, or products containing acetaminophen, was not

allowed within 24 hours prior to dosing of the Ortho Cyclen on Day 1 (Treatment A) and Day 14 (Treatment B) and for 96 hours after administration of Ortho Cyclen , since acetaminophen is known to affect the pharmacokinetics of oral contraceptives.
Ibuprofen was allowed at the investigator's discretion during the study for mild symptoms (e.g., headaches) in place of acetaminophen.
One subject (AN0013) was excluded from all PK analyses because of a non-zero pre-dose EE plasma concentration (see above). In addition, two subjects (AN 0003 and 0016) discontinued prematurely after receiving the Ortho Cylen alone treatment.

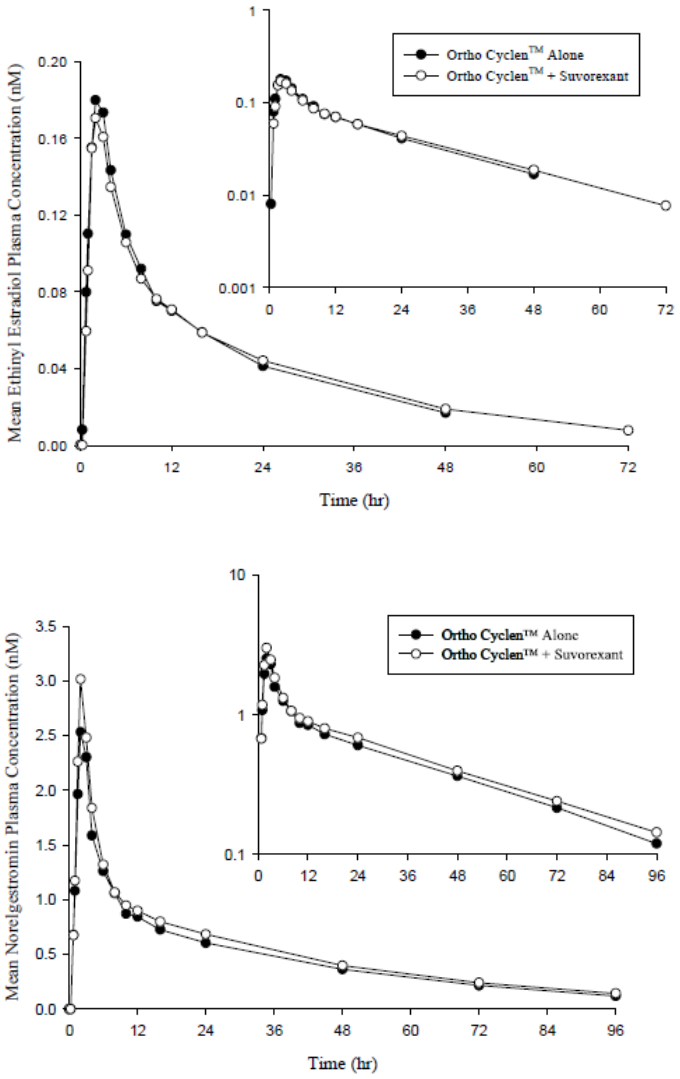
Pharmacokinetics of Ethinyl estradiol and Norelgestromin
Following the co-administration of single dose Ortho Cyclen (containing ethinyl estradiol and norgestimate) with 40 mg suvorexant on day 14 of once daily dosing of suvorexant alone for 18 days, the exposures of ethinyl estradiol and norelgestromin were similar to these when Ortho Cyclen was administered alone. The geometric mean ratio (Ortho Cyclen with suvorexant / Ortho Cyclen alone), and the corresponding 90% confidence interval for ethinyl estradiol $AUC_{0-\infty}$ was 1.07 and for norelgestromin $AUC_{0-\infty}$ was 1.16. In addition, no appreciable changes in T_{max} or in the apparent terminal half-life of ethinyl estradiol and norelgestromin were observed.

Summary of Pharmacokinetic Parameters of Ethinyl estradiol and Norelgestromin Following a Single Oral Dose of Ortho CyclenTM Alone or Coadministered on Day 14 of 18 Days of Once Daily PM Dosing of Suvorexant in Healthy Female Subjects

	Ortho Cyclen™ with MK-4305			Ortho Cyclen™ Alone			Ortho Cyclen™ with MK-4305 / Ortho Cyclen™ Alone		
	N	GM†	95 % CI	N	GM†	95 % CI	GMR	90 % CI	rMSE §
Ethinyl estradiol									
$AUC_{0-\infty}$ (nM•hr) †	17	3.14	(2.69, 3.67)	19	2.94	(2.52, 3.43)	1.07	(0.99, 1.16)	0.129
C_{max} (nM) †	17	0.169	(0.138, 0.206)	19	0.180	(0.148, 0.219)	0.94	(0.83, 1.06)	0.208
T_{max} (hr) ‡	17	2.0	(1.5, 6.0)	19	2.0	(1.5, 6.0)	.		.
Apparent terminal $t_{1/2}$ (hr) ‖	17	20.1	(4.9)	19	17.5	(3.9)	.		.
Norelgestromin									
$AUC_{0-\infty}$ (nM•hr) †	17	58.65	(53.08, 64.79)	19	50.74	(45.96, 56.02)	1.16	(1.11, 1.20)	0.066
C_{max} (nM) †	17	3.051	(2.540, 3.666)	19	2.829	(2.365, 3.383)	1.08	(0.95, 1.23)	0.220
T_{max} (hr) ‡	17	2.0	(1.0, 6.0)	19	2.0	(1.5, 8.0)	.		.
Apparent terminal $t_{1/2}$ (hr) ‖	17	31.3	(6.2)	19	29.4	(6.0)	.		.

† Back-transformed least squares mean from mixed effects model performed on natural log-transformed values.
‡ Median (min, max) for Tmax
‖ Harmonic mean (jackknife SD) for half-life.
§ rMSE=Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject %CV on the raw scale .
GMR= Least-Squares geometric mean ratio

Arithmetic Mean Plasma Concentration-Time Profile of Ethinyl Estradiol (above) and Norelgestromin (below) Following a Single Oral Dose of Ortho Cyclen Alone or Coadministered on Day 14 of 18 Days of Once Daily PM Dosing of Suvorexant in Healthy Female Subjects (Inset:Semi-log Scale) (N=19/ Ortho Cyclen Alone, N=17/ Ortho Cyclen + Suvorexant)



Pharmacokinetics of Suvorexant

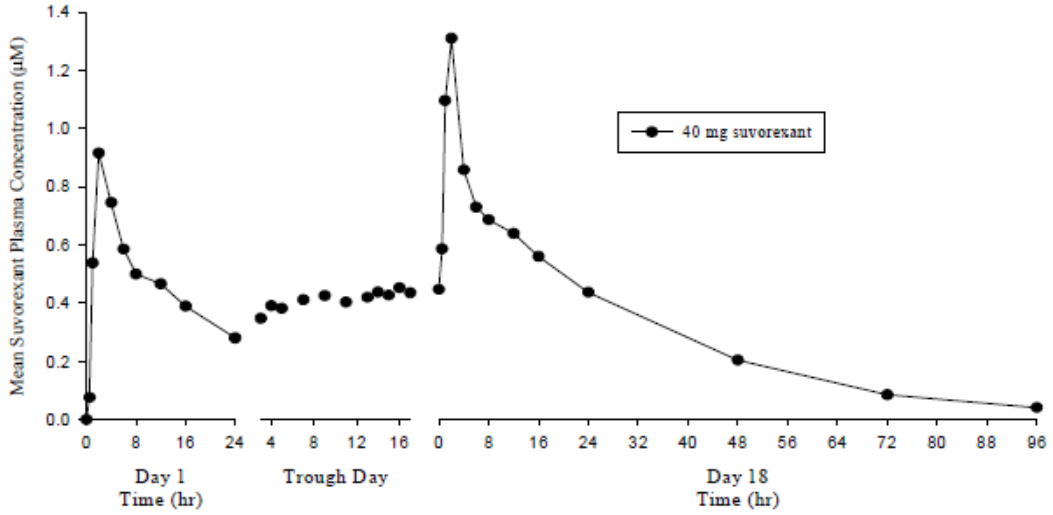
The pharmacokinetics of 40 mg of suvorexant administered once daily for 18 days, when Ortho Cyclen was co-administered on day 14, was also evaluated in this study. The statistical summary for the suvorexant PK parameters is presented in the table below. Healthy female subjects in this study achieved 90% of steady state suvorexant levels by Day 3 of multiple once daily dosing.

The mean accumulation ratio was 1.53 for $AUC_{0\text{-}24hr}$, consistent with the mean $t_{1/2}$ of 15.4 hours observed in this study.

Summary of Pharmacokinetic Parameters of Suvorexant (MK-4305) On Day 1 and Day 18 Following Once Daily PM Dosing of 40 mg Suvorexant, with a Single Oral Dose of Ortho CyclenTM Co-administered on Day 14 in Healthy Female Subjects

Pharmacokinetic Parameter	MK-4305 40-mg, Days 1-18 + Ortho Cyclen™, Day 14
Day 1 (Single Dose) (N= 19)	
$AUC_{0\text{-}24hr}$ (µM•hr) †	10.61 (9.49, 11.87)
C_{max} (µM) †	1.037 (0.909, 1.182)
C_{24hr} (µM) †	0.257 (0.220, 0.299)
T_{max} (hr) ‡	2.0 (1.0, 4.0)
Day 18 (Last Dose) (N=17)	
$AUC_{0\text{-}24hr}$ (µM•hr) †	16.28 (14.52, 18.25)
C_{max} (µM) †	1.409 (1.226, 1.620)
C_{24hr} (µM) †	0.421 (0.358, 0.494)
T_{max} (hr) ‡	2.0 (0.5, 2.0)
Apparent Terminal Half-life (hr) §	15.4 (3.8)
Accumulation Ratio: Day 18/ Day 1‖	
$AUC_{0\text{-}24hr}$	1.53 (1.43, 1.65)
C_{max}	1.36 (1.15, 1.60)
C_{24hr}	1.64 (1.41, 1.90)

Mean Plasma Concentration-Time Profile of Suvorexant Following Once Daily PM Dosing of 40 mg Suvorexant, with a Single Oral Dose of Ortho Cyclen Co-administered on Day 14 in Healthy Female Subjects (Linear Scale) (N=19/ Day 1, N=17/ Day 18)

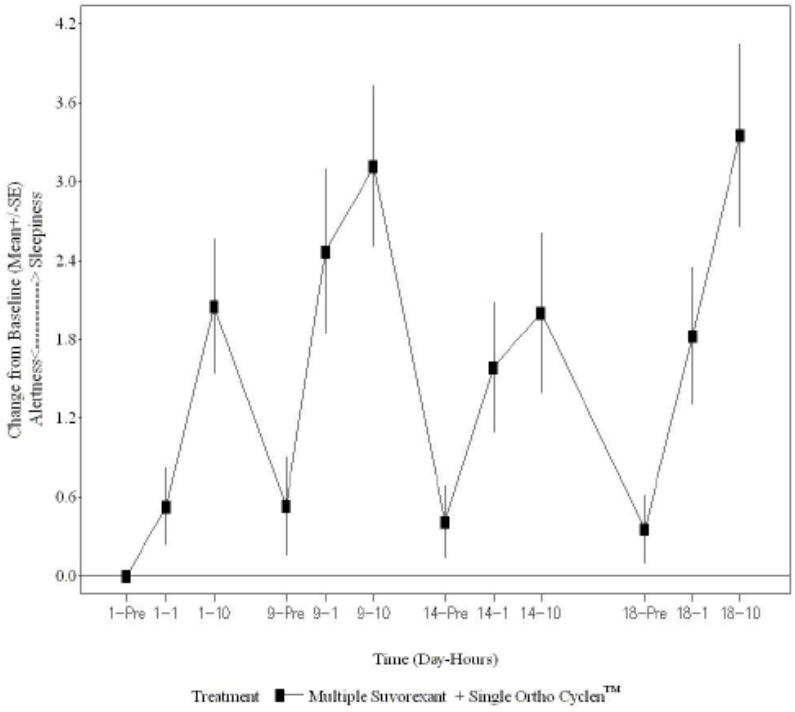


Pharmacodynamic Results:

The KSS Scale and Bond & Lader VAS were both administered at predose, 1 hr and 10 hr postdose on days 1, 3, 6, 9, 14 (suvorexant coadministered with OC), 15 and 18. Mean and standard error were calculated by timepoint, and plots were provided. Changes from baseline by day and timepoint for days 1, 9, 14 (when suvorexant was co-

administered with OC) and day 18 were plotted. Baseline was the pre-dose at each period for each treatment.
Suvorexant 40 mg, both administered alone (day 1, 9, 18) and with Ortho Cyclen (day 14), showed an increase in sleepiness/drowsiness as measured by both scales (VAS and KSS) at 1 and 10 h post-dose. Note: Increase in sleepiness at 10 h post dose argues against 40 mg dosing in this population (non-elderly females).
The changes from baseline by day on day 1, 9, 14 and 18 for KSS are presented below. For the KSS scale, 1 is very alert and 9 is very sleepy, great effort to keep awake.

Change (Mean +/- SE) from baseline of Karolinska Sleepiness Scale (KSS) Following Once Daily PM Dosing of 40 mg Suvorexant, with a Single Oral Dose of Ortho Cyclen Co-administered on Day 14 in Healthy Female Subjects (N = 19 Day 1, N=17 Day 14)



Safety:
Suvorexant was generally well tolerated in healthy young females. One serious clinical AE of appendicitis, was reported and was considered not drug related.
The most frequently reported AEs for subjects treated with 40 mg suvorexant on Days 1-13 were constipation and headache. The most frequently reported AEs for subjects treated with 40 mg suvorexant and Ortho Cyclen on Day 14 was nausea.

Conclusion: The results of this study indicate that impairment of contraceptive efficacy is unlikely. Co-administration of this oral contraceptive did not influence the pharmacokinetics of suvorexant.
Recommendations: No dose adjustment is needed for oral contraceptives when given in combination with suvorexant. No dose adjustment is needed for suvorexant when co-administered with oral contraceptives.

P015: A Study to Evaluate the Effect of Multiple Doses of MK-4305 on the Pharmacokinetics of Midazolam in Healthy Subjects

Objectives:
Primary: To evaluate the effect of multiple-dose MK-4305 on the pharmacokinetics of single-dose midazolam in healthy male and female subjects.
Secondary: To assess the safety and tolerability of multiple doses of MK-4305 when co-administered with an oral 2 mg dose of midazolam in healthy male and female subjects.
(2) To evaluate the effect of a single dose of MK-4305 on the pharmacokinetics of single-dose midazolam

Study Design*	2-part *, open-label study in healthy male and female subjects
Study Population	12 healthy male (10) and female (2) subjects, 23-48 years, BMI < 31 kg/m^2 11 completed the study
Treatment Group	Each subject received all treatments, see below.
Dosage and Administration	2 mg midazolam HCl syrup on Study Days 1, 3, 6, and 16 Multiple daily 80 mg oral doses of MK-4305 on Study Days 3 through 16 (14 total days of MK-4305 administration). On concomitant dosing days (Study Days 3, 6, and 16), the 2 mg midazolam dose was given 2 hours following the oral 80 mg dose of MK-4305. All drug doses were administered with 240 mL of water following an overnight fast.
PK Sampling: plasma	Midazolam: Plasma for midazolam analysis was collected pre-dose and at selected time points over 24 hours following administration of midazolam doses (Study Days 1, 3, 6, and 16). ** Plasma was collected for analysis of suvorexant at pre-dose and at selected time points *** over 72 hours following the 14th day of multiple daily MK-4305 dose administration (Study Day 16). Additionally, plasma for MK-4305 trough level analysis was collected prior to MK-4305 dosing on Study Days 3, 4, 5, 6, 8, 10, 12, 14, and 15
Analysis: plasma	LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL LC-MS/MS method for midazolam Range: 0.1 to 100 ng/mL
PK Assessment	C_{max}, t_{max}, AUC_{0-24}, AUC_{0-inf}, $t_{1/2}$ of suvorexant C_{max}, t_{max}, AUC_{0-inf}, $t_{1/2}$ of midazolam
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* The conduct of Part II of the study (40 mg of MK-4305) was contingent on the preliminary results of the pharmacokinetics of midazolam in subjects enrolled in Part I (80 mg of MK-4305). Part II was not conducted.
** Pre-dose, 15 min, 30 min, 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours post midazolam dosing
*** PK samples for suvorexant were collected at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, and 72 h post-dose

Bioanalytical Assays:

Suvorexant:

Plasma concentrations of suvorexant were determined using validated LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in the QBR.

The assay performance during the analysis of the plasma samples was acceptable.

Midazolam Assay:

Whole blood samples were collected in sodium heparinized tubes and centrifuged at 2500-3000 rpms at 4°C for 10 minutes. Plasma was stored at -70°C and processed for the analysis of midazolam plasma concentrations (b) (4)

Plasma concentrations of midazolam were determined using validated method of liquid-liquid extraction, followed by evaporation and reconstitution, with subsequent residue analysis via HPLC with tandem mass spectrometry. The lower limit of quantitation for midazolam was 0.10 ng/mL. The analytical range of quantitation was 0.10 to 100 ng/mL. Midazolam-d_4 maleate was used as internal standard (IS).

An assessment for potential interference of midazolam on MK-4305 was conducted, no interference was observed.

Note: In the NDA submission, the 2 reports (MK-4305 and Midazolam) are switched, e.g. 16.1.11.1 Midazolam Bioanalytical Report is actually the MK-4305 Bioanalytical Report. The Midazolam Bioanalytical Report can be found under 16.1.11.2.

The performance assays during the analysis of the plasma samples was acceptable.

Study Design Rationale

Suvorexant has shown in vitro DDI potential on CYP3A4, CYP2C19, or CYP1A2, through either inhibition or induction of these enzymes. Suvorexant was administered as multiple, daily doses for 14 days at doses that have generally been safe and well tolerated. It was expected that 2-3 days will provide sufficient time to attain steady state, and 14 days will provide sufficient time to maximally induce the CYP450 system.

Two different dose levels of MK-4305 (80 mg and 40 mg) were to be sequentially evaluated in this study. Per protocol, if there was no significant effect on midazolam during Part I of the study (80 mg suvorexant), evaluation of the lower dose (40 mg) of suvorexant would not be pursued. Based on the results from Part I of this study, Part II (40 mg dose level) was not conducted.

Note: This design is appropriate for achieving the objectives of this DDI study.

Pharmacokinetic Results:

Midazolam systemic exposure ($AUC_{0-\infty}$ and C_{max}) was similar after co-administration of midazolam with single dose suvorexant (Study Day 3) compared to midazolam administered alone. Midazolam T_{max} and $t_{1/2}$ estimates were similar under both conditions. Therefore, suvorexant has minimal potential for clinically meaningful reversible inhibition of CYP3A.

After co-administration of midazolam on Day 14 (Study Day 16) of multiple daily doses of suvorexant, midazolam $AUC_{0-\infty}$ increased by 47% compared to midazolam administered alone. The $AUC_{0-\infty}$ for midazolam following co-administration on Day 4 (Study Day 6) of multiple daily doses of 80 mg suvorexant increased approximately 25%

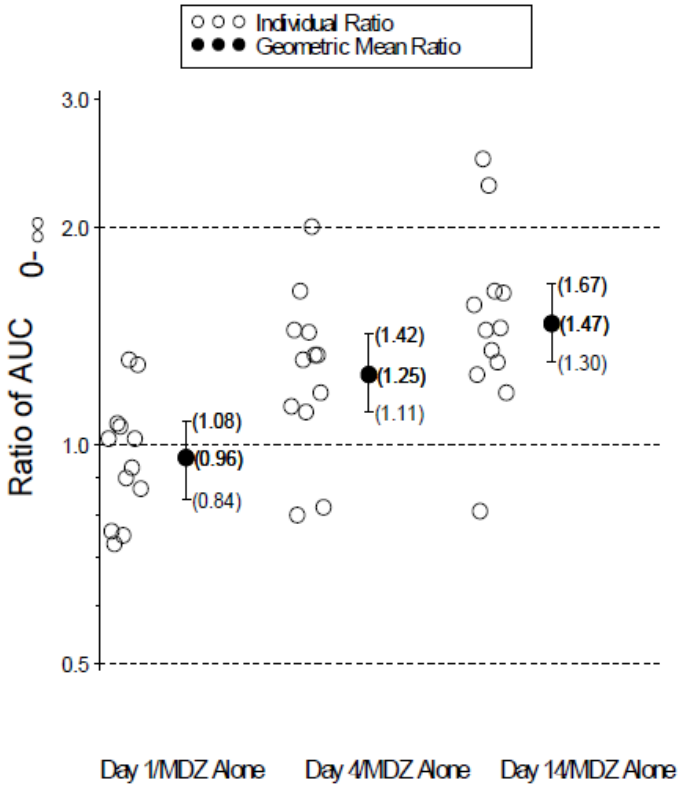
compared to midazolam administered alone. Generally, the effects on midazolam C_{max} were less than those observed for $AUC_{0-\infty}$. Midazolam $t_{1/2}$ was also increased following coadministration with multiple daily doses of suvorexant. These results suggest that suvorexant is a weak, time-dependent CYP3A inhibitor.

Statistical Comparisons of Midazolam Plasma Pharmacokinetic Parameters in Healthy Male and Female Adult Subjects Following the Single-dose Administration of 2 mg Midazolam Alone, 2 mg Midazolam Co-administered With the First Dose of Multiple Dose 80 mg MK-4305, and 2 mg Midazolam Co-administered Following Days 4 and 14 of Multiple Doses of 80 mg MK-4305 Q.D.

Parameter	Treatment	N	GM	95% CI	Comparison vs Midazolam Alone: Geometric Mean Ratio	90% CI	rMSE[†]
$AUC_{0-\infty}$[‡] (ng•hr/mL)	Midazolam Alone	12	26.20	(20.25, 33.91)	-	-	0.1807
	First Dose of Multiple Daily Doses of MK-4305 + Midazolam	12	25.08	(19.38, 32.46)	0.96	(0.84, 1.08)	-
	Multiple Daily Doses of MK-4305 (4 days) + Midazolam	12	32.85	(25.38, 42.52)	1.25	(1.11, 1.42)	-
	Multiple Daily Doses of MK-4305 (14 days) + Midazolam	12	38.55	(29.79, 49.90)	1.47	(1.30, 1.67)	-
C_{max}[‡] (ng/mL)	Midazolam Alone	12	9.57	(7.77, 11.78)	-	-	0.2033
	First Dose of Multiple Daily Doses of MK-4305 + Midazolam	12	7.94	(6.45, 9.77)	0.83	(0.72, 0.95)	-
	Multiple Daily Doses of MK-4305 (4 days) + Midazolam	12	10.13	(8.23, 12.48)	1.06	(0.92, 1.22)	-
	Multiple Daily Doses of MK-4305 (14 days) + Midazolam	12	11.76	(9.55, 14.48)	1.23	(1.07, 1.41)	-
T_{max}[‖] (hr)	Midazolam Alone	12	0.5	(0.5, 1.0)	-	-	-
	First Dose of Multiple Daily Doses of MK-4305 + Midazolam	12	1.0	(0.5, 1.5)	0.25[¶]	(0.01, 0.50)[¶]	-
	Multiple Daily Doses of MK-4305 (4 days) + Midazolam	12	1.0	(0.5, 1.1)	0.30[¶]	(0.25, 0.51)[¶]	-
	Multiple Daily Doses of MK-4305 (14 days) + Midazolam	12	1.0	(0.5, 1.0)	0.25[¶]	(0.24, 0.50)[¶]	-
Apparent Terminal $t_{1/2}$[§] (hr)	Midazolam Alone	12	3.3[§]	2.6[§]	-	-	-
	First Dose of Multiple Daily Doses of MK-4305 + Midazolam	12	3.8[§]	3.1[§]	-	-	-
	Multiple Daily Doses of MK-4305 (4 days) + Midazolam	12	4.7[§]	2.6[§]	-	-	-
	Multiple Daily Doses of MK-4305 (14 days) + Midazolam	12	4.5[§]	2.2[§]	-	-	-

rMSE: Root mean square error on log-scale. When multiplied by 100, provides estimate of the pooled coefficient of variation.
[‡]Back-transformed least squares mean and confidence interval from fixed effects model performed on natural log-transformed values.
[‖]Median (Min, Max) reported for T_{max}.
[§]Harmonic mean, jack-knife SD reported for $t_{1/2}$.
[¶]Median difference and CI from Hodges-Lehmann estimation reported for T_{max}.

Individual Midazolam $AUC_{0-\infty}$ Ratios, Geometric Mean Ratios, and 90% CI for a Single-dose Administration of 2 mg Midazolam Co-administered With 80 mg MK-4305 on Days 1, 4, and 14 of Multiple MK-4305 Doses Relative to a Single Dose of 2 mg Midazolam Administered Alone in Healthy Male and Female Adult Subjects (N = 12)

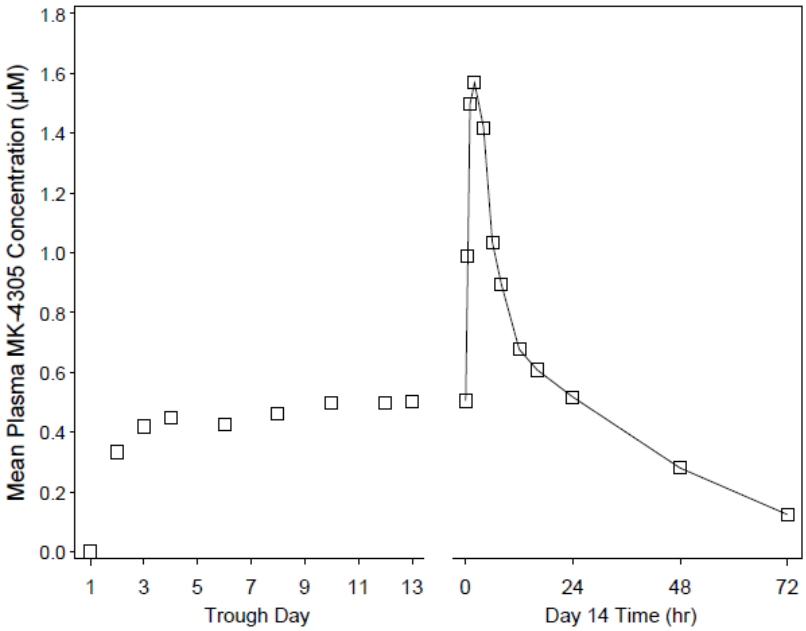


Recommendations: No dose adjustment is needed for CYP3A substrates when co-administration with suvorexant. The results of this study demonstrated that the exposure of CYP3A substrates could be increased by 47% after co-administration with multiple doses of 80 mg suvorexant. As the recommended dose of suvorexant now is 10-20 mg, its effect on CYP3A substrates is expected to be even less.

Suvorexant Plasma Concentrations

The mean trough concentrations as well as the mean Day 14 plasma suvorexant concentration-time profile are presented below. Suvorexant concentrations after multiple daily doses of 80 mg suvorexant were consistent with historical results.

Mean Trough (Predose) and Day 14 Plasma MK-4305 Concentration-time Profile in Healthy Male and Female Adult Subjects Following Multiple Daily Dose Administration of 80 mg MK-4305 for 14 Days Co-administered With Single Oral Doses of 2 mg Midazolam on Days 1, 4, and 14 (N = 12)



Note: Subject AN 0011 withdrew consent from study participation on Study Day 17 due to a personal reason unrelated to the study. This subject received all scheduled doses of suvorexant and midazolam prior to study withdrawal; however, the last 2 suvorexant blood sampling draws in the Study Day 16 (Day 14 of suvorexant dosing) were not obtained.

Safety:

Suvorexant was generally well tolerated in the healthy subjects in this study. No serious clinical laboratory or other significant AEs were reported during the study. Mild somnolence (100% of subjects) was the most frequently reported AE. One subject (AN 0012) failed to disclose a history of chronic schizophrenia at screening; this subject was treated on an out-patient basis with olanzapine for the adverse experience of acute psychosis on Day 22 through Day 24. No clinically meaningful relationships were observed for differences between clinical laboratory, vital signs, orthostatic vital signs, physical examinations, and ECGs as a function of treatment.

P016: A Study to Evaluate the Effect of Multiple Doses of MK-4305 on the Single Dose Pharmacokinetics of Digoxin

Objectives:

Primary: To evaluate the effect of multiple-dose MK-4305 on the pharmacokinetics of single-dose digoxin in healthy male and female subjects.

Secondary: To assess the safety and tolerability of multiple doses of MK-4305 co-administered with a 0.5 mg of digoxin dose in healthy male and female subjects.

Study Design	Open-label, randomized, 2-period crossover study
Study Population	20 healthy male (12) and female (8) subjects, 22-50 years, 19 completed the study
Treatment Group	Subjects received 2 different treatments, Treatment A (0.5 mg digoxin on Day 1) and Treatment B (oral doses of 40 mg MK-4305 administered once daily for 11 days with co-administration of a single oral dose of 0.5 mg digoxin on Day 4), in a randomized crossover design.
Dosage and Administration	Treatment A: single oral dose of 0.5 mg digoxin on Day 1. Treatment B: suvorexant 40 mg, QD for 11 days with co-administration of a single oral dose of 0.5 mg digoxin on Day 4 (when suvorexant had reached steady state). There was a minimum washout of 10 days from the last dose of study drug in Period 1 (either digoxin in Treatment A or suvorexant in Treatment B), to the first dose of study drug in Period 2. All doses were administered with 240 mL of water in the fasted state.
PK Sampling	Digoxin plasma samples were obtained for up to 120 hours (Treatment A) following the administration of digoxin. Digoxin plasma samples were obtained for up to 192 hours (Treatment B) following the co-administration of digoxin with MK-4305 (Day 4). * Urine was collected and assayed in both Treatments A and B for up to 48 hours post-dose for analysis of digoxin. ** Suvorexant: PK samples were collected just prior to suvorexant administration on Days 1, 2, 3, and 4 and on Day 12 for archive.
Analysis	LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL Digoxin was quantified in plasma by radioimmunoassay employing an iodinated digoxin tracer. The range of quantification was 0.150 to 8.00 ng/mL. Digoxin was quantified by radioimmunoassay directly from human urine that has been diluted 1:10 with human serum. Range for urine samples: 1.00 to 40.0 ng/mL
PK Assessment	C_{max}, t_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$, Cl_r and f_e of digoxin
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* Blood samples for the digoxin assay were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120 (144, 168 and 192 hrs postdose, Trt B).

** Urine was collected pre-dose and post-dose over the following time intervals: [0 to 12], [12 to 24], [24 to 36], and [36 to 48] hours after digoxin administration on Day 1 and Day 4

Bioanalytical Assays:

Suvorexant:

Plasma samples for suvorexant concentrations were archived and were not assayed.

Plasma for Digoxin Assay:

Whole blood (4mL) samples were collected into vacutainer containing sodium heparin as the anticoagulant and inverted 5 to 8 times. Immediately after collection, the blood containing tubes were placed on ice and centrifuged promptly at 1450 g for 15 minutes at 4°C to 10°C. After separation of the whole blood, the plasma was transferred in cryotubes and store at -80°C until transferred (b) (4)

Digoxin was quantified directly from heparinized human plasma. The plasma was pipetted into antibody coated tubes and quantified by a validated radioimmunoassay employing an iodinated digoxin tracer specific for digoxin. The assay required 100 µL of sample and the range of quantification was 0.150 to 8.00 ng/mL. Assay selectivity for the analyte at the radioimmunoassay conditions was met. An analyte interference check was performed to determine if samples fortified with MK-4305 interfered with the quantitation of digoxin in human plasma; no interference was observed.

Urine for Digoxin Assay

The total urine voided within the specified timed intervals was collected in a volumetric container. The total volume of urine collected during each timed interval and the exact start and stop times of each interval were recorded. Approximately a 4-mL aliquot was transferred to a properly labeled round bottom cryotube vial and stored at -80°C until shipment (b) (4)

Digoxin was quantified directly from human urine that has been diluted 1:10 with human serum. The diluted urine was pipetted into antibody-coated tubes and quantified by a validated radioimmunoassay using an iodinated tracer specific for digoxin. This assay required 200 µL sample volume of human urine diluted 1:10 in human serum. Samples were analyzed in duplicate and results are reported as the mean of the two wells analyzed. The range of quantification was 1.00 to 40.0 ng/mL.

The performance assays during the analysis of the samples was acceptable.

Study Design Rationale

Suvorexant is an inhibitor of human P-gp *in vitro* (IC_{50} 19 µM). This study evaluated the potential for co-administration of suvorexant to alter the pharmacokinetics of digoxin, a P-gp substrate. Since digoxin has a narrow therapeutic margin, a formal drug interaction study was conducted to evaluate the DDI potential of suvorexant. In order to evaluate the maximum potential for interaction, a single dose of digoxin was co-administered when suvorexant was at steady-state after 4 days of once daily dosing, and suvorexant administration continued for 7 days following digoxin treatment, while digoxin pharmacokinetic samples were being collected.

Note: This design is appropriate for achieving the objectives of this DDI study.

Pharmacokinetic Results:

One subject (AN 0019) discontinued. This subject did not have PK samples obtained prior to his discontinuation and was not included in the analysis.

The renal clearance was calculated by dividing the total amount of digoxin excreted in urine over the 48 hour collection period by the plasma digoxin $AUC_{0\text{-}48hr}$. The fraction excreted was calculated by dividing the total digoxin excreted in urine over the 48 hour collection period by the dose administered.

For the digoxin + MK-4305 treatment, 2 subjects (AN 0008 and AN 0016) had missing urine PK samples for the 36 to 48 hour time interval. Renal clearance was calculated by taking the quotient of the total digoxin excreted in urine over the 0 to 36 hour collection periods and plasma digoxin $AUC_{0\text{-}36hr}$ for these 2 subjects.

Concomitant administration of a single dose digoxin 0.5 mg with multiple daily doses of suvorexant 40 mg slightly increased $AUC_{0\text{-}last}$ by 27% and C_{max} by 21%. There was no statistically significant change in digoxin renal clearance when administered with suvorexant. The geometric mean ratio (digoxin with suvorexant/ digoxin alone) for renal clearance with corresponding 90% confidence intervals were 0.94 and (0.82, 1.08). The increase in digoxin concentrations in the presence of suvorexant generally occurred within the first 6-hours, while plasma concentrations in the terminal phase were unchanged.

Summary of Plasma PK Parameters of Digoxin Following a Single Oral Dose of 0.5 mg Digoxin Administered With and Without Multiple Doses of 40 mg Suvorexant (MK-4305) to Healthy Subjects

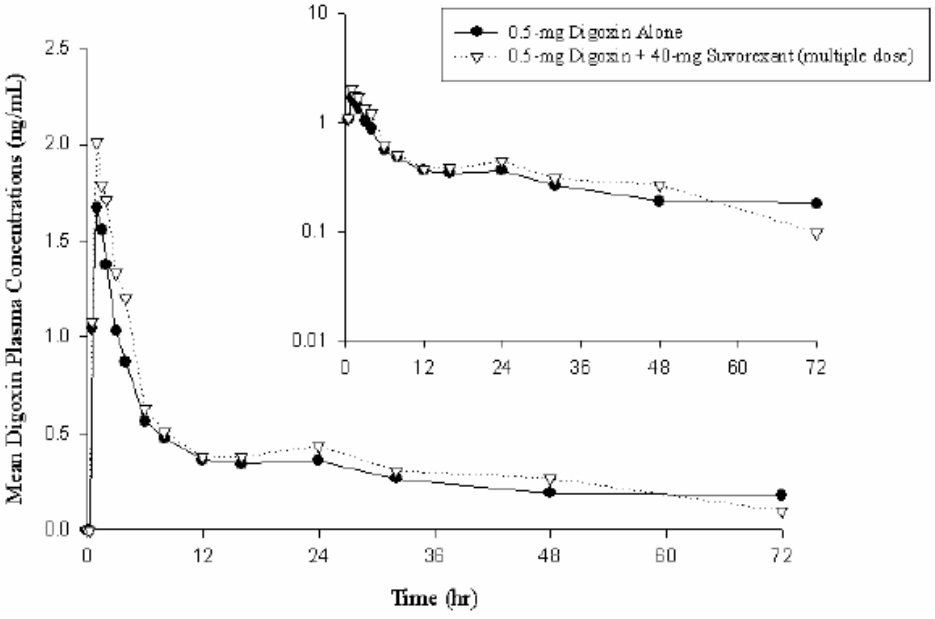
Pharmacokinetic Parameter	Digoxin Alone			Digoxin with MK-4305			Digoxin with MK-4305 / Digoxin alone	
	N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI
$AUC_{0\text{-}last}$ (hr•ng/mL)†	19	19.98	(16.60, 24.05)	19	25.27	(21.00, 30.43)	1.27	(1.12, 1.43)
C_{max} (ng/ml)†	19	1.82	(1.56, 2.12)	19	2.20	(1.89, 2.56)	1.21	(1.05, 1.40)
T_{max} (hr)‡	19	1.5	(0.5, 2.0)	19	1.0	(0.5, 4.0)	.	

Summary of Urinary PK Parameters of Digoxin Following a Single Oral Dose of 0.5 mg Digoxin Administered With and Without Multiple Doses of 40 mg Suvorexant (MK-4305) to Healthy Subjects

Pharmacokinetic Parameter	N	Geometric Mean for Treatment † (95% CI)		Geometric Mean (90% CI) for Treatment Ratio
		Digoxin Alone	Digoxin with MK-4305	Digoxin with MK-4305 / Digoxin Alone
Renal Clearance (mL/min)†	19	106.81 (90.82, 125.63)	100.53 (85.48, 118.24)	0.94 (0.82, 1.08)
Fraction Excreted (%)§	19	23.04 (19.83, 26.77)	26.02 (22.39, 30.23)	--

† Back-transformed least-squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
§ Urine collected through 48 hours.

Mean Plasma Concentration-Time Profile of Digoxin Following a Single Oral Dose of 0.5 mg Digoxin Administered With and Without Multiple Doses of 40 mg Suvorexant (MK-4305) to Healthy Subjects (N=19)



Recommendations: No dose adjustment is needed for digoxin when co-administered with suvorexant.

P024: A Study to Evaluate the Effect of Multiple Doses of Suvorexant (MK-4305) on the Single Dose Pharmacokinetics and Pharmacodynamics of Warfarin in Healthy Subjects

Objectives:

Primary: 1) To determine the effect of suvorexant at steady state on the plasma pharmacokinetics of warfarin for the R(+) and S(-)enantiomers of warfarin) following co-administration of a single dose of warfarin to healthy subjects. 2) To assess the safety and tolerability of administration of multiple doses of suvorexant with co-administration of a single dose of warfarin administered to healthy subjects.

Secondary: To determine the effect of suvorexant at steady state on the pharmacodynamics of warfarin as assessed by the International Normalized Ratio (INR) for prothrombin time following single-dose warfarin administration.

Study Design	Open-label, randomized, 2-period crossover study
Study Population	14 healthy male (12) and female (2) subjects, 23-50 years, 13 completed the study
Treatment Group	Subjects received 2 different treatments, Treatment A and Treatment B, in a randomized crossover design
Dosage and Administration	Treatment A: a single oral dose of 30 mg warfarin Treatment B: daily oral doses of 40 mg suvorexant for 20 consecutive days with co-administration of a single oral dose of 30 mg warfarin on Day 14. There was a minimum of 14 days from the last dose in Period 1 to the first dose in Period 2. All doses were administered in the fasted state with 240 mL of water.
PK Sampling	Blood samples for for R(+) and S(-) warfarin enantiomers were collected up to 168 h after warfarin administration* Suvorexant: PK samples for suvorexant were collected during Trearment B for archive only.
Analysis	LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL R(+) and S(-) warfarin: LC/MS/MS. Range 10 to 2500 ng/mL for both
PK Assessment	C_{max}, t_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$ of R(+) and S(-) warfarin
PD Assessment	Plasma coagulation rate as measured by the prothrombin time [PT and International normalized ratio (INR) values] **
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* Blood samples for for R(+) and S(-) warfarin enantiomers were collected at 0.5, 1, 2, 4, 12, 24, 48, 72, 96, 120, 144, 168 h post (warfarin) dose

** Samples for PT and INR were collected at pre- (warfarin) dose and at 1, 2, 4, 12, 24, 48, 72, 96, 120, 144, 168 h postdose in both trt periods

Bioanalytical Assays:

Suvorexant:

Plasma samples for suvorexant concentrations were archived and were not assayed.

Warfarin Assay:
Blood for determination of warfarin enantiomer plasma concentrations was drawn in sodium heparin containing tubes. The samples were immediately centrifuged (within 30 minutes) at 3000 rpm for 15 minutes at 4°C. The plasma was separated into cryotubes and stored at -20°C.
Plasma samples for R(+) and S(-) warfarin concentrations were analyzed (b) (4) using a validated method with turbo ion spray liquid LC/MS/MS and selected reaction monitoring (SRM) detection. The range of quantitation of the assay was 10 to 2500 ng/mL for both analytes.
The performance assays during the analysis of the samples was acceptable. The inter-assay precision (CV) of QC1, QC2, and QC3 samples was 5.9% for (R)-warfarin and 6.4% for (S)-warfarin. The inter-assay accuracy (%Dev) of the QC samples ranged from -0.5 to 7.0% for (R)-warfarin and from -4.0 to 9.0% for (S)-warfarin. No chromatographic interferences from MK-4305 were detected.

Blood for Prothrombin Time Determination (INR) and PT values
Blood was collected for measurement of prothrombin time determination (INR and PT values) in appropriate citrate tubes. The tubes were centrifuged immediately after collection for 15 minutes at 2000 rpm at room temperature. The plasma was either placed on ice for immediate testing or was transferred to a clean tube and refrigerated (for not more than 2 hours) until testing for the prothrombin time determination.

Study Design Rationale
The results of the in vitro induction studies indicated that suvorexant has potential to induce CYP3A4 and CYP1A2 mRNA, with lower induction potential for CYP2C9 mRNA. The degree to which the induction of new mRNA for the individual CYP enzyme leads to an increase in specific activity of the CYP enzyme is not known for CYP1A2 and CYP2C9. Although the likelihood for a clinically meaningful effect of suvorexant 40-mg/day on warfarin is low, the sponsor conducted a clinical drug interaction study due to the narrow therapeutic margin of warfarin. Previous studies have demonstrated that a sampling period of 168 hours was appropriate for assessing the pharmacokinetics of warfarin. A 14-day washout interval between periods was adequate given the $t_{1/2}$ of warfarin. If the 90% CIs for the $AUC_{0-\infty}$ geometric mean ratio (warfarin with suvorexant/warfarin alone) for both R(+) and S(-) warfarin fell within the bounds of [0.80, 1.25], then it was concluded that there is no evidence for a clinically meaningful PK interaction between warfarin and suvorexant. The bounds proposed for warfarin enantiomer PK are consistent with regulatory guidance for a narrow therapeutic index agent. In addition, the influence on steady-state concentrations of suvorexant on warfarin pharmacodynamics (INR values) was to be assessed in this study.
All prior medications were discontinued within 14 days or 5 half-lives of study start. Medications of particular concern for this study which were not permitted and were criterion for exclusion were NSAIDs, Al- or Mg-containing antacids, metal cations such as iron, multivitamins containing iron or zinc, or any medication which was an inducer or inhibitor of CYP3A4. Additionally, the maximum amount of vitamin K permitted in any multivitamin tablet was 25 µg.
This design is appropriate for achieving the objectives of this DDI study.

Pharmacokinetic Results:

All 14 subjects completed Treatment B of the study (suvorexant 40 mg + 30 mg warfarin) and were included in the PK and PD analysis of the of this treatment period. Thirteen of the 14 subjects completed Treatment A of the study (single dose warfarin 30 mg) and only these 13 subjects were included in the PK and PD analysis of this treatment period. In addition, S(-) warfarin apparent terminal half-life and $AUC_{0-\infty}$ were not reported for one subject, AN 0012. Due to a long terminal half life, there were insufficient time points in the terminal phase to characterize this subject's half-life; only 12 subjects were included in the analysis of $t_{1/2}$ and $AUC_{0-\infty}$ for S(-) warfarin.
The R(+) and S(-) enantiomers AUC and C_{max} values were similar when warfarin was administered in combination with suvorexant, compared to warfarin alone.
The geometric mean $AUC_{0-\infty}$ ratio (warfarin with suvorexant/warfarin alone) and corresponding 90% CI were 0.99 and (0.94, 1.04) for R(+) warfarin and 0.99 and (0.95, 1.04) for S(-) warfarin. Since these confidence intervals are within the bounds 0.80 and 1.25, the conclusion that there is no evidence for a clinically meaningful PK interaction between warfarin and suvorexant is supported.

Summary of PK Parameters of Warfarin Following Administration of a Single Oral Dose of 30 mg Warfarin and Daily Oral Doses of 40 mg Suvorexant (MK-4305) for 20 Days with Co-administration of a Single Oral Dose of 30 mg Warfarin on Day 14 (N=14 Warfarin with Suvorexant, N=13 Warfarin Alone)

	Warfarin with MK-4305		Warfarin Alone#		Warfarin with MK-4305 / Warfarin Alone
	N	GM† (95% CI)	N	GM†(95% CI)	GMR (90% CI)
R(+)Enantiomer					
$AUC_{0-\infty}$ (uM*hr)	14	322.57 (294.11, 353.79)	13	325.66 (296.56, 357.61)	0.99 (0.94,1.04)
AUC_{last} (uM*hr)	14	294.15 (271.72, 318.44)	13	295.82 (272.98, 320.58)	0.99 (0.95,1.04)
C_{max} (uM)	14	5.69 (5.21, 6.21)	13	6.02 (5.50, 6.59)	0.95 (0.87,1.03)
T_{max} ‡ (hr)	14	1.00 (0.50, 4.00)	13	1.00 (0.50, 2.00)	.
Apparent $t_{1/2}$‡ (hr)	14	46.4 (7.6)	13	47.6 (7.7)	.
S(-)Enantiomer					
$AUC_{0-\infty}$ (uM*hr)	13	239.55 (187.64, 305.82)	12#	241.46 (189.06, 308.38)	0.99 (0.95,1.04)
AUC_{last} (uM*hr)	14	242.76 (189.78, 310.54)	13	244.13 (190.81, 312.35)	0.99 (0.96,1.03)
C_{max} (uM)	14	5.86 (5.33, 6.44)	13	6.18 (5.60, 6.82)	0.95 (0.86,1.05)
T_{max} ‡ (hr)	14	1.00 (0.50, 2.00)	13	1.00 (0.50, 2.00)	.
Apparent $t_{1/2}$‡ (hr)	13	36.0 (9.5)	12#	37.3 (10.0)	.

Pharmacodynamic Results:

The geometric mean INR $AUC_{0-168hr}$ ratio (warfarin with suvorexant/warfarin alone) and 90% confidence interval were 1.06 and (1.03, 1.09), respectively. The geometric mean INRmax ratio (warfarin with suvorexant/warfarin alone) and 90% confidence interval were 1.09 and (1.05, 1.14), respectively. The lower limits of the 90% confidence intervals do not include one for both INR endpoints, indicating a statistically significant effect.

Summary of INR AUC_{0-168h} and INR_{max} Following Administration of a Single Oral Dose of 30 mg Warfarin and Daily Oral Doses of 40 mg Suvorexant (MK-4305) for 20 Days with Coadministration of a Single Oral Dose of 30 mg Warfarin on Day 14

	N	Warfarin + MK-4305 GM † (95% CI)	Warfarin Alone¶ GM † (95% CI)	Ratio Warfarin + MK-4305/warfarin alone GMR (90% CI)
$AUC_{0-168\ hr}$	14	237.50 (215.27, 262.02)	224.29 (203.25, 247.50)	1.06 (1.03, 1.09)
INRmax	14	1.96 (1.74, 2.21)	1.79 (1.59, 2.02)	1.09 (1.05, 1.14)

The slight increase in AUC_{0-168h} and INR_{max}, 6% and 9%, respectively, following co-administration of warfarin with suvorexant is not considered to be clinically meaningful. Note: This was confirmed with the Clinical Division (Dr. Illoh).

Safety:

One subject (AN0001) discontinued due to a lab AE (elevated AST) that occurred approximately 14 days after the last dose of 40 mg suvorexant. This subject completed all study procedures per protocol for Period 1 (warfarin and suvorexant) but not did participate in Period 2 (warfarin alone). The investigator rated this event as not related to study drug. The most frequently reported AE was somnolence (92.9% of subjects) during daily oral doses of 40 mg suvorexant for 20 consecutive days with co-administration of a single oral dose of 30 mg warfarin on Day 14.

One subject reported a brief episode (15 seconds) of muscle weakness, which began 1 hour and 8 minutes post dosing on Day 11 of 40 mg suvorexant dosing. According to the sponsor, this transient muscle weakness occurred during period of sleepiness and is inconsistent with cataplexy. (Cataplexy is a suddenly onset of muscle weakness that occurs during wakefulness and is usually triggered by strong emotion).

There were no bleeding related adverse events during treatment with warfarin when given alone or with suvorexant.

Recommendations: No dose adjustment is needed for warfarin when given in combination with suvorexant.

P026: A Study to Evaluate the Effect of Paroxetine on the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MK-4305

Objectives:

Primary: 1) To assess the safety and tolerability of the concurrent multiple-dose administration of suvorexant and paroxetine in healthy subjects.

2) To determine the effect of multiple-doses of paroxetine on the multiple-dose plasma concentration profile ($AUC_{0\text{-}24hr}$) of suvorexant in healthy subjects.

Secondary: To determine the effect of multiple-dose paroxetine dosing on the Digit Vigilance Test (DVT), a cognitive psychomotor test, following multiple-dose administration of suvorexant.

Study Design*	Randomized, double-blind, placebo-controlled, 3-period, fixed-sequence, parallel-group study in healthy subjects
Study Population	24 healthy male (14) and female (10) subjects, 21-64 years, 22 completed the study
Treatment Group	Subjects were randomized to 2 treatment sequences: Treatment Sequence 1 (ACD) or Sequence 2 (BCC). On Days 1 - 4, subjects received oral doses of 40 mg suvorexant (Treatment A) or placebo (Treatment B). On Days 6 - 15, all subjects received daily oral doses of 20 mg paroxetine and placebo (Treatment C). On Days 16 - 19, subjects received either Treatment C or daily oral doses of 20 mg paroxetine and 40 mg suvorexant (Treatment D). All subjects received a single dose of 20 mg paroxetine on Day 20.
Dosage and Administration	Treatment A: 40 mg suvorexant Treatment B: placebo Treatment C: daily oral doses of 20 mg paroxetine and placebo Treatment D: daily oral doses of 20 mg paroxetine and 40 mg suvorexant All doses of suvorexant were administered at approximately 10 pm, 30 minutes prior to lights out and all doses of paroxetine were administered in the morning (approximately 8 am).
PK Sampling	Suvorexant: PK samples for suvorexant were collected pre-dose and up to 24 h post-dose** Blood samples for paroxetine were collected pre-dose and up to 24 hours after dosing with paroxetine***
Analysis	LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL Paroxetine: LC-MS/MS. Range 0.250 to 50.0 ng/mL
PK Assessment	C_{max}, t_{max}, $AUC_{0\text{-}24h}$, for suvorexant and paroxetine
PD Assessment	CDR computerized battery (DVT, CRT, SRT, IDWR) **** DSST ****
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* see Study Design Rationale for details

** Days 1, 2, 3 predose; Day 4: predose, 0.5, 1, 2, 3, 4, 6, 9, 16 and 24 hours

*** Days 6, 10, 12, 13, 14, 15 pre-dose and Day 15: 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24 hours after dosing with paroxetine
**** At pre-dose and 9 h post-dose

Bioanalytical Assays:

Suvorexant:

Plasma concentrations of suvorexant were determined using validated LC-MS/MS method (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Paroxetine Assay:

Whole blood samples were collected into plastic vacutainers containing sodium heparin and processed for the analysis of paroxetine plasma concentrations.
The samples were centrifuged at approximately 4°C to 8°C at between 650-1450 RCF (x g) for 10 to 15 minutes. The plasma was transferred into cryotubes and stored at -20°C.
The analytical method for the determination of paroxetine concentrations is based on a solid-phase extraction of drug from human plasma. The drug and internal standard (paroxetine-d_6) were separated using reversed phase HPLC and detected with tandem mass spectrometry in the MRM mode. The method was validated with with a linear calibration range from 0.250 to 50.0 ng/mL. The analysis was performed (b) (4)
The performance assays during the analysis of the samples was acceptable. No chromatographic interferences from MK-4305 were detected.

Study Design Rationale

Sleep disturbances are common among patients with depression, thus, it is likely that suvorexant and an SSRI would be co-administered. This study was conducted to assess mainly the performance on psychomotor interaction between suvorexant and paroxetine, a SSRI. Paroxetine does not adversely affect performance on psychomotor and neurologic tests in healthy subjects, therefore, it would be anticipated that paroxetine administration alone will not impact psychomotor performance.
The study design in this protocol was consistent with the designs from 3 published zolpidem-SSRI studies: fixed sequence [sedative treatment followed by SSRI + sedative-hypnotic treatment].
Subjects were randomized into 1 of 2 treatment sequences. Subjects were randomized to Treatment Sequence 1 (ACD) or Sequence 2 (BCC). The purpose of Sequence 2 was for blinding of suvorexant treatment.
Subjects received Treatments A or B in Period 1 (Days 1 to 4). All subjects received Treatment C in Period 2 (Days 6 to 15), followed by either Treatments C or D in Period 3 (Days 16 to 19). On Day 20, a single dose of paroxetine was administered.
Blood samples for plasma suvorexant and paroxetine concentrations were collected at pre-dose and at specified time points over 24 hours. Pharmacodynamic assessments were performed approximately 9 hours following the suvorexant dose on the previous day, and prior to paroxetine dosing.
Four training sessions for the cognitive and psychomotor tests were completed by each subject during the pre-study visit.

	Prestudy		Period 1			Period 2		Period 3			
Study Day:	-14 to -2	-1	1-3	4	5	6-14	15	16	17-18	19	20
Treatment Sequence 1 (n=20)			MK	MK		P Pbo	P Pbo	P MK	P MK	P MK	P
Treatment Sequence 2 (n=2)			Pbo	Pbo		P Pbo	P Pbo	P Pbo	P Pbo	P Pbo	P
PK[a]				X	X[d]		X	X[d]		X	X[d]
PD	X[b]	X[e]		X[c]				X[c]		X[c]	

MK=MK-4305 (suvorexant), P=paroxetine, Pbo=suvorexant matching placebo. Suvorexant was dosed at approximately 10 PM, 30 minutes prior to lights out. Paroxetine was dosed at approximately 8 AM.

[a] For both suvorexant and/or paroxetine, samples for full pharmacokinetic profiles were collected immediately prior to and up to 24 hours following dosing on the corresponding day. Additional predose samples for paroxetine and suvorexant concentrations were collected on other days as per Table 9-2.

[b] Within 1 week of Day -1 subjects completed practice psychomotor tests. These evaluations were not captured in the database.

[c] Psychomotor tests were performed at approximately 7 AM, approximately 9 hours post-suvorexant previous-day dosing, and prior to paroxetine dosing, where applicable.

[d] Pharmacokinetic sampling denotes the continued sampling scheme started the previous day, not a separate pharmacokinetic assessment.

[e] Psychomotor tests were performed at approximately 7 AM.

Note: Study design is appropriate for achieving the objectives of this DDI study.

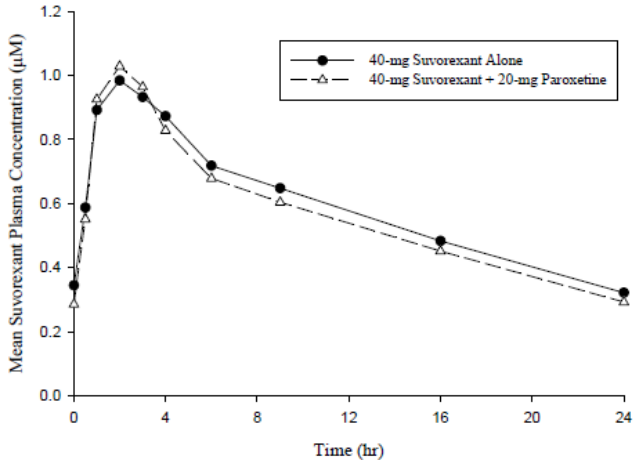
Pharmacokinetic Results:

There was no PK interaction between paroxetine and suvorexant. The absence of a PK drug interaction between paroxetine and suvorexant is consistent with the lack of potential for paroxetine for CYP3A mediated drug interactions (suvorexant is primarily metabolized by CYP3A) and the lack of potential for suvorexant for CYP2D6 mediated drug interactions (paroxetine is a CYP2D6 substrate).

Summary of PK Parameters of Suvorexant Following Multiple 40 mg Doses of Suvorexant Administered With and Without Multiple 20 mg Doses of Paroxetine to Healthy Subjects

Pharmacokinetic Parameter	Suvorexant Alone			Suvorexant + Paroxetine			(Suvorexant + Paroxetine / Suvorexant Alone)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0\text{-}24hr}$ (µM•hr) †	21	13.21	(11.15, 15.64)	18	12.84	(10.82, 15.22)	0.97	(0.92, 1.03)
C_{max} (µM)†	21	1.094	(0.954, 1.255)	18	1.148	(0.996, 1.323)	1.05	(0.96, 1.15)
T_{max} (hr) §	21	2.0	0.5, 4.0	18	2.0	1.0, 4.0	-	-

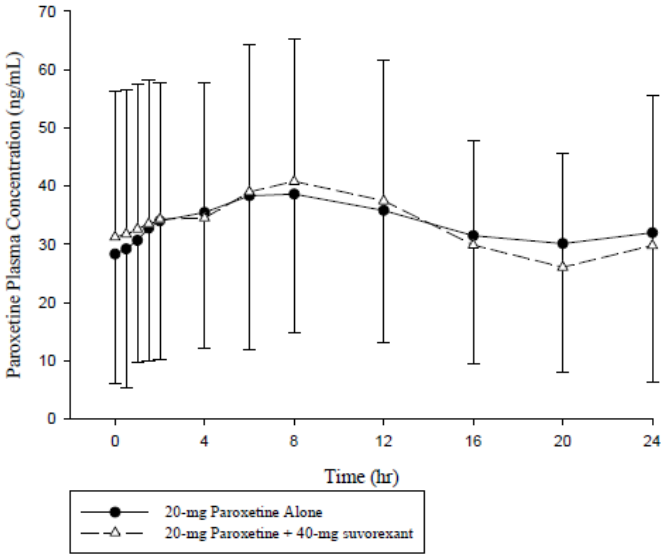
Mean Plasma Concentration Profiles of Suvorexant Following Multiple 40 mg Doses of Suvorexant Administered With and Without Multiple 20 mg Doses of Paroxetine to Healthy Subjects (N=21 for Suvorexant Alone, N=18 for Suvorexant+Paroxetine, Linear Scale)



Summary of PK Parameters of Paroxetine Following Multiple 20 mg Doses of Paroxetine Administered With and Without Multiple 40 mg Doses of Suvorexant to Healthy Subjects

Pharmacokinetic Parameter	Paroxetine Alone			Suvorexant + Paroxetine			(Suvorexant + Paroxetine / Paroxetine Alone)	
	N#	GM	95% CI	N#	GM	95% CI	GMR	90% CI
$AUC_{0\text{-}24hr}$ (ng/mL•hr)[¶]	18	671.0	(489.6, 919.5)	18	669.7	(488.7, 917.8)	1.00	(0.94, 1.06)
C_{max} (ng/mL)[†]	18	35.1	(26.0, 47.2)	18	38.2	(28.4, 51.4)	1.09	(1.03, 1.15)
T_{max} (hr)[§]	18	6.0	1.0, 12.0	18	6.0	6.0, 23.9	-	-

Mean (± SD) Plasma Concentration Profiles of Paroxetine Following Multiple 20 mg Doses of Paroxetine Administered With and Without Multiple 40 mg Doses of Suvorexant to Healthy Subjects (N=18 for Paroxetine Alone, N=18 for Suvorexant + Paroxetine, Linear Scale)



There was a high degree of intersubject variability in paroxetine concentrations and most subjects had paroxetine concentration-time profiles with increasing concentrations at 20 and 24 hours postdose. However, this was also observed for subjects in both the paroxetine alone and suvorexant with paroxetine treatments and in subjects receiving paroxetine and placebo in Sequence 2, suggesting that this behavior is not related to co-administration of suvorexant.

Pharmacodynamic Results:

There was no clinically significant pharmacodynamic interaction between suvorexant and paroxetine. The summary statistics for DVT reaction time are displayed in the Table below. No statistically significant difference was observed in the suvorexant alone treatment compared to suvorexant with paroxetine treatment.

Summary Statistics for "Digit Vigilance Reaction Time (msec)" Following Multiple 40 mg Doses of Suvorexant Administered With and Without Multiple 20 mg Doses of Paroxetine to Healthy Subjects

Treatment	N*	DVT Reaction Time (msec)		Mean Treatment Difference (Treatment - Baseline)		Mean Treatment Difference (Suvorexant with Paroxetine - Suvorexant Alone)		rMSE‡
		LS Mean†	95% CI	LS Mean†	90% CI	LS Mean†	90% CI	
Baseline§	22	417.09	(400.50, 433.67)	-	-	-	-	23.181
Suvorexant Alone	21	425.30	(408.49, 442.11)	8.21	(-3.71, 20.14)	-	-	
Paroxetine Alone	18	413.52	(396.05, 430.98)	-3.57	(-16.18, 9.04)	-	-	
Suvorexant + Paroxetine	18	428.87	(411.41, 446.34)	11.79	(-0.82, 24.40)	3.58	(-9.08, 16.23)	

Higher values indicate increased impairment.
§ Baseline is measurements on Day -1.
† LS Mean: Least-square mean.
‡ rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model.

Safety:

No serious adverse experiences (SAE) or laboratory AEs were reported. One subject discontinued on Day 3 in Period 1 (after receiving 2 PM doses of 40 mg suvorexant) due to abdominal pain. The subject had a history significant for multiple episodes of abdominal pain. The Investigator determined the event to be moderate in intensity and probably not related to study drug.

Fourteen (14) subjects reported a total of 58 clinical adverse experiences, of which 56 were mild and 2 were moderate in intensity. The most frequently reported AEs in the suvorexant (n=22), suvorexant + paroxetine (n=22), and paroxetine+ placebo groups were somnolence (13.6%), headache (13.6%), and headache (39.1%), respectively.

Recommendations: A general precaution should be advised when suvorexant is co-administered with drugs that produce CNS depressant effects due to potential additive effects (similar to the label of zolpidem).

P038: A 2-Part Study to Assess the Effects of Multiple Oral Doses of Rifampin and Diltiazem on the Single-Dose Pharmacokinetics of Suvorexant (MK-4305)

Objectives:

Primary: Part I: To assess the effect of multiple doses of rifampin, a strong CYP3A4 inducer, on the single-dose pharmacokinetic profile of suvorexant
Part II: To assess the effect of multiple doses of diltiazem, a moderate CYP3A4 inhibitor, on the single-dose pharmacokinetic profile of suvorexant
Secondary: To evaluate safety and tolerability of a single oral dose of suvorexant when co-administered with multiple oral doses of rifampin/ diltiazem.

Study Design	Two-part, open-label, fixed-sequence, randomized study in healthy subjects
Study Population	30 healthy subjects: 10 in part 1 and 20 in part 2 male (22) and female (8) subjects, 18-50 years 27 completed the study
Treatment Group	Part I [Period 1: Suvorexant Alone (Treatment A) and Period 2: Suvorexant with Rifampin (Treatment B)] Part II [Period 1: Suvorexant Alone (Treatment C) and Period 2: Suvorexant with Diltiazem (extended release) (Treatment D)]
Dosage and Administration	Treatment A: a single 40 mg oral dose of suvorexant on Day 1. Treatment B: daily oral doses of 600 mg rifampin for 17 days with co-administration of a single 40 mg oral dose of suvorexant on Day 14. Treatment C: a single 20 mg dose of suvorexant on Day 1. Treatment D: daily oral doses of 240 mg diltiazem for 6 days with co-administration of a single 20 mg oral dose of suvorexant on Day 2. There was a minimum 5 day washout between dosing in Period 1 and Period 2 in Part 1 and 4 days washout between dosing in Period 1 and Period 2 in Part 2. All study medications were administered in an open-label fashion, following an overnight fast in the morning.
PK Sampling	Suvorexant: PK samples for suvorexant and M9 were collected pre-dose and up to 96 h post-dose* Plasma samples for rifampin and diltiazem were archived and were not analyzed.
Analysis	LC-MS/MS method for MK-4305 and M9 Range: 1 to 1000 ng/mL for both analytes
PK Assessment	C_{max}, t_{max}, AUC_{inf}, for suvorexant and M9
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* at pre-dose and at 0.5, 1, 2, 4, 6, 9, 12, 16, 24, 36, 48, 72 and 96 hours after suvorexant dosing

Bioanalytical Assay:
Plasma concentrations of suvorexant and M9 were determined using validated LC-MS/MS methods (method DM-909 for suvorexant and DM-928 for M9). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Study Design Rationale
In vitro and in vivo preclinical data suggest that the primary clearance mechanism for suvorexant in humans is metabolism mediated by CYP3A4. This study was conducted to assess the effect of a potent CYP3A4 inducer (rifampin) and moderate CYP3A4 inhibitor (diltiazem) on suvorexant PK.
Rifampin is recognized to particularly increase hepatic and intestinal CYP3A4 expression by several folds via the binding and activation of the pregnane X receptor (PXR), thereby augmenting CYP3A4 gene transcription and subsequent protein synthesis. The dose of rifampin chosen for this study (600 mg administered once daily), is sufficient to potently induce the CYP3A4 system. For maximal induction of the CYP system with rifampin, dosing durations of 12-16 days are usually needed, as shown using verapamil.
Diltiazem is a moderate inhibitor of CYP3A4 both in vitro and in vivo. Diltiazem inhibition of CYP3A4 is noncompetitive and irreversible. Multiple oral dosing of diltiazem increased the plasma AUC of midazolam, an established probe drug for testing CYP3A4 inhibitors, by 3.7-fold. The suvorexant dose for this part of the study was 20 mg to provide a safety margin. The duration of diltiazem dosing prior to suvorexant dosing was 1 day. According to the sponsor, 1 day is long enough to ensure substantial CYP3A4 inhibition based on the recently completed study evaluating the effect of diltiazem pre-treatment duration on midazolam metabolism. The study showed that 1-day vs. 4-day pretreatment of diltiazem did not reveal a significant difference on midazolam exposure. Diltiazem was co-administered with suvorexant on Day 2, and for 4 subsequent days following the suvorexant administration in order to ensure continued diltiazem-mediated CYP3A4 inhibition during the entire 96-hr suvorexant PK sampling scheme in Period 2.
Note: Study design is appropriate for achieving the objectives of this DDI study.

Pharmacokinetic Results:

Three subjects discontinued the study: AN 0016 discontinued at post-study visit after completing treatments for Periods 1 and 2, AN 0020 discontinued due to difficulty with venipuncture after completing Day 1 treatment, AN 0023 discontinued due to family emergency after completing Period 1 treatment.

Part 1 PK Results:

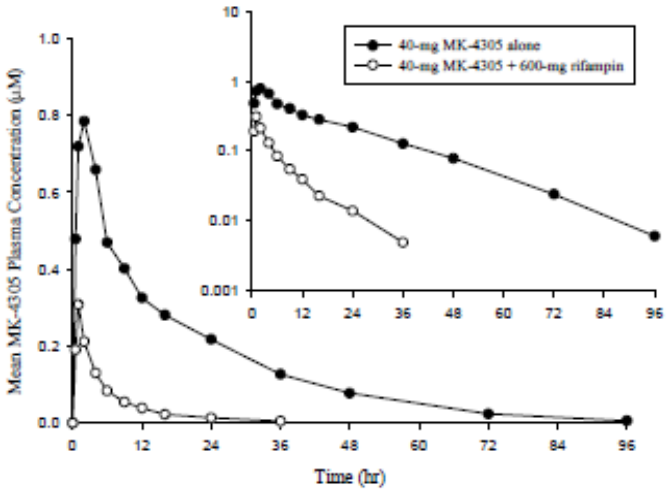
Following once-daily dosing of 600 mg rifampin, suvorexant exposure ($AUC_{0-\infty}$) was significantly reduced. The impact on C_{max} was slightly less than that on AUC. M9 $AUC_{0-\infty}$ and C_{max} were also significantly decreased after coadministration with rifampin, consistent with CYP3A involvement in the biotransformation of M9. Although rifampin induces other CYP450s and P-gp, suvorexant is not a P-gp substrate, therefore the reported results are likely attributable to CYP3A mechanisms.

Summary of Pharmacokinetic Parameters of Suvorexant (MK-4305) and M9 Following a Single 40 mg Dose of Suvorexant Alone or Following Concomitant Administration with Multiple Doses of 600 mg Rifampin in Healthy Subjects

	MK-4305 Alone			MK-4305 + Rifampin			(MK-4305 + Rifampin / MK-4305 Alone)	
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (µM•hr) †	10	13.63	(10.53, 17.64)	10	1.68	(1.30, 2.17)	0.12	(0.11, 0.14)
C_{max}(µM)†	10	0.852	(0.702, 1.033)	10	0.305	(0.252, 0.370)	0.36	(0.31, 0.42)
T_{max} (hr) §	10	2.0	(0.5, 4.0)	10	1.0	(0.5, 2.0)	.	
Apparent terminal $t_{1/2}$(hr) ‖	10	12.9	2.2	10	7.7	3.4	.	

	MK-4305 Alone			MK-4305 + Rifampin			(MK-4305 + Rifampin / MK-4305 Alone)	
M9 PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (µM•hr) †	10	16.21	(12.77, 20.58)	10	3.72	(2.93, 4.72)	0.23	(0.21, 0.25)
C_{max}(µM)†	10	0.859	(0.738, 1.000)	10	0.665	(0.571, 0.774)	0.77	(0.70, 0.86)
T_{max} (hr) §	10	4.0	(2.0, 4.0)	10	1.0	(1.0, 2.0)	.	
Apparent terminal $t_{1/2}$(hr) ‖	10	15.0	2.5	10	8.3	3.7	.	

Arithmetic Mean Plasma Concentration-Time Profile of Suvorexant (MK-4305) Following a Single 40 mg Dose of Suvorexant (MK-4305) Alone or Following Concomitant Administration with Multiple Doses of 600 mg Rifampin in Healthy Subjects (Inset: Semi-log Scale) (N=10)



Part 2 PK Results:

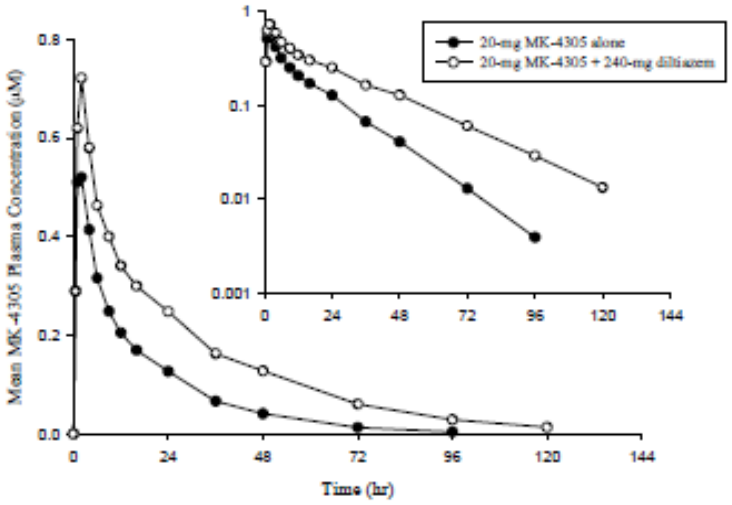
Administration of diltiazem with a single 20 mg dose of suvorexant significantly (2-fold) increased suvorexant $AUC_{0-\infty}$ with a less pronounced effect on C_{max} (1.22). Suvorexant mean $t_{1/2}$ values were slightly prolonged while T_{max} remained generally unaffected. Co-administration of diltiazem also increased M9 $AUC_{0-\infty}$ (1.36), with a decrease in C_{max} observed. Similar trends in mean apparent $t_{1/2}$ and median T_{max} of M9 to those reported for the parent were observed.

Part II: Summary of Pharmacokinetic Parameters of Suvorexant (MK-4305) and M9 Following a Single 20 mg Dose of Suvorexant Alone or Following Concomitant Administration with Multiple Doses of 240 mg Diltiazem in Healthy Subjects

	MK-4305 Alone			MK-4305 + Diltiazem			(MK-4305 + Diltiazem / MK-4305 Alone)	
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (μM•hr) †	20	7.88	(6.57, 9.46)	18	16.13	(13.38, 19.44)	2.05	(1.82, 2.30)
C_{max}(μM)†	20	0.622	(0.543, 0.713)	18	0.756	(0.657, 0.871)	1.22	(1.09, 1.36)
T_{max} (hr) §	20	1.5	(1.0, 4.0)	18	2.0	(1.0, 4.0)	.	
Apparent terminal $t_{1/2}$(hr) ‖	20	12.4	3.3	18	16.1	5.3	.	

	MK-4305 Alone			MK-4305 + Diltiazem			(MK-4305 + Diltiazem / MK-4305 Alone)	
M9 PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (μM•hr) †	20	7.67	(6.48, 9.08)	18	10.45	(8.81, 12.39)	1.36	(1.27, 1.47)
C_{max}(μM)†	20	0.420	(0.377, 0.467)	18	0.356	(0.319, 0.398)	0.85	(0.79, 0.92)
T_{max} (hr) §	20	4.0	(1.0, 6.1)	18	4.0	(2.0, 6.0)	.	
Apparent terminal $t_{1/2}$(hr) ‖	20	13.6	3.4	18	18.0	6.5	.	

Mean Plasma Concentration-Time Profile of Suvorexant (MK-4305) Following a Single 20 mg Dose of Suvorexant (MK-4305) Alone or Following Concomitant Administration with Multiple Doses of 240 mg Diltiazem in Healthy Subjects (Inset: Semi-log Scale) (N=20 for Suvorexant (MK-4305) Alone, N=18 for Suvorexant (MK-4305) Coadministered with Diltiazem)



Safety:

There were no serious adverse experiences (SAE) or laboratory AEs in this study. No subject discontinued because of an AE.

The most frequently reported clinical AEs were somnolence (N=10 subjects in Part I; N=20 subjects in Part II), and abnormal dreams (N=4 subjects in Part I; N = 2 subjects in Part II). Two subjects reported three events of abnormal dreams after receiving suvorexant 20 mg and rifampin 600 mg in period 2 day 14. Two subjects reported two events of abnormal dreams after receiving suvorexant 20 mg in period 1 day 1.

In Part II, two subjects reported three events of abnormal dreams. One subject reported the event of abnormal dreams following suvorexant 20 mg SD; one subject experienced 2 occurrences of abnormal dreams following a single 240 mg dose of diltiazem plus a single 20 mg dose of suvorexant on Day 2 of Period 2.

Five clinical adverse experiences (4 in Part I and 1 in Part II) were considered Events of Clinical Interest: Part I: euphoric mood (n=1), sleep paralysis (n=1), hypnogogic hallucination (n=1), and hypnopomic hallucination (n=1). All 4 ECIs occurred in Period 1, when subjects received a single 40 mg oral dose of suvorexant (AM dosing). One ECI (n = 1), euphoric mood, was reported in Part II. This ECI occurred on Day 2 in Period 2 when the subject received a single 20 mg oral dose of suvorexant plus a 240 mg oral dose of diltiazem.

Recommendations: The suvorexant dose in subjects receiving moderate CYP3A4 inhibitors needs to be reduced by half. The sponsor needs to develop a lower strength tablet.

The efficacy of suvorexant dose in subjects receiving CYP3A4 inducers may be decreased.

1.4 Healthy Subjects PD and PK/PD Studies

P002: A Randomized, Double-Blind, Placebo-Controlled Five Period, Crossover, Study to Evaluate the Effects of Single Doses of MK-4305 on Polysomnogram (PSG) in Healthy Male Subjects

Objectives:

Primary: To determine the effect of a single dose of MK-4305 on Slow Wave Activity (SWA) in healthy male subjects

Secondary: To determine the effect of a single dose of MK-4305 on REM sleep duration

Exploratory: 1) To determine the PK profile of MK-4305 during night time administration. 2) To explore the effects of MK-4305 on sleep parameters in healthy subjects by objective PSG

Study Design*	Single-dose, randomized, double-blind, placebo-controlled, 5-period crossover study
Study Population	22 healthy male subjects (18-44 years), 19 completed
Treatment Group	In treatment Periods 1 -4, subjects were to receive: Treatment A (MK-4305, 10 mg), Treatment B (MK-4305, 50 mg), Treatment C (MK-4305, 100 mg), Treatment D (Placebo). In Treatment Period 5, subjects were to receive either Trt A , Trt B or Trt C, based on the allocation schedule.
Dosage and Administration	MK-4305 or placebo was administered at night for all treatment periods after ≥ 4-hour fast. There was at least a 96 hour wash-out between each treatment period for any given subject. Treatment A: 10 mg MK-4305 Treatment B: 50 mg MK-4305 Treatment C: 100 mg MK-4305 Treatment D: placebo
PK Sampling: plasma	Treatment periods 1-4: PK samples were collected at pre-dose and at 0.5, 1, 12, 16, 24, 48 h post-dose Treatment period five: at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24 and 48 h post-dose
Analysis	Plasma: LC-MS/MS method for MK-4305 and metabolite M9 Range: 1 to 1000 ng/mL for both analytes
PK Assessment	C_{max}, $C_{4h,}$ t_{max}, AUC_{0-24}, AUC_{0-inf}, $t_{1/2}$ of MK-4305 and metabolite M9
PD Assessment	Polysomnography (PSG) ** Power spectral analysis of EEG data was performed to determine SWA (delta power) in the first 1/2 of the night, as well as power in other frequency bands by treatment. Karolinska Sleepiness Scale (KSS) Bond and Lader Visual Analog Scale (VAS)
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* Lights were turned out after 1 hour post-dose

** PSG recording started one hour post drug administration and lasted for 8 hours throughout the night.

Bioanalytical Assay:

Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using validated LC-MS/MS methods (method DM-909 for suvorexant and DM-928 for M9). The assay performance during the validation was acceptable, details of the validation are presented in Section 2.6.1 in QBR.

The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:

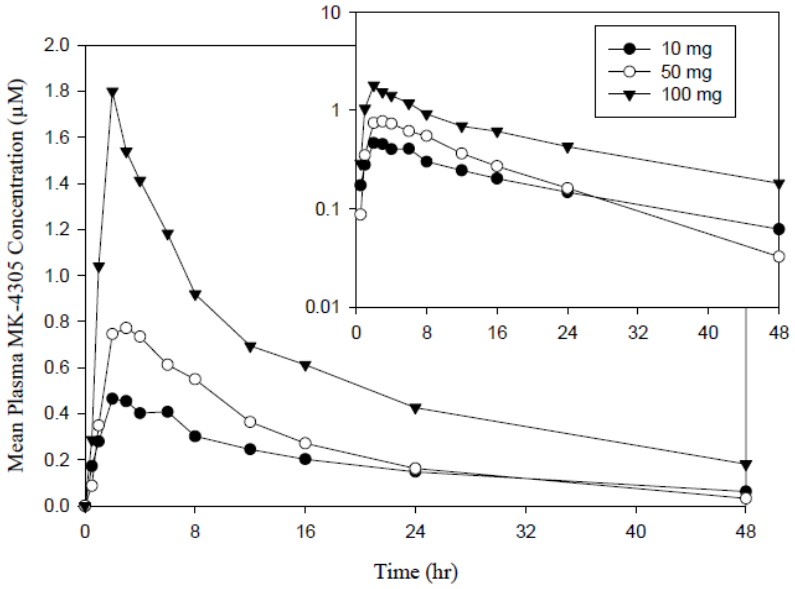
No subjects reported taking prior medications. Nineteen of the 22 subjects who completed the study (and had complete PK and PD data) were included in the PK and PD analysis. The total number of subjects in this study were divided among the three doses to obtain full concentration-time profiles for each subject in Period 5 (N=5 in 10 mg, N=7 in 50 mg and N=7 in 100 mg).

The MK-4305 and M9 pharmacokinetic parameters from Period 5 are summarized in the Table below.

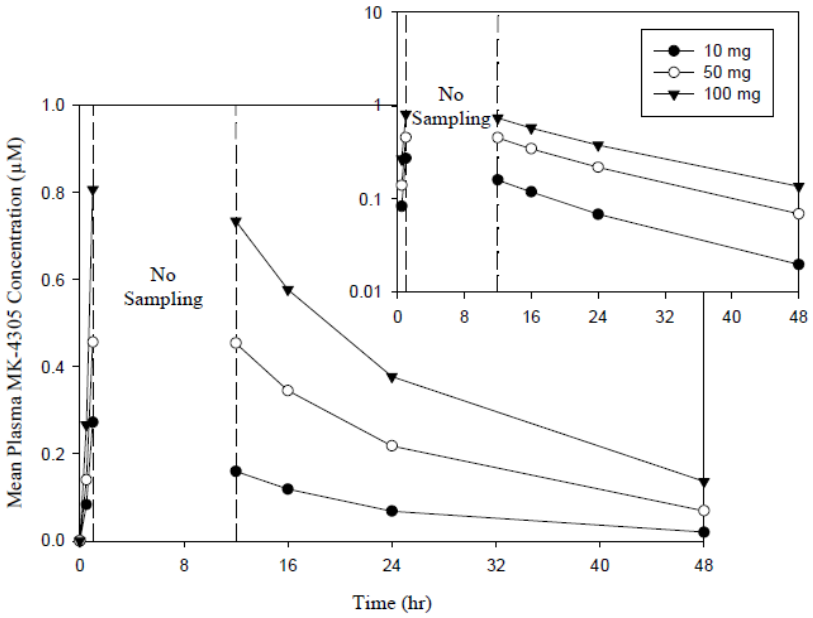
Summary for MK-4305 and M9 Pharmacokinetic Parameters Following Single Dose Administration of 10 mg, 50 mg and 100 mg MK-4305 in Healthy Male Subjects (Period 5)

Pharmacokinetic Parameter	10 mg N = 5	50 mg N = 7	100 mg N = 7
MK-4305			
$AUC_{0\text{-}inf}$ † (µM*hr)	6.69 (3.63, 12.35)	10.87 (6.48, 18.24)	29.76 (17.74, 49.95)
$AUC_{0\text{-}24hr}$ † (µM*hr)	4.94 (3.07, 7.93)	8.57 (5.74, 12.80)	19.07 (12.77, 28.47)
$AUC_{0\text{-}4hr}$ † (µM*hr)	1.27 (0.74, 2.18)	1.83 (1.16, 2.89)	4.62 (2.93, 7.28)
C_{max} † (µM)	0.44 (0.29, 0.67)	0.87 (0.61, 1.24)	2.12 (1.48, 3.02)
C_{24hr} † (µM)	0.08 (0.04, 0.15)	0.15 (0.08, 0.27)	0.38 (0.21, 0.71)
C_{4hr} † (µM)	0.33 (0.19, 0.57)	0.63 (0.40, 1.00)	1.33 (0.84, 2.10)
T_{max} ‡ (hr)	3.0 (1.0, 6.0)	3.0 (2.0, 8.0)	3.0 (2.0, 6.0)
Apparent terminal $t_{1/2}$ § (hr)	9.0 (7.2)	10.8 (3.6)	13.1 (5.8)
M9			
$AUC_{0\text{-}inf}$ † (µM*hr)	6.50 (4.05, 10.43)	12.67 (8.50, 18.89)	26.80 (17.98, 39.95)
$AUC_{0\text{-}24hr}$ † (µM*hr)	4.57 (3.07, 6.81)	9.72 (6.95, 13.61)	18.80 (13.44, 26.31)
$AUC_{0\text{-}4hr}$ † (µM*hr)	0.70 (0.38, 1.29)	1.24 (0.74, 2.07)	3.38 (2.01, 5.66)
C_{max} † (µM)	0.32 (0.21, 0.48)	0.79 (0.56, 1.13)	1.69 (1.19, 2.41)
T_{max} ‡ (hr)	6.0 (4.0, 8.00)	6.0 (2.0, 8.0)	4.0 (2.0, 6.0)
Apparent terminal $t_{1/2}$ § (hr)	9.7 (6.7)	10.8 (2.8)	13.2 (3.9)

Mean MK-4305 Plasma Concentrations (µM) Versus Time (hr) Following a Single Dose Administration of 10 mg, 50 mg or 100 mg MK-4305 in Healthy Young Male Subjects, Period 5 (N=5 for 10 mg, N=7 for 50 and 100 mg) (Semi-log Inset)



Mean MK-4305 Plasma Concentrations (µM) Versus Time (hr) Following a Single Dose Administration of 10 mg, 50 mg and 100 mg MK-4305 in Healthy Young Male Subjects, Periods 1-4 (N=21 for 10 mg, N=20 for 50 and 100 mg)



Pharmacodynamic Results:

The primary endpoint in this study was SWA in the first half of the night (μV2/Hz; micro-voltage squared per Hz), which was defined as the power spectral density of delta frequency band in the first 4-hr of the 8-hr PSG recording. The secondary endpoint was REM sleep duration (min) during the 2nd half of the night (REM2) which was defined by the duration of REM Stage during the second 4-hr during the 8-hr PSG recording.
The primary hypothesis, that at least one dose of MK-4305 (10, 50 or 100 mg) produces an increase in slow wave activity (> 20% increase) in the first half of the night compared to placebo during PSG assessment, and the secondary hypothesis, that at least one dose of MK-4305 (10, 50 or 100 mg) produces an increase in REM2 duration (>20% increase) in the second half of the night compared to placebo during PSG assessment, were not satisfied.

Summary Statistics for SWA Data During the First Half of the Night and REM Data During the Second Half of the Night Following a PM Single Dose Administration of 10 mg, 50 mg or 100 mg MK-4305 in Healthy Young Male Subjects

End-points	Treat-ment	N	Raw Value		Geometric Mean[†]		GMR [†]	
			Mean	SD	Mean	95% CI	Mean	90% CI
SWA (μV^2)	Placebo	20	102.03	55.27	90.83	(73.49,112.26)		
	10 mg	19	104.98	50.32	94.89	(76.71,117.37)	1.04	(0.95,1.15)
	50 mg	20	107.01	53.72	96.88	(78.39,119.74)	1.07	(0.97,1.17)
	100 mg	20	98.84	47.26	89.67	(72.55,110.82)	0.99	(0.90,1.08)
REM2 (min)	Placebo	20	63.75	14.01	62.15	(54.95,70.30)		
	10 mg	19	67.39	18.76	64.78	(57.10,73.49)	1.04	(0.91,1.19)
	50 mg	20	66.95	12.36	65.78	(58.16,74.40)	1.06	(0.93,1.21)
	100 mg	20	72.95	23.55	69.50	(61.44,78.60)	1.12	(0.98,1.27)

[†] Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.
rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. For log-transformed variables, rMSE*100% approximates the within-subject % CV on the raw scale. rMSE=0.175 for SWA; rMSE=0.247 for REM2.
SWA = slow wave activity in the first half of the night
REM2 = is sleep duration in the 2nd half of the night

PSG parameters were exploratory endpoints in this study. Latency to persistent sleep (LPS) measured sleep onset, and wake after sleep onset (WASO) measured sleep maintenance. MK-4305 dose dependently decreased LPS and WASO. A corresponding increase in sleep efficiency (SE) was observed.
Additional exploratory PD endpoints included psychomotor performance tests such as Simple Reaction Time (SRT), Choice Reaction Time (CRT), and Digit Symbol Substitution Test (DSST). The effects of MK-4305 on psychomotor performance were evaluated at 10 hr post dose as exploratory measurement of next-day residual effect. At 100 mg, there was a small statistically significant increase on reaction time (msec) for both SRT and CRT. There was no statistically significant change on SRT, CRT, and DSST at 10 and 50 mg.

Summary Statistics for Sleep Endpoints LPS, WASO, SEI Following a PM Single Dose Administration of 10 mg, 50 mg or 100 mg MK-4305 in Healthy Young Male Subjects

			Raw Value		Geometric Mean		G.M.R	
Endpoints	Treatment	N	Mean	SD	Mean	95% CI	Mean	90% CI
LPS (min)	Placebo	20	18.87	18.31	12.60	(7.22,21.98)		
	10 mg	19	16.65	17.60	9.11	(5.16,16.07)	0.72	(0.43,1.23)
	50 mg	20	7.39	7.91	4.50	(2.58,7.86)	0.36	(0.21,0.60)
	100 mg	20	6.09	5.74	2.88	(1.65,5.02)	0.23	(0.14,0.39)
WASO (min)	Placebo	20	22.75	9.65	20.75	(16.61,25.91)		
	10 mg	19	19.76	13.54	16.69	(13.33,20.90)	0.80	(0.69,0.93)
	50 mg	20	15.93	7.75	14.51	(11.61,18.12)	0.70	(0.60,0.81)
	100 mg	20	15.65	7.10	14.07	(11.26,17.57)	0.68	(0.59,0.79)
SE (%)	Placebo	20	91.66	3.62	91.59	(90.25,92.95)		
	10 mg	19	93.14	3.87	93.02	(91.63,94.43)	1.02	(1.00,1.03)
	50 mg	20	95.20	1.92	95.18	(93.78,96.59)	1.04	(1.02,1.05)
	100 mg	20	95.89	1.91	95.87	(94.47,97.30)	1.05	(1.03,1.06)

LPS = latency to onset of persistent sleep, which is duration of time measured from lights off to the first epoch of 20 consecutive epochs of sleep stage (stage 1, 2, 3, 4 or REM). Definition is same as Phase III.

WASO = wake after sleep onset which is the duration of wake stage after sleep onset. Definition of WASO is same as WASO4 in Phase III studies.

SE = sleep efficiency index which is Total Sleep Time/ time in bed x 100. Definition is same as Phase III.

Summary Statistics for Simple Reaction Time (SRT), Choice Reaction Time (CRT) and Number Correct for Digit Symbol Substitution Test (DSST) Following a PM Single Dose Administration of 10 mg, 50 mg or 100 mg MK-4305 or Placebo in Healthy Young Male Subjects

				Raw Value		Mean Cfb†		Difference from PBO	
End-point	Treat-ment	Hour	N	Mean	SD	Mean	95% CI	Mean	90% CI
CRT	Placebo	Predose	20	394.11	64.48				
		10 hr	20	400.60	51.72	6.49	(-5.38,18.35)		
	10 mg	Predose	19	388.21	50.43				
		10 hr	19	407.21	56.84	18.78	(6.59,30.96)	12.29	(-1.93,26.51)
	50 mg	Predose	20	395.55	52.35				
		10 hr	20	414.13	67.62	18.58	(6.72,30.45)	12.10	(-1.94,26.13)
	100 mg	Predose	20	391.71	51.21				
		10 hr	20	417.69	57.09	25.98	(14.11,37.85)	19.49	(5.46,33.52)
DSST	Placebo	Predose	20	65.35	13.94				
		10 hr	20	64.35	12.84	-1.00	(-3.99,1.99)		
	10 mg	Predose	19	64.74	10.46				
		10 hr	19	62.79	9.66	-2.11	(-5.17,0.95)	-1.11	(-4.41,2.19)
	50 mg	Predose	20	63.30	11.99				
		10 hr	20	61.25	12.92	-2.05	(-5.04,0.94)	-1.05	(-4.30,2.20)
	100 mg	Predose	20	64.65	10.77				
		10 hr	20	60.85	10.86	-3.80	(-6.79,-0.81)	-2.80	(-6.05,0.45)
SRT	Placebo	Predose	20	240.07	29.17				
		10 hr	20	247.96	29.72	7.89	(-1.32,17.10)		
	10 mg	Predose	19	243.61	30.56				
		10 hr	19	258.01	33.95	15.03	(5.60,24.46)	7.14	(-2.63,16.91)
	50 mg	Predose	20	240.79	28.68				
		10 hr	20	256.42	38.62	15.63	(6.42,24.84)	7.74	(-1.89,17.36)
	100 mg	Predose	20	235.70	27.84				
		10 hr	20	257.23	32.78	21.53	(12.32,30.74)	13.64	(4.02,23.26)

† change from baseline

PD Conclusions:

- MK-4305 did not enhance slow wave activity during the first half of the sleep period in healthy male subjects at doses up to 100 mg.
- MK-4305 did not enhance REM sleep duration during the second half of the sleep period in healthy male subjects at doses up to 100 mg.
- MK-4305 significantly reduced wake after sleep onset (WASO) ($p<0.05$). The geometric mean for WASO (MK-4305 dose/placebo) was 0.80, 0.70, and 0.68 at 10, 50 and 100 mg of MK-4305, respectively.
- At 50 and 100mg, MK-4305 also significantly reduced latency to persistent sleep (LPS) and increased sleep efficiency (SEI) ($p<0.05$).
- There was no clear evidence of next-day residual effect of MK-4305 at 10 and 50 mg, whereas 100 mg was associated with mild next-day residual effect as assessed by objective and subjective measurements.

Safety:

No serious clinical AEs were reported. No subjects discontinued due to an AE. The most frequently reported adverse experiences were somnolence and headache. Somnolence was reported in the morning after PM administration of MK-4305 or placebo, and was more frequently reported (20%) by subjects receiving MK-4305 100 mg than by subjects receiving 50 mg, 10 mg MK-4305 or placebo (<5%). One subject reported a rash on 2 occasions: 3 and 8 days following 100 mg and 10 mg MK-4305 respectively. Both rashes were rated as mild in intensity and were considered to be probably not related to study drug by the investigator.

P021: A Single Dose Study to Evaluate the Effects of Single Doses of MK-4305 Versus Active Comparator on Safety and Psychomotor Performance in Healthy Elderly Subjects

Objectives:

Primary: To evaluate the safety and tolerability of a single oral dose of MK-4305 administered at bedtime in healthy elderly male and female subjects.

Exploratory: (1) To assess the effects of single doses of MK-4305 30-mg and zolpidem 5-mg administered at bedtime on Choice Reaction Time (CRT), and Immediate and Delayed Word Recall (IDWR) in healthy elderly male and female subjects

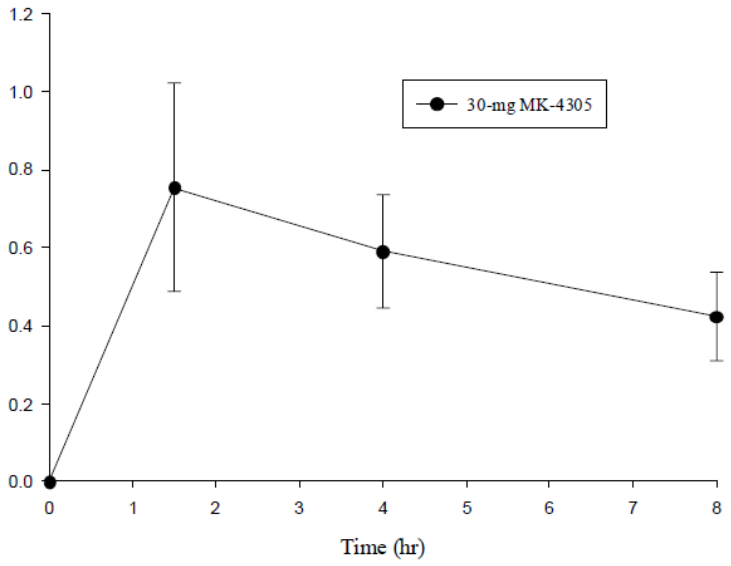
(2) To assess the effects of single doses of MK-4305 30-mg and zolpidem 5-mg administered at bedtime on body sway in healthy elderly male and female subjects

Study Design	Single-dose, randomized, double-blind, double-dummy, placebo-controlled 3-period crossover study
Study Population	12 healthy elderly male (7) and female (5) subjects (65-76 years), 11 completed
Treatment Group	Subjects were randomized to receive a sequence of 3 treatments: 30 mg MK-4305, 5 mg zolpidem or placebo. Subjects were awakened at two times in the middle of the night (1.5 and 4 hours post-dose) and in the morning (8 hours post-dose).
Dosage and Administration	All treatments were administered at ~9 PM after a 4 hour fast and lights out in the clinic was ~30 minutes post-dose. Treatment A: 30 mg MK-4305 Treatment B: 5 mg zolpidem Treatment C: placebo
PK Sampling: plasma	PK samples were collected at pre-dose and at 1.5, 4 and 8 h post-dose for the analysis of MK-4305 and possible analysis of zolpidem
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL for MK-4305 Samples were not analyzed for zolpidem.
PK Assessment	$C_{1\ 5h}$, $C_{4h,}$ C_{8h} of MK-4305
PD Assessment	CRT test at pre-dose and at 1.5, 4 and 8 h post-dose IDWR test at pre-dose at 4 h post-dose Body sway test at pre-dose and at 1.5, 4 and 8 h post-dose
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

Bioanalytical Assay:
PK samples were not analyzed for zolpidem.
Plasma concentrations of suvorexant were determined using validated LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:
Patients were permitted to take concomitant therapies, mostly for the treatment of symptoms associated with influenza and cold. These medications were judged not to have an effect on the assessment of the study objectives.
Mean suvorexant plasma concentrations (μM) versus time plot following a single dose administration of 30 mg daily in healthy elderly male and female subjects is presented below.

Mean (SD) Suvorexant Plasma Concentrations (μM) Versus Time Following a Single Dose Administration of 30 mg Suvorexant in Healthy Elderly Male and Female Subjects (N=11)



Pharmacodynamic Results:
Body sway
For zolpidem (5 mg) versus placebo comparison, there was a statistically significant impairment on body sway as measured by A95 (for both Eyes Open and Eyes Closed conditions) with zolpidem at 1.5 hours. The effects were not statistically significant at 4 and 8 hour post-dose.
For suvorexant (30 mg) versus placebo comparison, there was a statistically significant impairment on body sway as measured by A95 in the Eyes Open condition at 1.5 hours.

However, there was no statistically significant difference between suvorexant and placebo at 1.5 hours in the Eyes Closed condition. The impairment with suvorexant was less than zolpidem on A95 at 1.5 hr (for Eyes Closed).
The effect of suvorexant on body sway was not statistically significant at 4 and 8 hours post-dose in either condition.

Summary Statistics for Body Sway Following a Single PM Dose of 30 mg Suvorexant (MK-4305), 5 mg Zolpidem or Placebo in Healthy Elderly Male and Female Subjects

Body Sway Endpoint A95 - Eyes Open (cm^2)

Treatment	Time	N	Value (cm^2)		Fold Change from Baseline		Ratio versus Placebo		Ratio versus Zolpidem	
			GM †	SE †	GM ‡	95 % CI	GMR‡	95 % CI	GMR ‡	95 % CI
Placebo	Predose	12	1.19	0.17	.	.	.	.	.	.
	1.5 Hours	11	1.17	0.24	1.04	(0.79, 1.37)	.	.	.	.
	4 Hours	12	1.46	0.24	1.22	(0.94, 1.59)	.	.	.	.
	8 Hours	12	1.44	0.18	1.21	(0.93, 1.57)	.	.	.	.
Zolpidem 5 mg	Predose	11	0.97	0.15	.	.	.	.	.	.
	1.5 Hours	11	1.96	0.43	2.06	(1.56, 2.71)	1.97	(1.37, 2.83)§	.	.
	4 Hours	11	1.41	0.24	1.48	(1.12, 1.95)	1.21	(0.85, 1.73)	.	.
	8 Hours	11	1.28	0.17	1.34	(1.02, 1.77)	1.11	(0.78, 1.58)	.	.
MK-4305 30 mg	Predose	11	1.14	0.22	.	.	.	.	.	.
	1.5 Hours	11	1.74	0.42	1.56	(1.18, 2.05)	1.49	(1.04, 2.14)§	0.76	(0.53, 1.08)
	4 Hours	11	1.77	0.40	1.59	(1.21, 2.09)	1.30	(0.91, 1.85)	1.07	(0.75, 1.54)
	8 Hours	11	1.39	0.24	1.24	(0.94, 1.64)	1.03	(0.72, 1.46)	0.93	(0.65, 1.33)

Body Sway Endpoint A95 - Eyes Closed

Treatment	Time	N	Value (cm^2)		Fold Change from Baseline		Ratio versus Placebo		Ratio versus Zolpidem	
			GM†	SE†	GM‡	95 % CI	GMR‡	95 % CI	GMR‡	95 % CI
Placebo	Predose	12	1.46	0.32	.	.	.	.	.	.
	1.5 Hours	11	1.46	0.27	1.14	(0.83, 1.57)	.	.	.	.
	4 Hours	12	1.90	0.36	1.30	(0.96, 1.77)	.	.	.	.
	8 Hours	12	2.01	0.29	1.38	(1.01, 1.87)	.	.	.	.
Zolpidem 5 mg	Predose	11	1.32	0.32	.	.	.	.	.	.
	1.5 Hours	11	3.15	0.68	2.43	(1.77, 3.34)	2.13	(1.41, 3.21§†)	.	.
	4 Hours	11	1.55	0.27	1.19	(0.87, 1.64)	0.91	(0.61, 1.36)	.	.
	8 Hours	11	1.75	0.42	1.35	(0.98, 1.86)	0.98	(0.66, 1.46)	.	.
MK-4305 30 mg	Predose	11	1.45	0.39	.	.	.	.	.	.
	1.5 Hours	11	2.17	0.66	1.52	(1.11, 2.09)	1.33	(0.88, 2.01)	0.63	(0.42, 0.94)§
	4 Hours	11	2.21	0.49	1.55	(1.13, 2.13)	1.19	(0.79, 1.77)	1.30	(0.86, 1.95)
	8 Hours	11	2.12	0.33	1.49	(1.08, 2.04)	1.08	(0.72, 1.61)	1.10	(0.73, 1.65)

CRT
Suvorexant 30 mg statistically significantly increased Total Reaction Time at 1.5 hours whereas no specific trend was observed for zolpidem 5 mg. None of the comparisons for Immediate Word Recall – Number Correct and Delayed Word Recall – Number correct were statistically significant.

PD Conclusions:

- Following Zolpidem 5mg, at 1.5 hour post-dose, body sway as measured by A95 increased by 97% and 113% at eyes-open and eyes-closed conditions, respectively, indicating impaired balance. There were no statistically significant differences from placebo at 4 or 8 hours post-dose.
- Following suvorexant 30mg, at 1.5 hours post-dose, A95 increased 49% at eyes-open condition only with no statistically significant difference from placebo at eyes-closed condition. There were no statistically significant differences from placebo at 4 or 8 hours post-dose.
- Neither MK-4305 30 mg nor zolpidem 5 mg impaired episodic memory at 4 hour post dose.
- MK-4305 30 mg significantly prolonged reaction time indicating slowed information processing and impaired attention at 1.5 hour, but not at 4 and 8 hour post dose.

Safety:

MK-4305 and zolpidem were generally safe and well tolerated in healthy elderly subjects. There were no serious adverse experiences (SAE) or laboratory adverse experiences reported. Of the twelve (12) subjects randomized, 11 completed and 1 discontinued. Subject AN 0009 discontinued due to the clinical adverse experience of erythematous rash, which occurred in Period 1, 1.5 hours after dosing with placebo.

P022: A Randomized, Double-Blind Study to Assess the Effect of MK-4305 on corrected QT Intervals in Healthy Male and Female Subjects

This was a double-blind, randomized, placebo-controlled, 4-period, crossover study in healthy male and female volunteers was conducted to evaluate the potential effects of a 60 mg dose and supratherapeutic doses (150 mg and 240 mg combined) of suvorexant on ventricular repolarization by quantitative analysis of corrected QT intervals in healthy subjects.

This study has been reviewed by the Interdisciplinary Review Team.
Interdisciplinary Review Team Summary: The largest upper bounds of the 2-sided 90% CI for the mean difference between Suvorexant and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established.

PK Summary:
The results for plasma Suvorexant pharmacokinetic parameters following single doses of suvorexant (60, 150 and 240 mg), are summarized in the table below.

Summary Suvorexant Pharmacokinetic Parameters for Subjects Following Single Doses of 240-mg, 150-mg, or 60-mg Suvorexant in Healthy Male and Female Subjects

	$AUC_{0\text{-}24hr}$ (μM·hr)[†,§]			C_{max} (μM)[§]			T_{max} (hr)[§]		
	240 mg	150 mg	60 mg	240 mg	150 mg	60 mg	240 mg	150 mg	60 mg
N	17[‡]	29	45	18	29	45	18	29	45
GM	31.75	22.42	12.06	2.598	1.996	1.178	--	--	--
95%CI	(28.2, 37.9)	(21.1, 24.8)	(11.5, 13.5)	(2.28, 3.18)	(1.86, 2.25)	(1.13, 1.29)	--	--	--
%CV	30.3	23.4	28.2	33.2	24.2	24.8	--	--	--
Median	32.58	23.96	12.57	2.572	2.007	1.206	2.1	2.1	2.1
Min	19.14	11.81	6.17	1.583	1.131	0.446	1.1	1.1	1.1
Max	47.24	34.08	21.75	4.413	3.526	1.807	4.1	4.1	4.2

[†] For AN 35 (60 mg) and AN 41 (240 mg), the actual collection time for the 24 hour timepoint occurred just prior to 24 hours postdose. It was not possible to extrapolate to $AUC_{0\text{-}24hr}$; therefore, AUC_{all} used for the calculation of summary statistics.
[‡] AN 24 (240 mg) did not have values post 4 hours so no $AUC_{0\text{-}24hr}$ was calculated.
[§]AN 39 (150 mg) did not have a value at 2 hours postdose so all parameters are based on available plasma concentrations only.
GM=Geometric Mean; Max=Maximum; Min=Minimum; CI=Confidence Interval; CV=Coefficient of Variation of geometric mean.

P025: A Study to Evaluate the Abuse Potential of MK-4305

Objectives:

Primary: (1) To assess the relative abuse liability of suvorexant compared to placebo in recreational polydrug users, as measured by Drug Liking VAS. (2) To confirm the abuse liability of zolpidem compared to placebo as measured by the Drug Liking VAS, in order to confirm study validity.

Study Design	2-part*, Single-dose, randomized, double-blind, balanced, placebo- and active comparator controlled 6-way crossover study
Study Population	73 healthy male (38) and female (35) recreational polydrug users (20-53 years), 36 completed Part II (main part of the study)
Treatment Group	6 Treatment Sessions: 1. Placebo 2. zolpidem 15 mg 3. zolpidem 30 mg 4. suvorexant 40 mg 5. suvorexant 80 mg 6. suvorexant 150 mg
Dosage and Administration	Treatment Periods were separated by at least 10 days to minimize potential carry-over effects. All study drug was administered in the fasted state (8 hours prior to and 4 hours after dosing).
PK Sampling: plasma	PK samples were collected at pre-dose and at 1.5 h post-dose for the analysis of MK-4305 and possible analysis of zolpidem
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL for MK-4305 Samples were not analyzed for zolpidem.
PK Assessment	$C_{1\ 5h}$ of MK-4305
PD Assessment	assessed from 0.5 to 24 hours post dose using ARCI scales and VASs for High and Alertness/Drowsiness, Drug Liking, Good Effects, Bad Effects, Any Effects, Overall Drug Liking', Take Drug Again', Bowdle VAS, Subjective Drug Value and Drug Similarity, Choice Reaction Time, Divided Attention Test.
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* Part I was conducted to ensure that subjects who are enrolled in Part II demonstrate liking and tolerability to the primary active comparator and an appropriate placebo response.

Bioanalytical Assay:
PK samples were not analyzed for zolpidem.
Plasma concentrations of suvorexant were determined using validated LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:
Blood samples for pharmacokinetic archive were collected in Part II of the study at pre-dose and at 1.5 hours post-dose in each period for suvorexant and/or zolpidem quantitation. Suvorexant samples were analyzed for compliance to confirm the exposure of suvorexant. No PK parameters were calculated.
Suvorexant plasma concentrations following single dose administration of suvorexant in healthy recreational polydrug users were in line with those observed in other studies: mean values at 1.5 h post-dose of 1.12, 1.73 and 2.48 μM after suvorexant 40, 80 or 150 mg, respectively.
Analysis of zolpidem plasma samples was to be contingent upon the PD results. Since the PD results were consistent with the anticipated outcomes and those reported in the scientific literature, zolpidem samples were not analyzed.

Pharmacodynamic and Safety Conclusions:

- Suvorexant and Zolpidem demonstrated greater abuse potential than placebo in recreational polydrug users, as measured by the “Drug Liking" VAS.
- Suvorexant showed similar abuse potential as zolpidem as measured by the “Drug Liking" VAS.
- Both suvorexant and zolpidem showed greater abuse potential than placebo on other positive measures of drug abuse potential; the effects of suvorexant were generally similar to zolpidem abuse potential. However, on High VAS, ARCI MBG subscale and Bowdle VAS, all doses of suvorexant showed statistically significantly less effect than zolpidem 30 mg.
- There was no apparent dose-response for suvorexant on positive measures of drug abuse potential, whereas higher dose (30 mg) of zolpidem appeared to have greater effects than the low dose (15 mg) on most measures.
- Suvorexant and zolpidem demonstrated comparable pharmacological effects and impairment on psychomotor performance at doses evaluated in this study.
- Suvorexant (40, 80 and 150 mg) and zolpidem (15 and 30 mg) were generally well tolerated in recreational polydrug users following single dose administration. The incidence of abuse potential AEs was generally lower following administration of suvorexant than zolpidem.

P035: A Multiple Dose Study to Evaluate Next Day Effects of MK-4305 (Suvorexant) on Driving Performance in Healthy Non-Elderly Subjects

Objectives:

Primary: To evaluate the next day residual effects of suvorexant as assessed by highway driving performance after single dose administration in healthy non-elderly male and female subjects.

Secondary: 1. To investigate the next day effects of zopiclone 7.5 mg on mean standard deviation of lateral position (SDLP) in highway driving tests in healthy non-elderly subjects and demonstrate assay sensitivity of the clinical trial.

2. To evaluate the next day residual effects of suvorexant as assessed by highway driving performance after repeated dose administration in healthy non-elderly male and female subjects.

Study Design	Randomized, double-blind, double-dummy, placebo and active controlled, multiple oral dose, 4-period crossover study
Study Population	28 healthy subjects (21-64 years) : male (13) and female (15)
Treatment Group	Treatment A: 40 mg suvorexant for 8 days, Treatment B: 20 mg suvorexant for 8 days, Treatment C: 7.5 mg zopiclone on Day 1 and Day 8 only, Treatment D: placebo for 8 days
Dosage and Administration	All doses of study drug were administered in the evening at bedtime. On Day 1 and Day 8, study drug was administered after an approximate 4 hour fast. On Days 2 - 7, there was no restriction of food and water to study drug administration. There was a minimum 7-day washout between each treatment dosing period for any given subject.
PK Sampling: plasma	PK samples were collected at pre-dose and at 11 h post-dose on Day 2 and Day 9 for the analysis of MK-4305 and zopiclone
Analysis: Plasma	LC-MS/MS method for MK-4305. Range: 1 to 1000 ng/mL Zolpidem: LC-MS/MS method with a linear calibration range from 0.30 to 150 ng/mL
PK Assessment	C_{11h} of MK-4305 and zolpidem on Day 2 and Day 9
PD Assessment	Highway Car Driving Assessment*, Driving Instructor VAS, Body Sway Test, Bond-Lader VAS, Word Learning Test, and DSST
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* The Car Driving Assessment occurred within 15 minutes of the 9 hour post-dose time point (e.g., latest 9 hours and 15 minutes postdose).

Bioanalytical Assay:

Plasma concentrations of suvorexant were determined using validated LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Plasma concentrations of zopiclone were determined using a validated method with liquid-liquid extraction of drug from human plasma. The drug and internal standard were separated using reverse-phase HPLC and detected with LC-MS/MS. The LLOQ for this method was 0.30 ng/mL with a linear calibration range from 0.30 to 150 ng/mL.
The assay performance during the analysis of the plasma samples was acceptable.
Zopiclone plasma concentrations were reported in units of ng/mL.

Pharmacokinetic Results:

Pharmacokinetic samples for suvorexant and zopiclone determinations were not collected from subject AN0007 due to phlebotomy difficulties.
For the 40 mg suvorexant treatment, a plasma concentration value BLQ for AN0005 (Day 2, 11 hours post Day 1 dose) was excluded from the calculation of summary statistics.

Individual Suvorexant Plasma Concentrations Following PM Administration of Suvorexant (MK-4305) 20 mg and 40 mg Multiple Doses Once Daily for 8 Days in Healthy Non-Elderly Subjects (N=27)

	Suvorexant Plasma Concentrations (µM)			
	Treatment: Suvorexant 20 mg		Treatment: Suvorexant 40 mg	
AN	Day 2/11 hr	Day 9/11 hr	Day 2/11 hr	Day 9/11 hr
0001	0.328	0.288	0.406	0.408
0002	0.355	0.489	0.512	0.793
0003	0.228	0.286	0.395	0.526
0004	0.277	0.490	0.422	0.742
0005	0.221	0.280	---†	0.352
0006	0.397	0.673	0.523	0.876
0007	---‡	---‡	---‡	---‡
0008	0.346	0.658	0.516	0.804
0009	0.215	0.386	0.426	0.549
0010	0.231	0.216	0.299	0.358
0011	0.336	0.366	0.598	0.690
0012	0.434	0.556	0.630	0.778
0013	0.167	0.262	0.322	0.282
0014	0.306	0.315	0.361	0.397
0015	0.173	0.261	0.471	0.425
0016	0.401	0.631	0.889	0.935
0017	0.349	0.440	0.509	0.749
0018	0.211	0.394	0.498	0.633
0019	0.248	0.402	0.372	0.513
0020	0.207	0.251	0.357	0.413
0021	0.259	0.332	0.452	0.526
0022	0.325	0.305	0.343	0.406
0023	0.363	0.635	0.707	1.032
0024	0.301	0.440	0.642	0.660
0025	0.375	0.382	0.578	0.307
0026	0.343	0.485	0.467	0.200
0027	0.200	0.351	0.433	0.322
0028	0.228	0.232	0.411	0.226
AM	0.290	0.400	0.482	0.552
SD	0.076	0.137	0.133	0.229
%CV	28	34	26	47
Median	0.301	0.382	0.459	0.526
Min	0.167	0.216	0.299	0.200
Max	0.434	0.673	0.889	1.032

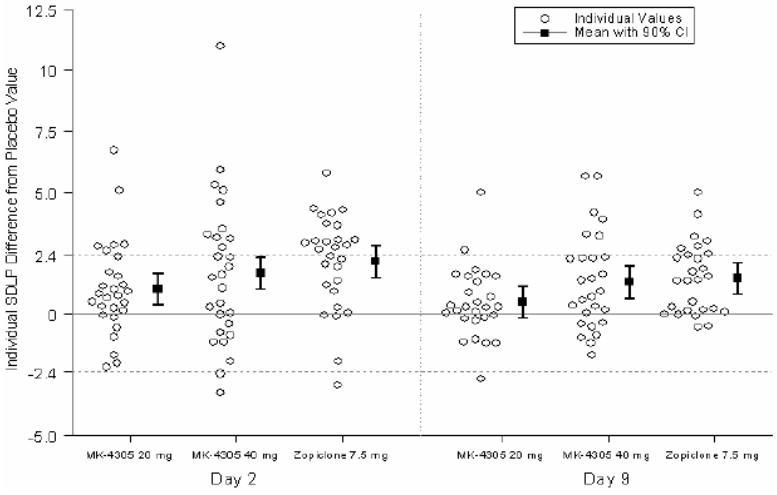
AM: Arithmetic Mean; SD: Standard Deviation; %CV: Percent Coefficient of Variation
† BLQ value excluded from the calculation of summary statistics
‡ Sample not collected at the discretion of the Principal Investigator due to phlebotomy difficulties.

Pharmacodynamic Results:

Driving performance after both single dose and multiple repeated doses of suvorexant were assessed in this study to evaluate whether there might be initial residual effects followed by tolerance.

The primary endpoint was SDLP (in centimeters) from the highway driving test. In the standardized highway driving test, subjects operated a specially instrumented vehicle over a 100 km primary highway circuit to maintain a constant speed of 95 km/h and a steady lateral position between the delineated boundaries of the slower traffic lane. SDLP was calculated as the square root of the pooled lateral position variance. SDLP is an integrated measure of road tracking error or "weaving".

Zopiclone was used as an active control as it had consistently shown an increase on SDLP (~2.5 cm) in the highway driving tests at 10 hours postdose comparable to those found for alcohol when blood alcohol concentration is 0.5 g/L or more. Alcohol at a blood concentration of 0.5 mg/mL, which is the legal level in many countries, produced a mean increase on SDLP of ~2.4 cm. Therefore, 2.4 cm was used as the non-inferiority bound in the current study. SDLP was analyzed both by mean analysis and symmetry analysis. The symmetry analysis was conducted to evaluate potential effects on the population distribution: for each treatment comparison it was determined if there was a significant difference in the number of individuals with an increase in SDLP >2.4 cm (worsening) vs. the number of subjects who had a decrease in SDLP below -2.4 cm (improvement).
Based on mean SDLP analysis, suvorexant did not impair highway driving performance following single- and multiple- 20 mg and 40 mg doses. However, the symmetry analysis of SDLP revealed that there was a statistically greater number of subjects with SDLP treatment difference of >2.4 cm than those with SDLP <-2.4 cm on Day 2 for both suvorexant doses and for zopiclone. On Day 9 (following 8 consecutive days dosing), there was a significantly greater number of subjects with SDLP treatment difference of >2.4 cm than those with SDLP <-2.4 cm after 40 mg but not after 20 mg suvorexant.



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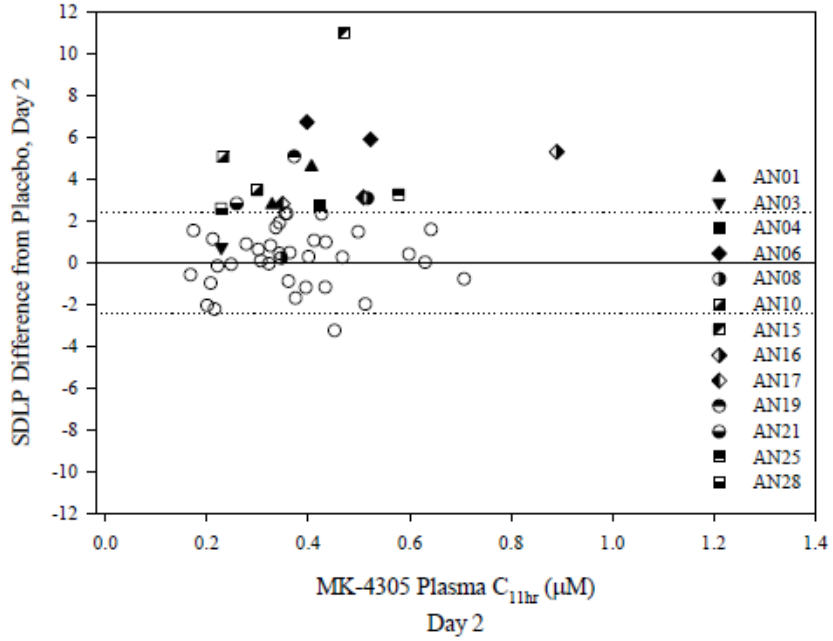
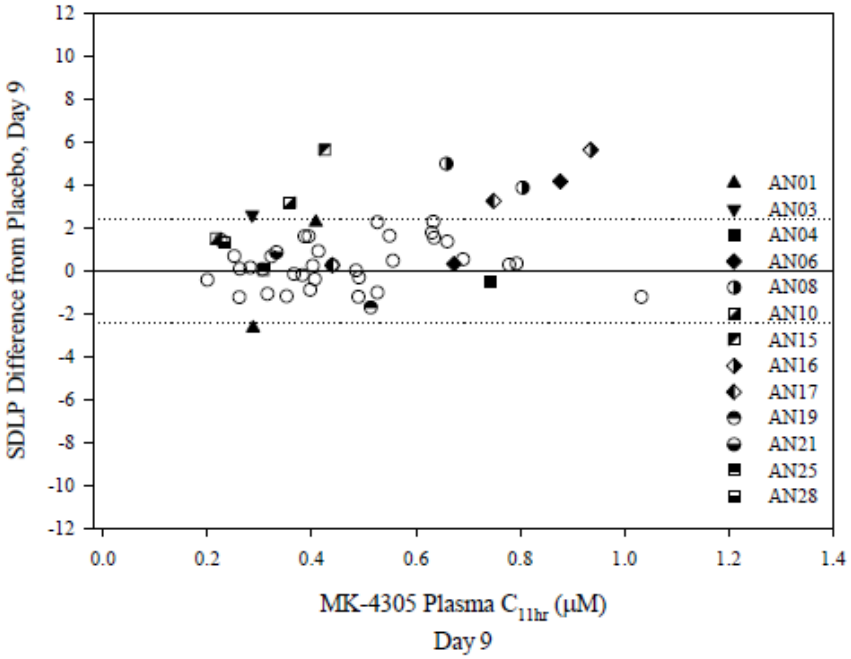
The treatment difference of SDLP was generally larger with the high dose (40 mg) than low dose (20 mg). The treatment difference on Day 9 was smaller for both suvorexant doses as compared to Day 2, suggesting tolerance effects.
In addition, there was a statistically significant increase in standard deviation of speed (SDS) on Day 2 for zopiclone, 20 mg suvorexant and 40 mg suvorexant compared to placebo, suggesting impairment on driving performance. On Day 9, only 40 mg suvorexant had a statistically significant effect on SDS compared with placebo. Statistically significant decreases in delayed recall were observed on Day 2 for zopiclone and 40 mg suvorexant, but not on Day 9.

Four female subjects prematurely stopped the driving test due to somnolence after driving for 29 to 57 minutes: three subjects following 40 mg suvorexant on Day 2 (AN0006, AN0007 and AN0016); two subjects following 20 mg suvorexant, one each on Day 9

(AN0007) and on Day 2 (AN0021). Among them, AN0016 had the highest C_{11h} levels in the group, Subjects AN0006 and AN021 had comparable C_{11h} levels with the other subjects in the group and subject AN0007 had no PK samples collected.

Pharmacokinetic and pharmacodynamic plots of the individual SDLP differences from placebo and suvorexant plasma concentrations (C_{11hr}) on Days 2 and 9 are presented below. Subjects exceeding 2.4 cm SDLP difference from placebo on Day 2 or Day 9 following 20 mg or 40 mg suvorexant administration are identified with a shaded symbol. There was no apparent trend between suvorexant plasma concentration and SDLP difference from placebo.





P039: A Multiple Dose Study to Evaluate Next Day Effects of MK-4305 (Suvorexant) on Driving Performance in Healthy Elderly Subjects

Objectives:

Primary: To evaluate the next day residual effects of suvorexant as assessed by highway driving performance after single dose administration in healthy elderly male and female subjects.

Secondary: 1. To investigate the next day effects of zopiclone 7.5 mg on mean standard deviation of lateral position (SDLP) in highway driving tests in healthy elderly subjects and demonstrate assay sensitivity of the clinical trial.

2. To evaluate the next day residual effects of suvorexant as assessed by highway driving performance after repeated dose administration in healthy elderly male and female subjects.

Study Design	Randomized, double-blind, double-dummy, placebo and active controlled, multiple oral dose, 4-period crossover study
Study Population	24 healthy elderly subjects (65-76 years): 14 male and 10 female
Treatment Group	Treatment A: 30 mg suvorexant for 8 days, Treatment B: 15 mg suvorexant for 8 days, Treatment C: 7.5 mg zopiclone on Day 1 and Day 8 only, Treatment D: placebo for 8 days
Dosage and Administration	All doses of study drug were administered in the evening at bedtime ~11:15 p.m. On Day 1 and Day 8, study drug was administered after an approximate 4 hour fast. On Days 2 - 7, there was no restriction of food and water to study drug administration. There was a minimum 7-day washout between each treatment dosing period for any given subject.
PK Sampling: plasma	PK samples were collected at pre-dose and at 8 h and 11 h post-dose on Day 2 and Day 9 for the analysis of MK-4305 and zopiclone and at 8 h post-dose on Day 5 for the analysis of MK-4305 only
Analysis: Plasma	LC-MS/MS method for MK-4305. Range: 1 to 1000 ng/mL Zolpidem: LC-MS/MS method with a linear calibration range from 0.30 to 150 ng/mL
PK Assessment	C_{8h} and C_{11h} of MK-4305 and zolpidem on Day 2 and Day 9 C_{8h} of MK-4305 on Day 5
PD Assessment	Highway Car Driving Assessment*, Driving Instructor VAS, Body Sway Test, Bond-Lader VAS, Word Learning Test, and DSST
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* The Car Driving Assessment occurred within 15 minutes of the 9 hour post-dose time point (e.g., latest 9 hours and 15 minutes postdose).

Bioanalytical Assay:

Plasma concentrations of suvorexant were determined using validated LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.

The assay performance during the analysis of the plasma samples was acceptable.

Plasma concentrations of zopiclone were determined using a validated method with liquid-liquid extraction of drug from human plasma. The drug and internal standard were separated using reverse-phase HPLC and detected with LC-MS/MS. The LLOQ for this method was 0.30 ng/mL with a linear calibration range from 0.30 to 150 ng/mL.

The assay performance during the analysis of the plasma samples was acceptable.

Zopiclone plasma concentrations were reported in units of ng/mL.

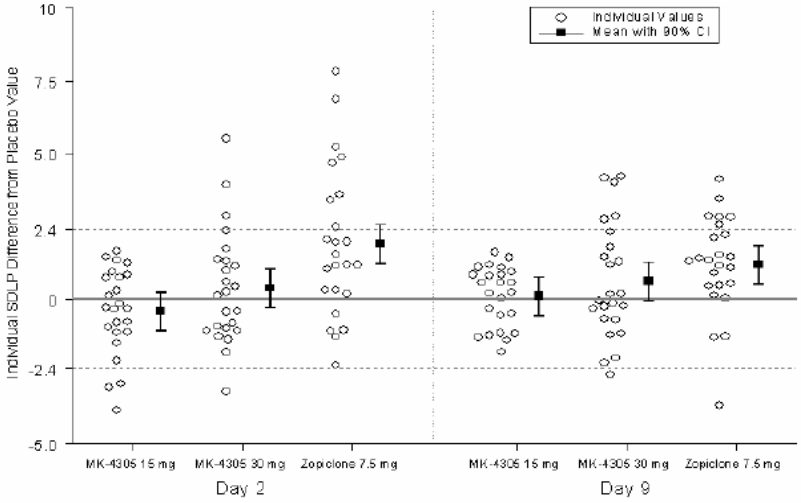
Pharmacokinetic Results:

The individual suvorexant plasma concentrations and summary statistics for all subjects are presented below.

		MK-4305 Plasma Concentration (μM)											
		Treatment: MK-4305 15 mg						Treatment: MK-4305 30 mg					
		Day 2		Day 5	Day 9			Day 2		Day 5	Day 9		
AN	Gender	8 hr	11 hr	8 hr	Predose[†]	8 hr	11 hr	8 hr	11 hr	8 hr	Predose[†]	8 hr	11 hr
0025	Male	0.331	0.282	0.494	0.241	0.452	0.442	0.443	0.401	0.640	0.385	0.794	0.686
0026	Male	0.188	0.175	0.232	0.131	0.248	0.252	0.291	0.293	0.400	0.208	0.403	0.419
0027	Female	0.260	0.252	0.377	0.189	0.418	0.405	0.477	0.407	0.645	0.338	0.617	0.535
0028	Female	0.360	0.317	0.393	0.292	0.549	0.504	0.495	0.426	0.634	0.495	0.714	0.626
0029	Male	0.416	0.301	0.375	0.202	0.352	0.371	0.594	0.457	0.545	0.352	0.631	0.515
0030	Male	0.337	0.303	0.476	0.286	0.504	0.478	0.442	0.399	0.681	0.445	0.710	0.703
0031	Male	0.160	0.156	0.271	0.096	0.262	0.262	0.283	0.244	0.404	0.191	0.451	0.416
0032	Female	0.247	0.230	0.347	---[‡]	0.446	0.343	0.619	0.447	0.553	0.330	0.527	0.511
0033	Female	0.409	0.387	0.657	0.500	0.659	0.614	0.640	0.687	1.630	0.891	1.275	1.241
0034	Male	0.322	0.275	0.488	0.329	0.507	0.528	0.488	0.400	0.666	0.513	0.835	0.711
0035	Male	0.308	0.239	0.306	0.180	0.370	0.362	0.331	0.313	0.533	0.307	0.618	0.587
0036	Female	0.310	0.305	0.569	0.348	0.557	0.538	0.528	0.507	0.836	0.560	0.807	0.812
0037	Male	0.217	0.152	0.193	0.047	0.259	0.198	0.336	0.252	---[‡]	0.111	0.389	0.312
0038	Male	0.311	0.320	---[‡]	0.247	0.517	0.484	0.583	0.551	0.782	0.491	0.842	0.770
0039	Male	0.256	0.266	---[‡]	0.186	0.400	0.393	0.547	0.511	0.672	0.299	0.640	0.642
0040	Female	0.389	0.393	0.735	0.510	0.696	0.664	0.586	0.521	0.317	0.869	1.130	1.141
0041	Female	---[‡]	0.257	0.411	0.228	0.374	0.381	0.340	0.335	0.831	0.532	0.972	0.969
0042	Female	0.292	0.241	0.474	0.262	0.505	0.453	0.457	0.444	0.749	0.476	0.880	0.733
0043	Female	0.458	0.394	0.534	0.213	0.529	0.463	0.589	0.607	0.746	0.384	0.856	0.788
0044	Male	0.297	0.248	0.243	0.075	0.264	0.231	0.262	0.217	0.448	0.163	0.369	0.388
0045	Male	0.206	0.179	0.345	0.144	0.326	0.290	0.408	0.314	0.487	0.232	0.628	0.523
0046	Male	0.226	0.211	0.355	0.212	0.353	0.328	0.403	0.358	0.530	0.375	0.577	0.550
0047	Male	0.228	0.185	0.280	0.108	0.293	0.266	0.312	0.257	0.401	0.183	0.549	0.449
0048	Female	0.176	0.147	0.209	0.094	0.217	0.206	0.278	0.227	0.347	0.212	0.362	0.339
Male & Female	N	23	24	22	23	24	24	24	24	23	24	24	24
	AM	0.291	0.259	0.398	0.223	0.419	0.394	0.447	0.399	0.629	0.389	0.691	0.640
	SD	0.081	0.073	0.144	0.120	0.132	0.127	0.122	0.125	0.266	0.198	0.235	0.235
	%CV	29.2	30.0	37.6	63.9	33.4	34.9	29.3	32.8	36.8	55.0	35.3	36.6
	Median	0.297	0.254	0.376	0.212	0.409	0.387	0.450	0.401	0.634	0.363	0.635	0.607
	Min	0.160	0.147	0.193	0.047	0.217	0.198	0.262	0.217	0.317	0.111	0.362	0.312
	Max	0.458	0.394	0.735	0.510	0.696	0.664	0.640	0.687	1.630	0.891	1.275	1.241

Pharmacodynamic Results:

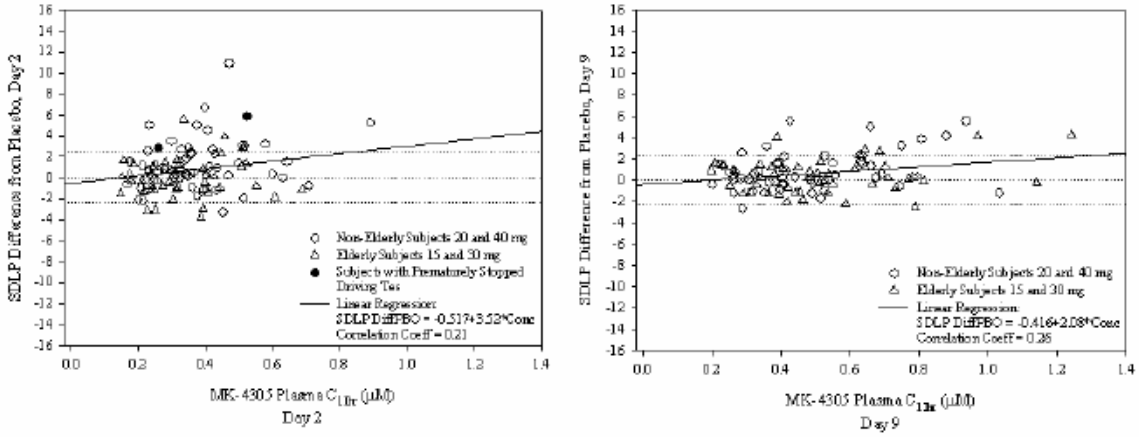
Based on mean SDLP analysis, suvorexant at did not impair highway driving performance in elderly subjects following single- and multiple- 15 mg and 30 mg doses. However, based on symmetry analysis of SDLP, it appears that there was a greater number of subjects with SDLP treatment difference of >2.4 cm than those with SDLP <-2.4 cm on Day 2 for the high (30 mg) suvorexant dose and for zopiclone.



Suvorexant (15 mg and 30 mg) did not show any statistically significant effect on SDS, word recall and body sway area, following single and multiple dose administration.

Plasma concentrations at 11 hr postdose were measured in both driving studies (035 and 039) and the PK/PD relationship was explored for SDLP. There was a dose response on SDLP (especially for the non-elderly study), but a weak correlation between C_{11hr} and treatment difference on SDLP.

SDLP Differences From Placebo vs Suvorexant Plasma Concentrations (C_{11hr}) in Non-Elderly and Elderly Subjects on Day 2 (left panel) and Day 9 (right panel).



Subjects whose driving was prematurely stopped due to somnolence were identified (no PK sample was available for AN007, AN016 repeat period data is shown)

Adverse Experiences of Special Interest

AN 0033, a 72-year-old white female, experienced two episodes of non-serious, moderate adverse experiences of cognitive impairment after administration of zopiclone 7.5 mg tablet in Treatment Period 1 and after administration of suvorexant 30 mg tablet in Treatment Period 3 that were considered by the Investigator to be probably related to study drug. The first episode of cognitive impairment (following zopiclone 7.5 mg treatment) occurred approximately 8.5 hours after Day 8 dosing in the beginning of the car driving assessment.
The second episode of cognitive impairment (following suvorexant 30 mg treatment) occurred approximately 10 hours after Day 8 dosing about 50 minutes into the car driving assessment. In both episodes, the subject caused several dangerous situations during the car driving assessment which led the principle investigator to believe that she may have had some cognitive impairment.
Note: This subject had the highest suvorexant plasma levels of all subjects (1.275 μM).

Conclusion: Based on the results of the two highway driving studies (035 and 039), the only suvorexant dose, which did not cause next-day impairment on driving performance, is 15 mg.

P040: A Study to Evaluate the Respiratory Safety of MK-4305 (Suvorexant) Following a Single Dose Administration in Healthy Subjects

Objectives:

Primary:

To evaluate the effect of a single dose of suvorexant on mean oxygen saturation (SaO_2) during total sleep time (TST) as measured by pulse oximetry.

Secondary:

To evaluate the proportion of the night in which SaO_2 is less than 90% following a single dose administration of suvorexant and placebo.

Study Design	Double-blind, placebo-controlled, 3-period crossover study in healthy subjects
Study Population	12 healthy nonsmoking subjects (25-50 years): 8 male and 4 female
Treatment Group	Subjects received 3 different treatments, Treatments A, B, and C, in a randomized crossover design. Treatment A: a single oral supratherapeutic dose of 150 mg suvorexant; Treatment B: a single therapeutic dose of 40 mg suvorexant; Treatment C: placebo.
Dosage and Administration	All study drugs were administered in the evening after ~4-hour fast. Study drug or placebo was administered in the evening at approximately 0.5 hours before bedtime ("lights off").
PK Sampling: plasma*	Blood samples for determination of suvorexant concentrations were collected at predose and at specified time points: pre-dose, 0.5 h, 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 60 and 84 hours post-suvorexant dose in each treatment period.
Analysis: Plasma	LC-MS/MS method for MK-4305. Range: 1 to 1000 ng/mL
PK Assessment	C_{max}, t_{max}, AUC_{0-4}, AUC_{0-24}, AUC_{0-inf}, $t_{1/2}$ of MK-4305
PD Assessments	8-hour PSG recording and SaO_2 monitoring
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* Plasma samples were collected “through the wall” during the PSG recordings (1, 2, 3, 4, and 6-hour time points); unsuccessful PK samples were not repeated.

Bioanalytical Assay:

Plasma concentrations of suvorexant were determined using validated LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.

The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:

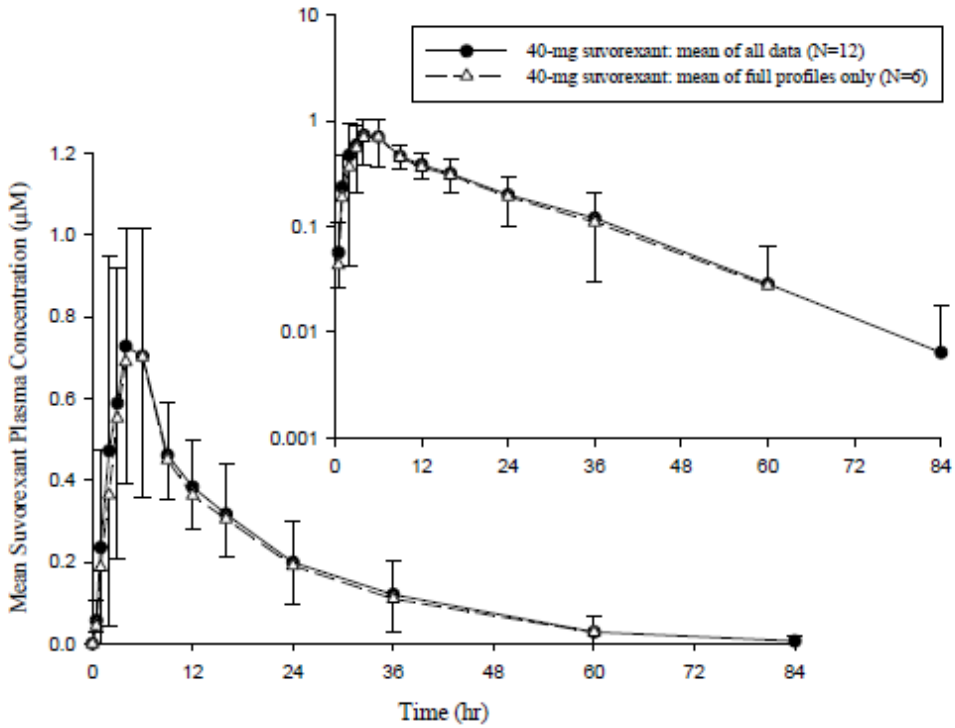
All 12 subjects were included in the PK analysis, however some subjects (listed in Table below) had missing samples and did not have an AUC, Cmax, or Tmax calculated. All subjects with missing samples had an apparent terminal t½ calculated.

Subjects With Missing Pharmacokinetic Samples by Treatment

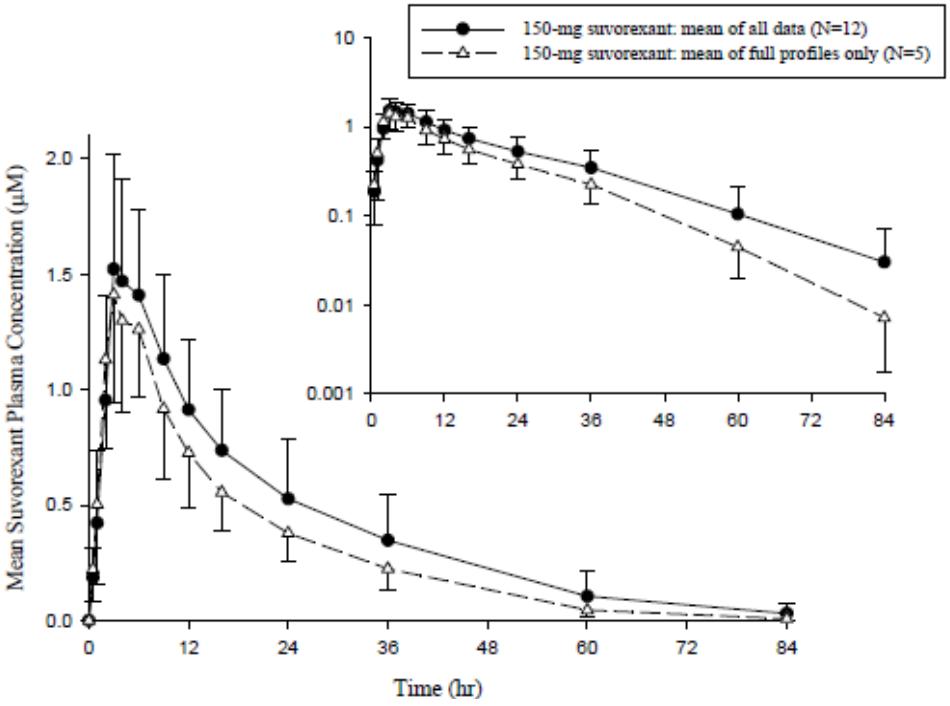
Suvorexant Treatment	Number of Subjects	Allocation Numbers
Treatment A (150 mg)	7	0001, 0003, 0006, 0007, 0008, 0009, 0010
Treatment B (40 mg)	6	0003, 0004, 0006, 0007, 0008, 0011

Mean plasma concentration-time profiles of suvorexant for subjects with complete PK profiles were compared with those from all available data following administration of a 40 mg or a 150 mg single dose of suvorexant and are presented in the figures below. Missing pharmacokinetic samples during the "through the wall" collection period did not appear to have an impact on the mean plasma concentration-time profiles for either dose. The summary of suvorexant plasma PK parameters following single-dose administration of 40 mg or 150 mg suvorexant is presented in the table below.

Mean (± SD) Plasma Concentrations (µM) of Suvorexant of Subjects With Full PK Profiles Only Compared With Mean of All PK Data Following Administration of a 40 mg Single Dose of Suvorexant to Healthy Subjects (Linear Scale; Inset=Semi-Log)



Mean (± SD) Plasma Concentrations (µM) of Suvorexant of Subjects With Full PK Profiles Only Compared With Mean of All PK Data Following Administration of a 150 mg Single Dose of Suvorexant to Healthy Subjects (Linear Scale; Inset=Semi-Log)



Plasma Pharmacokinetic Parameters Following Single-Dose Administration of 40 mg or 150 mg Suvorexant to Healthy Subjects

AN	Suvorexant 40 mg					Suvorexant 150 mg				
	$AUC_{0-\infty}$ (µM•hr)	AUC_{0-24hr} (µM•hr)	C_{max} (µM)	T_{max} (hr)	Apparent terminal $t_{½}$ (hr)	$AUC_{0-\infty}$ (µM•hr)	AUC_{0-24hr} (µM•hr)	C_{max} (µM)	T_{max} (hr)	Apparent terminal $t_{½}$ (hr)
AM	12.65	8.98	0.909	--	10.0†	24.94	18.15	1.587	--	11.1†
SD	4.53	1.86	0.278	--	1.8‡	7.43	4.69	0.351	--	3.1‡
GM	11.99	8.77	0.873	--	--	23.93	17.61	1.555	--	--
% CV	37.6	25.4	32.1	--	--	34.6	28.9	22.7	--	--
Median	11.97	9.64	0.902	3.5	9.9	26.60	18.92	1.569	4.0	11.6
Min	6.63	5.33	0.538	3.0	7.8	14.16	11.39	1.139	3.0	7.5
Max	20.54	10.40	1.358	6.0	16.4	33.06	23.08	2.093	6.0	19.0

AN = Allocation Number; AM = Arithmetic Mean; SD = Standard Deviation; GM = Geometric Mean
†Harmonic mean; ‡Jack-knife SD; §Value excluded due to missing one or more "through the wall" pharmacokinetic samples

Pharmacodynamic Results

Single-dose suvorexant did not produce a clinically significant reduction of mean SaO_2 during TST in healthy subjects, as compared to placebo. The least-squares mean difference between 150 mg suvorexant and placebo was 0.00 and the corresponding 90% confidence interval was (-0.90, 0.90). The least-squares mean difference between 40 mg

suvorexant and placebo was -0.33. In both cases, the lower bound of the 90% confidence interval fell completely above -5%. Similar comparisons for mean SaO_2 during wake, NREM, and REM sleep stages were also done. The mean SaO_2 during wake, NREM, and REM sleep stages, following a single dose of suvorexant, was generally similar to that observed in the placebo group.

Statistical Analysis of Pharmacodynamic Endpoints Following Single-Dose Administration of 150 mg Suvorexant, 40 mg Suvorexant, or Placebo to Healthy Subjects (N=12)

Endpoint	Suvorexant 150 mg	Suvorexant 40 mg	Placebo	Difference (Suvorexant 150 mg - Placebo) of LSmean (90% CI)	Difference (Suvorexant 40 mg - Placebo) of LSmean (90% CI)	MSE‡
	LSmean (95% CI)	LSmean (95% CI)	LSmean (95% CI)			
Mean SaO_2 (%) during TST	96.67 (95.79, 97.55)	96.33 (95.45, 97.21)	96.67 (95.79, 97.55)	-0.00 (-0.90, 0.90)	-0.33 (-1.23, 0.57)	1.64
Mean SaO_2 (%) during Wake	96.83 (96.09, 97.58)	96.75 (96.00, 97.50)	97.25 (96.50, 98.00)	-0.42 (-1.22, 0.38)	-0.50 (-1.30, 0.30)	1.29
Mean SaO_2 (%) during NREM	96.75 (95.89, 97.61)	96.17 (95.31, 97.02)	96.75 (95.89, 97.61)	-0.00 (-0.87, 0.87)	-0.58 (-1.45, 0.29)	1.53
Mean SaO_2 (%) during REM	96.67 (95.79, 97.55)	96.33 (95.45, 97.21)	96.83 (95.95, 97.71)	-0.17 (-1.07, 0.73)	-0.50 (-1.40, 0.40)	1.64
AHI §	-0.82 (-2.62, 0.99)	0.15 (-1.65, 1.95)	-0.63 (-2.44, 1.17)	-0.18 (-1.68, 1.31)	0.78 (-0.71, 2.28)	4.49

‡ Estimate of within-subject variance.
§AHI = apnea-hypopnea index. For AHI test, change from baseline is analyzed where screening PSG visit serves as baseline, mean = 3.62, SD = 3.26, (N=12).
SaO_2 = Oxygen Saturation, TST = Total Sleep Time.

One subject, AN0005, had SaO_2 values less than 90% in both suvorexant treatment groups. The percentage of time for SaO_2 below 90% ranged from 0.1% to 0.3% of total sleep time, except for AN0011 in the 40 mg suvorexant treatment with 12.4% of total sleep time below 90%, but this subject did not have SaO_2 values less than 90% on 150 mg.
Note: Suvorexant exposure in Subject AN0005 was close to the average exposure for the treatment group after both 40 and 150 mg doses. There was no PK data for Subject AN0011 after suvorexant 40 mg.
In addition, since the confidence intervals for the mean between-treatment difference in AHI change from baseline include zero, it was concluded that there was no statistically significant increase in AHI for either suvorexant dose relative to placebo.

Safety:
No serious clinical, laboratory, other significant AEs were reported during the study.
There were no discontinuations due to an adverse experience.
Dizziness (3 subjects), headache (2 subjects), and somnolence (2 subjects) were the most frequently reported adverse experiences following 150 mg suvorexant.
All AEs were rated mild in intensity.

1.5 Efficacy and Safety Studies

P006: A Phase IIb, Multicenter, Randomized, Double-Blind Placebo Controlled, 2-period Adaptive Crossover Polysomnography Study to Evaluate the Safety and Efficacy of MK-4305 in Patients with Primary Insomnia

Objectives:

- To evaluate the efficacy of MK-4305 compared with placebo in improving sleep efficiency (SE) as measured by polysomnography (PSG) on Night 1 and at the end of 4 weeks of treatment, where SE is defined as 100 times total sleep time (minutes) divided by time in bed (minutes)
- To evaluate the safety and tolerability of MK-4305

Study Design*	Randomized, multicenter, double-blind (with in-house blinding), placebo-controlled, 2-period cross-over PSG study to assess the safety, and efficacy of four doses of suvorexant (10, 20, 40, and 80 mg) in the treatment of patients with primary insomnia*
Study Population**	254 male and female patients in the U.S. and Japan, 228 completed
Treatment Group	See treatment sequence below***
Dosage and Administration	Treatment A: 10 mg MK-4305 Treatment B: 20 mg MK-4305 Treatment C: 40 mg MK-4305 Treatment D: 80 mg MK-4305 Treatment E: placebo
PK Sampling: plasma	9 h post-dose (C_{9h})
Analysis	Plasma: LC-MS/MS method for MK-4305 Range: 1 to 1000 ng/mL
PK Assessment	C_{9h}
PD Assessment	PSG parameters: sleep efficiency (SE), total sleep time (TST), wake after sleep onset (WASO), and latency to persistent sleep (LPS)
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* This design was equivalent to four separate 2-treatment 2-period crossover trials with patients in each trial receiving one of the four MK-4305 doses and placebo.
Duration of each treatment period was 4 weeks, with a single-blind placebo run-in period prior to treatment period 1 and a single-blind placebo washout of a minimum of 7 days between treatment period 1 and treatment period 2.
Each treatment period included 3 visits: occurring on Night 1, Day 14, and Night 28. On Nights 1 and 28 (at the beginning and end of each treatment periods) patients stayed overnight for an 8-hour PSG recording and were instructed to administer study drug 30 minutes prior to the PSG recording. On non-PSG nights, patients were instructed to take study drug once nightly, immediately (within 5 to 10 minutes) prior to lights out, throughout the entire study.

** Study Population:

Patient Disposition	Placebo	MK4305 10mg	MK4305 20mg	MK4305 40mg	MK4305 80mg	*Study Overall
Screening Failures						469
Randomized	249	62	61	59	61	254
Female (age range)	147 (18 to 64)	34 (23 to 63)	40 (25 to 64)	32 (26 to 64)	34 (18 to 64)	148 (18 to 64)
Male (age range)	102 (20 to 63)	28 (25 to 62)	21 (23 to 60)	27 (20 to 63)	27 (22 to 60)	106 (20 to 63)
Completed	235	60	57	59	55	228
Discontinued	14	2	4		6	26

*** Treatment Sequence:

Treatment Sequence	Sample Size (n)	Period 1	Period 2
1	26 completers	MK-4305 10 mg	Placebo
2	26 completers	Placebo	MK-4305 10 mg
3	26 completers	MK-4305 20 mg	Placebo
4	26 completers	Placebo	MK-4305 20 mg
5	26 completers	MK-4305 40 mg	Placebo
6	26 completers	Placebo	MK-4305 40 mg
7	26 completers	MK-4305 80 mg	Placebo
8	26 completers	Placebo	MK-4305 80 mg

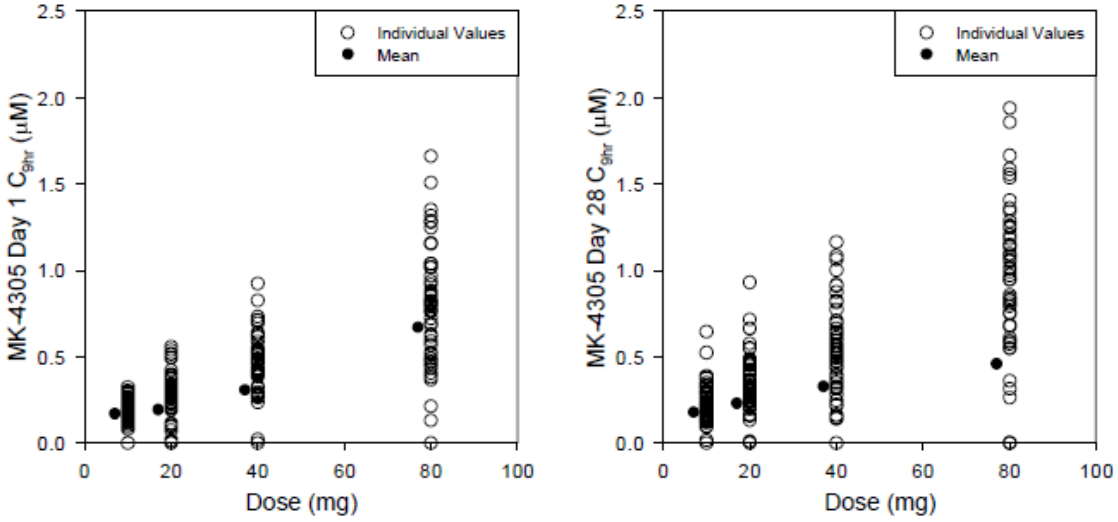
Bioanalytical Assay:

Plasma concentrations of suvorexant were determined using validated LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:

Individual and geometric mean suvorexant plasma C_{9hr} values following single and multiple dose (treatment day 28) administration (10 – 80 mg) in pooled non-Japanese and Japanese primary insomnia patients are presented below.

Individual and Geometric Mean MK-4305 Plasma C_{9hr} Values (µM) Versus Dose Following Single (Left) and Multiple-Dose (Right) Administration of 10 to 80 mg in Pooled Non-Japanese and Japanese Primary Insomnia Patients



Summary of Pharmacokinetic Parameters of MK-4305 Following Oral Dose Administration of MK-4305 10- to 80-mg for 28 Days in Pooled non-Japanese and Japanese Primary Insomnia Patients

Dose	N	C_{9hr} (µM)
	Day 1[†]	
10 mg	61	0.171 (0.120, 0.243)
20 mg	59	0.195 (0.136, 0.279)
40 mg	58	0.309 (0.215, 0.444)
80 mg	60	0.671 (0.470, 0.959)
	Day 28 (Last Day)[†]	
10 mg	59	0.179 (0.125, 0.256)
20mg	57	0.231 (0.160, 0.332)
40 mg	55	0.328 (0.226, 0.475)
80 mg	56	0.460 (0.319, 0.664)

[†] Back-transformed least squares mean and 95% confidence interval from a linear mixed effects model with fixed effects for dose, day and dose-by-day interaction and a random effect for subject performed on natural log-transformed values.

Square root of conditional mean squared error (residual error) from a linear mixed effects model is 0.995 for C_{9hr}.

Comment: Less than dose proportional increase in C_{9h}.

Pharmacodynamic Results:

All doses of suvorexant (10 mg, 20 mg, 40 mg and 80 mg) were superior to placebo in improving insomnia as measured by the primary efficacy endpoint, sleep efficiency (SE),

at Night 1 and Week 4, and as measured by the secondary efficacy endpoint, wakefulness after persistent sleep onset (WASO), at Night 1 and Week 4.
No dose of MK-4305 was superior to placebo in improving sleep onset as measured by the secondary efficacy endpoint, latency to onset of persistent sleep (LPS); however, since there was evidence of a carryover effect for LPS (Period 1 improvement in LPS did not diminish in period 2 even though patients were on placebo), analysis of Period 1 only showed evidence of efficacy for all doses, including 10 mg:

Percent decrease in latency to persistent sleep

	Night 1		Week 4	
10 mg	**49%**	**p = 0.02***	**58%**	**p = 0.02***
20 mg	51%		67%	
40 mg	68%		54%	
80 mg	54%		58%	

*nominal p-values

Safety:

No serious adverse events were reported in this study.
The percent of patients with drug-related AEs after the low doses (10 and 20 mg) was comparable to placebo: 4.8%, 6.6% and 6.8% for suvorexant 10 mg, 20 mg and placebo, respectively, and significantly higher for the higher MK-4305 doses: 20.3% and 23.0% for suvorexant 40 mg and 80 mg.
In addition, the following AEs of concern were reported in this study:
Sleep paraysis in 2 Asian males, on MK4305 80mg and 40mg
Hallucination in 1 Asian male on MK4305 40mg and 1 White female on 80mg
Excessive Daytime Sleepiness of severe intensity: 63 year old White female on 80mg

Reviewer's Comment: The efficacy and safety data from this study suggest little benefit of suvorexant doses higher than 10-20mg.

Phase 3 Studies (P028 and P029): Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Study to Evaluate the Safety and Efficacy of MK-4305 in Patients with Primary Insomnia

These confirmatory efficacy trials were similarly designed to evaluate the efficacy and safety of suvorexant in replicate core 3-month Treatment Phases.

Patients were recruited to either the Questionnaire-only cohort (Q-Cohort) or the PSG plus-Questionnaire cohort (PQ-Cohort). Overall, 75% of the patients in the study were to be randomized to the PQ-cohort. Patients in both cohorts completed daily sleep questionnaires via an electronic diary (e-diary). Patients in the PQ-Cohort additionally underwent PSG assessments.

Patients were randomized in a 3:2:3 ratio to receive either suvorexant HD, suvorexant LD, or placebo. A of total 916 and 881 patients completed P028 and P029, respectively.

The dose of suvorexant received was determined by age group as follows:

Non-elderly (18 to <65 years): suvorexant HD (40 mg) or LD (20 mg)

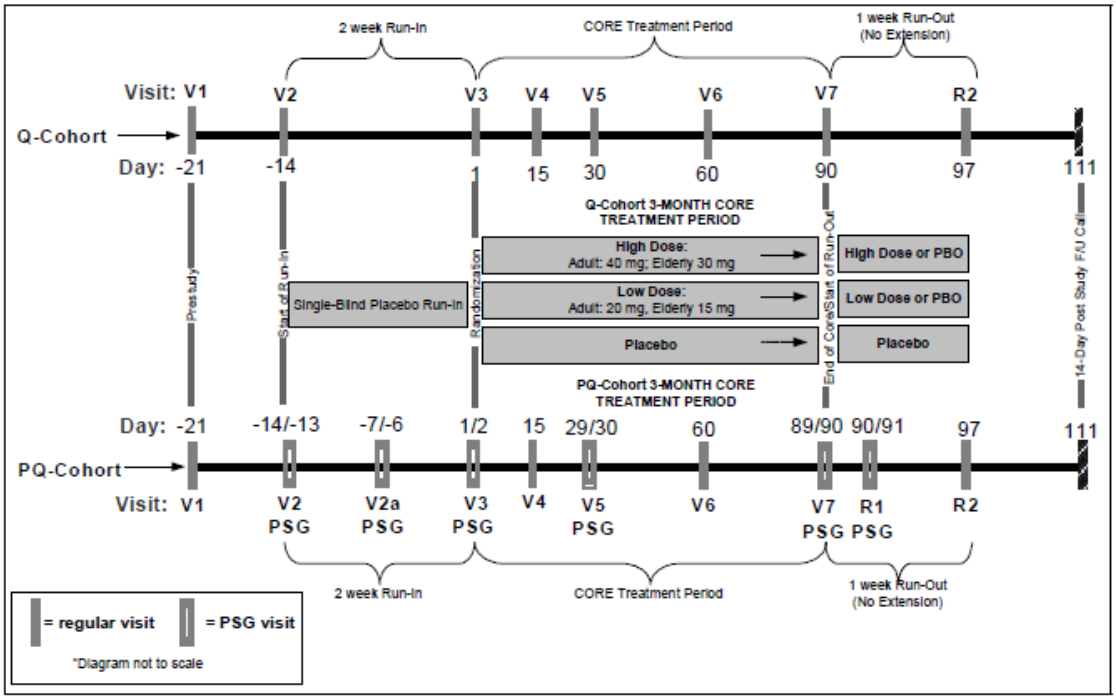
Elderly (≥ 65 years): suvorexant HD (30 mg) or LD (15 mg)

During the Treatment Phase, all patients returned to the clinic after randomization for visits at the end of Week 2, and the end of Months 1, 2, and 3. For patients in the PQ-Cohort, the visits at Night 1 and the end of Months 1 and 3 were overnight PSG visits.

Treatments Administered:

Patients were instructed to take study medication nightly, immediately prior to bedtime (within 5-10 minutes). During PSG visits for patients in the PQ-Cohort, study medication was orally administered approximately 30 minutes before bedtime.

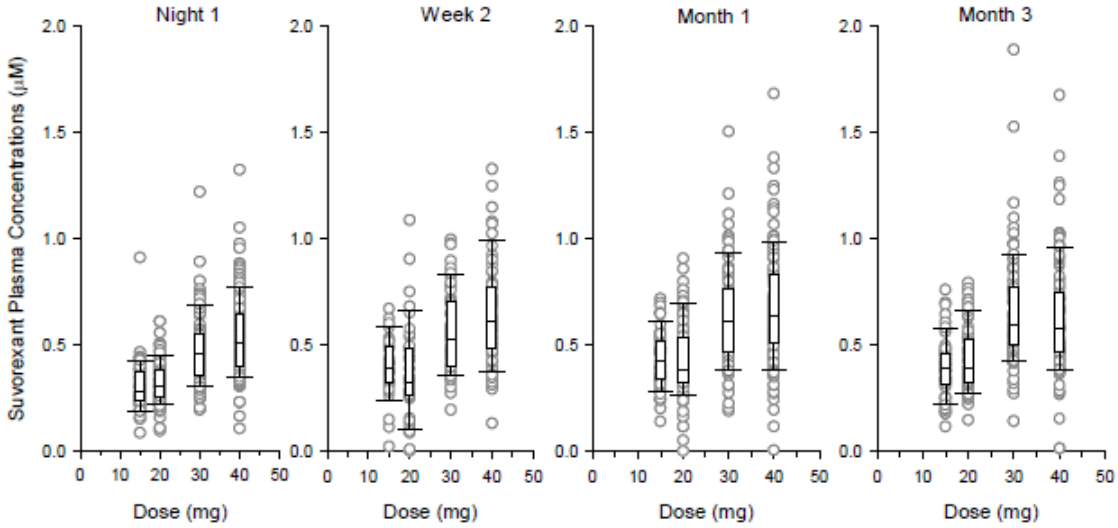
Study Design Flow Diagram: 3-Month Treatment Phase, no Extension



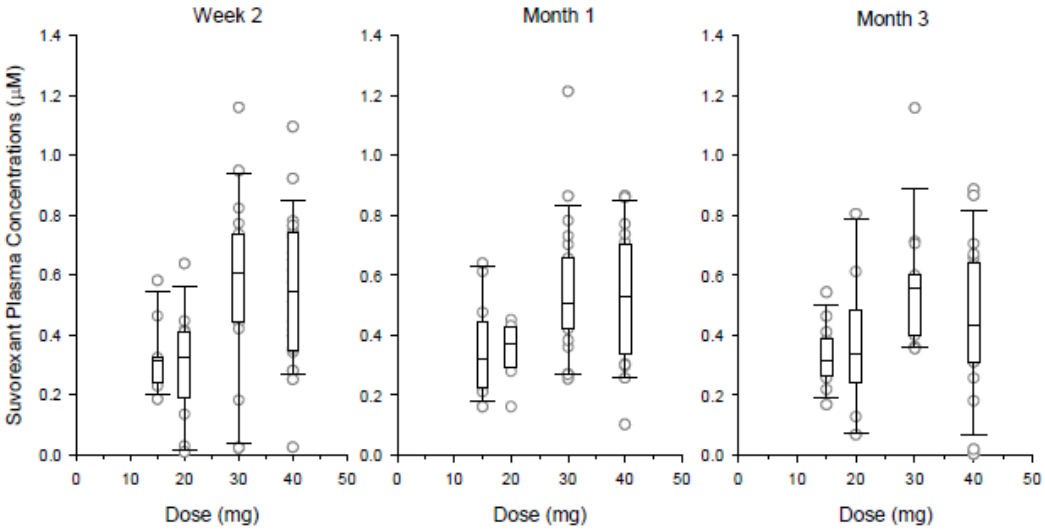
Bioanalytical Assay:
Plasma concentrations of suvorexant were determined using LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:
In the PQ cohort, PK samples were collected at approximately 9 hours post-dose at Night 1, Month 1, and Month 3. Pharmacokinetic samples obtained at Week 2 in this cohort could have been collected at any time of the day during the Week 2 visit (floating sample).
In the Q cohort, all PK samples (Week 2, Month 1, and Month 3) were intended to be floating samples.
Individual suvorexant plasma concentration values falling within the 7 – 13 post-dose time range following suvorexant administration in non-elderly (20 and 40 mg) and elderly (15 and 30 mg) primary insomnia patients are presented in the tables below for non-Japanese (PQ Cohort) and Japanese subjects (Q cohort).

Individual Plasma Concentrations of Suvorexant (MK-4305) in the 7 - 13 post-dose Time Range Following Once Daily Oral Dose Administration of Suvorexant in Non-Japanese Primary Insomnia Patients in the PQ Cohort



Individual Plasma Concentrations of Suvorexant (MK-4305) in the 7 - 13 post-dose Time Range Following Once Daily Oral Dose Administration of Suvorexant in Japanese Insomnia Patients in the Q Cohort

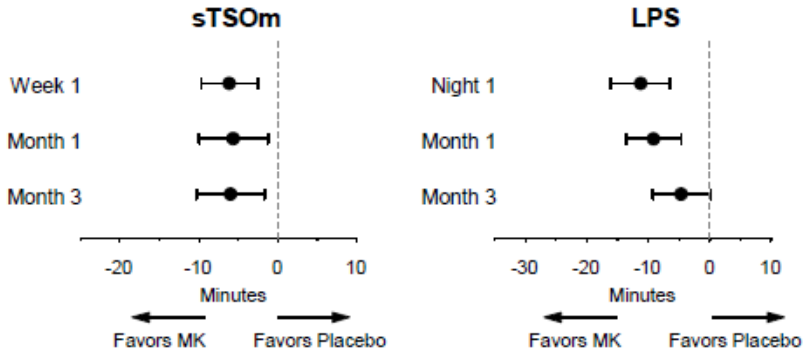


Within each cohort and at each dose, suvorexant plasma concentration values were largely similar across the duration of treatment (Week 2, Month 1 and Month 3). No formal statistical evaluation was performed, however visual inspection of Japanese and non-Japanese data suggests that suvorexant plasma concentrations are comparable between groups.

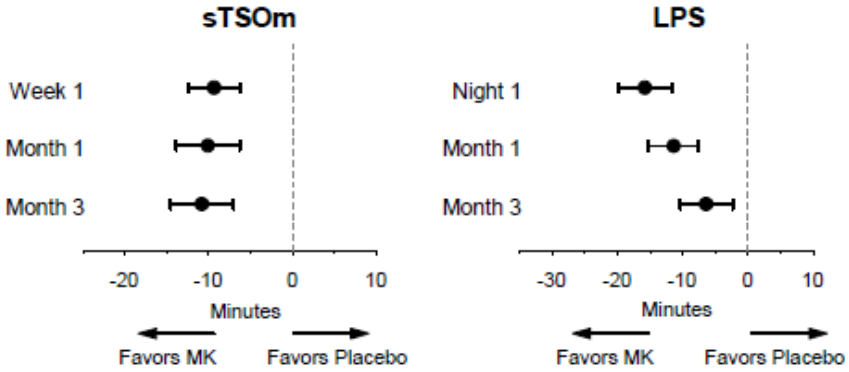
Efficacy Analyses Results

In the primary efficacy analyses on the objective (polysomnography [PSG]) measures of sleep onset and sleep maintenance (LPS and WASO), both dose groups showed statistically significant effectiveness compared to placebo in both elderly and non-elderly patients on days 1, 28 and 90.
Evaluation of suvorexant LD efficacy in the Phase 3 program was a secondary objective in one of the confirmatory trials (P028) and both studies were underpowered for the comparison of LD to placebo. The similarity of the efficacy study designs (P028 and P029) allowed for a pooled analysis of suvorexant LD compared to placebo, which provided adequate power for exploratory analyses. The results of the Phase 3 trials as well as the analysis of the pooled population (P028+P029) suggest efficacy for suvorexant LD.

Estimated Difference and 95% Confidence Intervals for Change from Baseline in Sleep Onset Efficacy Endpoints (Pooled P028+P029)

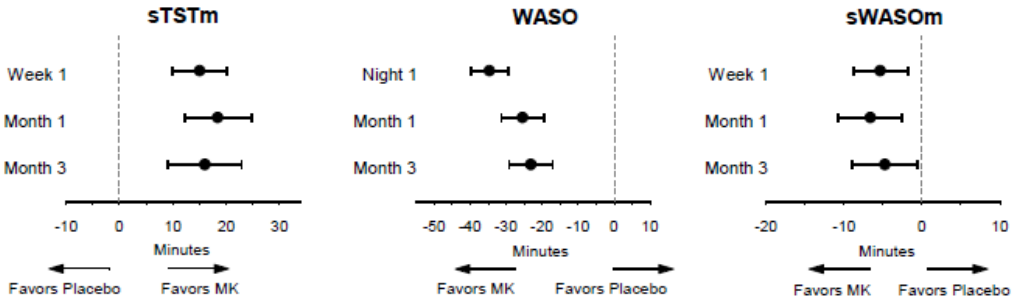


MK-4305 Low Dose (LD) versus Placebo

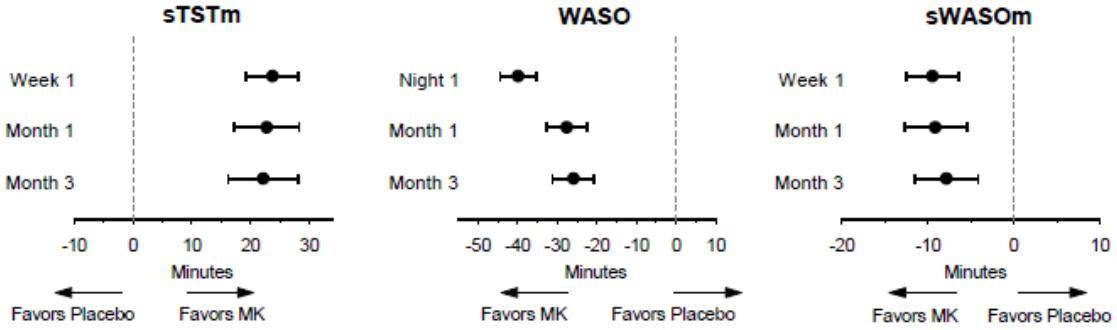


MK-4305 High Dose (HD) versus Placebo

Estimated Difference and 95% Confidence Intervals for Change from Baseline in Sleep Maintenance Efficacy Endpoints (Pooled P028+P029)



MK-4305 Low Dose (LD) versus Placebo



MK-4305 High Dose (HD) versus Placebo

Safety:

Overall, the incidence of one or more AEs reported at the LD was similar to placebo and increased at the HD.

Residual effect AE terms of somnolence and fatigue (<13% for somnolence and <4% for fatigue), exhibit a dose dependency in rate (PBO≤LD<HD).

For dose/exposure-response and dose/exposure safety relationships, please refer to the Pharmacometrics Review and the QBR, Sections 2.2.3 through 2.2.5. In summary, for all objective measures of sleep maintenance and onset (e.g. WASO, LPS) the dose (exposure) -response relationship was flat in the 15-40 mg range, although there was a dose-dependent improvement in some subjective measures of sleep maintenance (e.g., sWASO).

Reviewer's Comments:

No clear dose/exposure-response relationship was observed for the objective measures of sleep and there was no significant difference in exposure between elderly (15 mg) and non-elderly patients (20 mg). Based on the reviewer's analyses, the dose of 15 mg would be reasonable starting dose for both elderly and non-elderly patients.

4.1.6 Biopharmaceutics Studies

P007: A 5-Period, Crossover, Single Dose Study to Evaluate the Comparative Pharmacokinetics of 4 Formulations of MK-4305

Objectives:

- To assess and compare the pharmacokinetics ($AUC_{0-\infty}$, C_{max}) of three new solid dose formulations (P1, P2 and P3) of MK-4305 compared to the reference MK-4305 oral-compressed tablet (Formulation T1) following single 60-mg oral doses administered to healthy subjects.*
- To assess the effect of a standard high-fat breakfast on the plasma PK parameters of MK-4305 (Formulation P1, P2 and P3) under fed versus fasted conditions following single oral dose (60 mg) administration to healthy subjects

Study Design	Randomized, Open-Label, Partially-Fixed Sequence, 5-Period Crossover study in healthy male subjects
Study Population	18 male healthy subjects, 22-45 years, 17 completed
Treatment Group	Treatment A: 60 mg T1 Treatment B: 60 mg P1 Treatment C: 60 mg P2 Treatment D: 60 mg P3
Dosage and Administration	In Periods 1 to 4, subjects received one of the four formulations (T1, P1, P2 or P3) as a single oral dose of 60 mg MK-4305 in the fasted state. In Period 5, 18 subjects were divided into 3 groups of six subjects. Each group received a single dose of Formulation P1, Formulation P2 or Formulation P3 as a single oral dose of 60 mg MK-4305 following a standard high-fat breakfast. There was a minimum 96 hour washout between study drug administrations in each treatment period for any subject.
PK Sampling: plasma	PK samples for suvorexant were collected at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 h post-dose
Analysis	Plasma: LC-MS/MS method for suvorexant Range: 1 to 1000 ng/mL
PK Assessment	$AUC_{0-\infty}$, AUC_{0-4hr}, C_{4hr}, AUC_{0-24hr}, C_{max}, T_{max}, and apparent terminal $t_{½}$
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* Food had an effect on the PK profile of the initial Phase I formulation T1: a high-fat meal decreased suvorexant $AUC_{0-\infty}$ by 7.0% and C_{max} by 46%. The data obtained from this study was used to support Phase II clinical development with a new biocomparable and stable formulation with a similar pharmacokinetic to the reference initial Phase I formulation (T1) with less food effect.

Bioanalytical Assay:

Plasma concentrations of suvorexant were determined using a validated LC-MS/MS method (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:

Seventeen of the 18 subjects who completed the study (and had complete PK data) were included in the primary analysis of pharmacokinetics. Subject AN0015 discontinued after the completion of Period 3 (before Periods 4, 60 mg P3 and 5, P3 fed). Due to the concomitant use of indomethacin to treat an AE, data from Period 3 was excluded from the PK analysis. This was the only use of concomitant therapy during the study. For AN 0015, only period 1 and 2 data were included in the PK analysis.

Summary of Pharmacokinetic Results Following Single-Dose AM Administration in the Fasted and Fed State of Three Formulations of 60 mg MK-4305 to Healthy Subjects

		Fasted			Fed			Fed/Fasted	
Formulation	PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
P1	$AUC_{0-\infty}$ (µM·hr) †	6	16.40	(10.18, 26.44)	6	19.30	(11.97, 31.10)	1.18	(1.01,1.37)
	C_{max} (µM) †	6	1.473	(1.079, 2.010)	6	1.208	(0.885, 1.648)	0.82	(0.57, 1.18)
	T_{max} (hr) §		2.0	1.0, 4.0		4.0	0.5, 6.0	--	--
	Half-life (hr) ‖		11.1	6.0		11.6	6.1	--	--
P2	$AUC_{0-\infty}$ (µM·hr) †	6	14.76	(10.15, 21.47)	6	15.70	(10.80, 22.84)	1.06	(0.86,1.32)
	C_{max} (µM) †	6	1.138	(0.823, 1.572)	6	1.401	(1.014, 1.936)	1.23	(1.13, 1.34)
	T_{max} (hr) §		2.0	1.0, 4.0		2.0	2.0, 4.0	--	--
	Half-life (hr) ‖		10.1	3.9		10.0	4.1	--	--
P3	$AUC_{0-\infty}$ (µM·hr) †	5	16.02	(13.29, 19.31)	5	16.38	(13.58, 19.74)	1.02	(0.90,1.16)
	C_{max} (µM) †	5	1.358	(1.014, 1.817)	5	1.356	(1.013, 1.815)	1.00	(0.87, 1.14)
	T_{max} (hr) §		1.0	1.0, 4.0		4.0	2.0, 4.0	--	--
	Half-life (hr) ‖		10.2	1.8		9.5	2.0	--	--

Summary of PK Results Following Single-Dose AM Administration in the Fasted State of Four Formulations of 60 mg MK-4305 to Healthy Subjects

		Formulation				
		T1 (N=17)	P1 (N=18)	P2 (N=18)	P3 (N=17)	rMSE‖
$AUC_{0-\infty}$ (μM•hr)	GM†	16.76	17.26	17.30	17.70	0.146
	(95% CI)	(13.26,21.19)	(13.66,21.80)	(13.70,21.85)	(14.00,22.38)	
	GMR† vs. T1		1.03	1.03	1.06	
	90% CI		(0.95, 1.12)	(0.95,1.12)	(0.97,1.15)	
	p-value 1, p-value 2‡ (α1=0.05, α2=0.05)§		(<0.0001, <0.0001)	(<0.0001, <0.0001)	(<0.0001, <0.0001)	
C_{max} (μM)	GM	1.672	1.531	1.199	1.278	0.204
	(95% CI)	(1.439,1.943)	(1.321, 1.775)	(1.035,1.390)	(1.100,1.485)	
	GMR vs. T1		0.92	0.72	0.76	
	90% CI		(0.82,1.03)	(0.64,0.81)	(0.68,0.86)	
	p-value 1, p-value 2‡ (α1=0.016, α2=0.016)§		(0.0002, <0.0001)	(0.3635, <0.0001)	(0.1082, <0.0001)	
AUC_{0-4hr} (μM•hr)	GM	4.34	4.07	3.57	3.84	0.190
	(95% CI)	(3.78,4.99)	(3.55,4.67)	(3.11,4.09)	(3.34,4.41)	
	GMR vs. T1		0.94	0.82	0.88	
	90% CI		(0.84,1.05)	(0.74,0.92)	(0.79,0.99)	
AUC_{0-24hr} (μM•hr)	GM	11.98	12.42	11.62	12.22	0.120
	(95% CI)	(10.36,13.87)	(10.74,14.37)	(10.05,13.44)	(10.56,14.14)	
	GMR vs. T1		1.04	0.97	1.02	
	90% CI		(0.97,1.11)	(0.91,1.04)	(0.95,1.09)	
C_{4hr} (μM)	GM	0.954	1.022	0.900	0.920	0.213
	(95% CI)	(0.839,1.084)	(0.902,1.158)	(0.794,1.019)	(0.810,1.045)	
	GMR vs. T1		1.07	0.94	0.97	
	90% CI		(0.95,1.21)	(0.84,1.07)	(0.85,1.09)	
T_{max} (hr)	Median	2.0	2.0	2.0	1.0	
	Min, Max	0.5, 4.0	1.0, 4.0	1.0, 4.0	1.0, 4.0	
Half-life (hr)	Harmonic Mean (jack-knife SD)	10.5 (4.6)	10.3 (4.1)	12.0 (4.5)	10.2 (3.7)	

† GM: Geometric mean computed from least squares estimate from a linear mixed model performed on the natural-log transformed values.

‡ P-value 1 tests the null hypothesis that the treatment ratio is less than 0.70 versus the alternative that the ratio is ≥ 0.70. P-value 2 tests the null hypothesis that the treatment ratio is greater than 1.43 versus the alternative that the ratio is ≤ 1.43.

§ Significance level for which p-value is compared to evaluate hypothesis (see Statistical Methods section for details). If p-value 1< α1 and p-value 2 < α2 for both $AUC_{0-\infty}$ and C_{max} then the hypothesis is met for that formulation.

‖ rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject %CV on the raw scale.

PK Summary:
Formulation P2 was chosen for Phase II/III for the following reasons:
P2 demonstrated less PK variability with fasted administration compared to P1.
P2 also exhibited smaller effects on T_{max} and acceptable variability of the fed/fasted ratios for $AUC_{0-\infty}$ and C_{max} following a high fat meal. The performance of P2 was in good agreement with the pH-insensitive nature of the formulation design for P2.

The comparison of the plasma concentration-time profiles of T1 and P2 formulations showed that they are similar, with a GMR for suvorexant $AUC_{0-\infty}$ = 1.03. Although there was a reduced GMR suvorexant C_{max} = 0.72 for P2 compared to T1, the reduced variability of the PK profile for $AUC_{0-\infty,}$ C_{max} and C_{4hr} for P2 under both fasted and fed conditions supports its selection as the suvorexant clinical formulation for Phase II/III.

Safety:

No serious clinical AEs were reported. The most frequently reported AEs were somnolence (100% of subjects) and dizziness (34% of subjects). One subject (AN0015), a 41 year old white man, discontinued due to an episode of gout 4 hours following a single dose of MK-4305 60 mg T1 in Period 3. The investigator rated this event as moderate in intensity and probably not related to study drug. The subject had a history of gout that was not revealed to the site during the screening.
No laboratory AEs were reported.

P020: A Study to Evaluate the Effect of Food on the Pharmacokinetics of MK-4305 (Suvorexant) in Healthy Subjects

Objective:
To compare the effect of a high-fat breakfast on the plasma pharmacokinetics of suvorexant final market image (FMI) tablet to pharmacokinetics in the fasted state after administration of a single oral dose of suvorexant 40 mg FMI tablet in healthy adult subjects.

Study Design	Open-label, 2-period, randomized, crossover study in healthy subjects
Study Population	9 male and 5 female healthy subjects, 19-48 years, 12 completed*
Treatment Group	Treatment A, a single oral dose of 40 mg suvorexant following an 8-hour fast. Treatment B, a single oral dose of 40 mg suvorexant following a standard high-fat breakfast
Dosage and Administration	Treatment A: 40 mg suvorexant in the fasted state Treatment B: 40 mg suvorexant in the fed state There was a minimum of 6 days between the doses in Periods 1 and 2
PK Sampling: plasma	PK samples for suvorexant were collected at pre-dose and at 0.5, 1, 2, 4, 6, 9, 12, 24, 48, 72 and 96 h post-dose
Analysis	Plasma: LC-MS/MS method for suvorexant Range: 1 to 1000 ng/mL
PK Assessment	$AUC_{0-\infty}$, C_{max}, T_{max}, and apparent terminal $t_{½}$
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

*Two subjects did not return for dosing in Period 2 due to lack of transportation and were excluded from the PK analysis.

Bioanalytical Assay:

Plasma concentrations of suvorexant were determined using a validated LC-MS/MS method (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:

In a previous phase 1 biocomparison study (Study P007) in a limited number of subjects (n=6), a small food effect on suvorexant pharmacokinetics was found following a single 60 mg dose (formulation PMF) administered following a high-fat breakfast relative to the fasted state, with an approximately 20% increase in C_{max} and no apparent effect on AUC. The current study was conducted to determine the effect of a standard high-fat breakfast on the pharmacokinetics of suvorexant following a single 40 mg dose of the FMI tablet

formulation, which is the maximum Phase III clinical dose. The P2 (FMI) formulation, used in the Phase 3 trials (P028, P029), was slightly modified from the P2 (PMF) formulation used in the Phase IIb study (P006) and Phase 3 Long Term Safety Study (P009). The FMI formulation is the commercial formulation; it is compositionally identical to the PMF (see QBR, Section 2.5.2 for details).

Results from this study indicate that there is no food effect on the overall suvorexant exposure at the highest proposed clinical dose. The GMR and 90% confidence interval [Fed / Fasted] for $AUC_{0-\infty}$ was 0.98 (0.91, 1.07).
Suvorexant absorption was largely unchanged, with GMR and 90% confidence interval (Fed / Fasted) for C_{max} of 1.09 (0.90, 1.33). There was a statistically significant increase in T_{max} from 1.5 hours in the fasted state to 3.0 hours in the fed state.

Summary of Pharmacokinetic Parameters of Suvorexant Following Administration of a Single Oral Dose of 40 mg Suvorexant (MK-4305) Following High-Fat Breakfast or Fasted States (N=12)

Pharmacokinetic Parameter	MK-4305 Fasted			MK-4305 Fed			(MK-4305 Fed/ MK-4305 Fasted)		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE ‡
$AUC_{0-\infty}$ (µM•hr) †	12	13.19	(10.60, 16.41)	12	12.99	(10.44, 16.16)	0.98	(0.91, 1.07)	0.113
C_{max} (µM) †	12	0.982	(0.769, 1.253)	12	1.067	(0.836, 1.362)	1.09	(0.88, 1.34)	0.279
T_{max} (hr) §,	12	1.5	(1.0, 4.0)	12	3.0	(1.0, 6.0)	1.5 #	(1.0, 3.0) #	--
Apparent Terminal $t_{1/2}$ (hr) ‖	12	10.9	3.4	12	11.6	3.6	--	--	--

† Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
§ Median, minimum, maximum.
# Hodges-Lehmann estimate and distribution-free 90% confidence interval for median difference ($t_{1/2}$).
‖ Harmonic mean, jack-knife SD.
‡ rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject %CV on the raw scale.
GM: Geometric mean, GMR: Geometric mean ratio, CI: Confidence interval

Conclusion: The results from this study indicate that there is no food effect on the overall suvorexant exposure, however the Tmax was increased by 1.5 h with food. For faster sleep onset, suvorexant should not be administered with or immediately after a meal.

Comment: The lower strengths to be developed (5 and 10 mg) should have proportional composition and other CMC supportive info in order to claim that the food effect on 40mg can be applied to them.

Safety:

Suvorexant was generally well tolerated in the healthy young men and women in this study. All clinical adverse experiences were considered to be mild or moderate. Mild somnolence, reported by 13 subjects, was the most frequently reported AE. No serious clinical, laboratory, other significant adverse experiences were reported during the study.

P041: A Bio-Comparison Study of Suvorexant (MK-4305) Formulation Batches in Healthy Subjects

Objectives:

- To assess the pharmacokinetics ($AUC_{0-\infty}$, C_{max}) and to evaluate the comparative bioavailability of 3 test formulations (A, D, E) of suvorexant compared to the reference suvorexant oral tablet (Formulation C) following single 40-mg oral doses administered to healthy subjects.*
- To compare the in vitro disintegration time of suvorexant to in vivo plasma pharmacokinetics ($AUC_{0-\infty}$ and C_{max}) following single 40-mg oral doses administered to healthy subjects in order to establish an in vitro - in vivo correlation (IVIVC).*

Study Design	Open-label, 4-period, Crossover Study
Study Population	6 male and 6 female healthy subjects, 31-56 years, all 12 completed the study
Treatment Group	In Periods 1 to 4: four formulations* of 40 mg suvorexant administered as single doses under fasted conditions. 1. Formulation A: (b) (4) 2. Formulation C (Current Phase 3 Reference Clinical Supplies): (b) (4) 3. Formulation D: (b) (4) 4. Formulation E: (b) (4)
Dosage and Administration	Four formulations of 40 mg suvorexant administered as single doses under fasted conditions.
PK Sampling: plasma	PK samples for suvorexant were collected at pre-dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48 and 72 h post-dose
Analysis	Plasma: LC-MS/MS method for suvorexant Range: 1 to 1000 ng/mL
PK Assessment	$AUC_{0-\infty}$, AUC_{0-1h}, AUC_{0-2h} , C_{max}, T_{max}, and apparent terminal $t_{½}$
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* The formulations had the same drug and excipient content (b) (4)

Bioanalytical Assay:

Plasma concentrations of suvorexant were determined using LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:

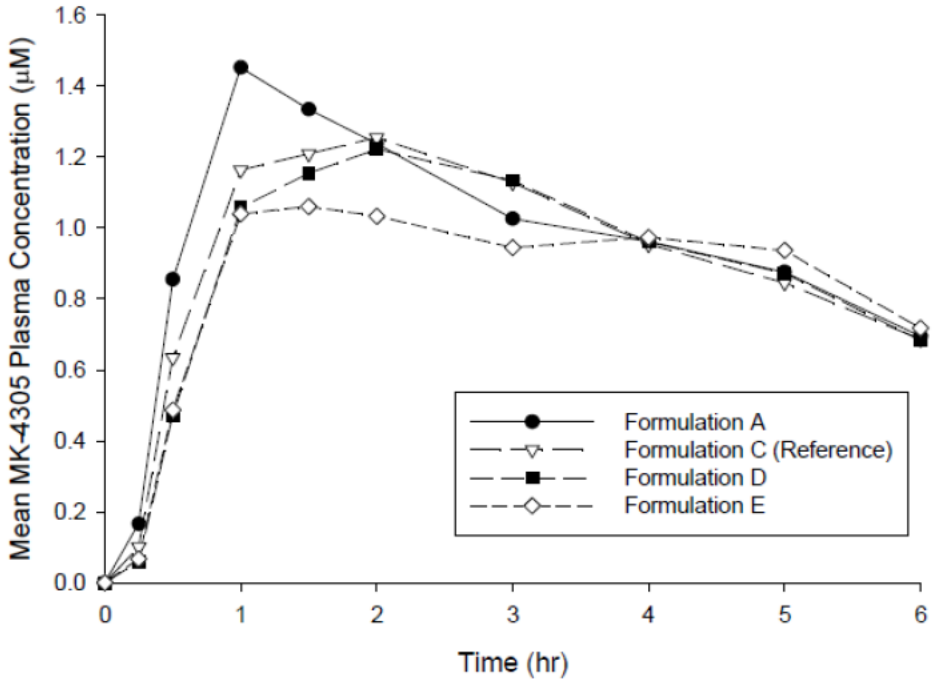
The summary statistics for suvorexant PK parameters to assess the biocomparability of each of the test formulations relative to the reference is presented below.
The overall exposure ($AUC_{0-\infty}$) was generally similar for each of the test formulations relative to reference. The observed mean C_{max} for the test formulations [redacted] (b) (4) [redacted] (D, E) were ~13-14% less than that for the mean of the reference (C), whereas the observed mean C_{max} for the test formulation [redacted] (b) (4) [redacted] (A) was ~7% greater than that for the mean of the reference (C).

Statistical Analysis of Suvorexant Pharmacokinetics Following Single Dose Administration of 40 mg MK-4305 as Three Test Formulations (A, D, E) and Reference Phase III Formulation (C) to Healthy Subjects (N=12)

Pharma-cokinetic Parameter	Geometric Mean † for Treatment (% CV)				Geometric Mean (90% CI for GMR) for Treatment Ratio		
	Formulation A	Formulation C	Formulation D	Formulation E	A/C	D/C	E/C
$AUC_{0-\infty}$ (µM·hr)	21.56 (24.3)	22.11 (23.5)	21.32 (23.6)	22.64 (18.5)	0.98 (0.89, 1.07)	0.96 (0.88, 1.06)	1.02 (0.93, 1.12)
C_{max} (µM)	1.59 (35.1)	1.48 (23.2)	1.29 (40.0)	1.28 (14.7)	1.07 (0.90, 1.28)	0.87 (0.73, 1.04)	0.86 (0.72, 1.03)
AUC_{0-4hrs} (µM·hr)	4.09 (30.5)	3.95 (22.5)	3.45 (36.2)	3.43 (22.8)	1.04 (0.90, 1.19)	0.87 (0.76, 1.01)	0.87 (0.75, 1.00)
T_{max} (hr) ‡	1.3 [0.5,5.0]	1.8 [1.0,3.0]	1.5 [1.0,5.0]	1.3 [1.0,5.0]	--	--	--
Apparent $t_{1/2}$ (hr) §	14.9 (4.8)	15.1 (3.6)	15.0 (5.1)	15.9 (5.0)	--	--	--

† Back-transformed least squares means from mixed effects model performed on natural log-transformed values (% CV).
‡ Median [Min, Max]
§ Harmonic Mean (Jack-Knife Standard Deviation)

Mean Plasma Concentration Profiles over Time (0 - 6 hours) for Suvorexant Pharmacokinetics Following Single Dose Administration of 40 mg MK-4305 as Three Test Formulations (A, D, E) and Reference Phase III Formulation (C) to Healthy Subjects (N=12)



Note: This study was conducted (b) (4) The IVIVC report was reviewed by ONDQA.

Safety:

There were no serious clinical and laboratory AEs and no subjects discontinued due to AE. Three subjects reported a total of 6 clinical adverse experiences. Subject AN 0007 experienced sleep paralysis approximately 1 hour following a single 40 mg oral dose of suvorexant (Formulation C). The investigator rated this event as moderate in intensity and definitely related to study drug. The duration of this event was 7 minutes.
Note: The suvorexant exposure (AUC and C_{max}) after administration of Formulation C to this subject was comparable to that of the rest of the subjects.

Of the remaining five adverse experiences: all were considered mild in intensity; 3 were considered possibly drug-related (two headaches and one nightmare).

P042: A Trial to Evaluate the Pharmacokinetics and the Effect of Food on Pharmacokinetics of Suvorexant (MK-4305) Final Market Image (FMI) Tablet in Japanese

Objective:
To assess the effect of a standard Japanese breakfast on suvorexant pharmacokinetic parameters after the administration of single 40 mg oral dose of suvorexant (FMI tablet) in healthy Japanese subjects

Study Design*	Open-label, 2-period, randomized, crossover study in healthy Japanese subjects*
Study Population	6 male and 6 female healthy Japanese subjects, 21-48 years, all 12 completed the study
Treatment Group	Treatment A, a single oral dose of 40 mg suvorexant following an 8-hour fast. Treatment B, a single oral dose of 40 mg suvorexant following a standard Japanese breakfast
Dosage and Administration	Treatment A: 40 mg suvorexant in the fasted state Treatment B: 40 mg suvorexant in the fed state There was a minimum of 6 days between the doses in Periods 1 and 2
PK Sampling: plasma	PK samples for suvorexant were collected at pre-dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72 and 96 h post-dose
Analysis	Plasma: LC-MS/MS method for suvorexant Range: 1 to 1000 ng/mL
PK Assessment	$AUC_{0-\infty}$, C_{max}, T_{max}, and apparent terminal $t_{½}$
PD Assessment	none
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

* This study was not conducted as a randomized study. Treatments in a given treatment period were to be randomly assigned according to a computer-generated allocation schedule and both males and females should have been allocated to both treatment sequences.
However, in this study all males were assigned to the AB sequence (fasted Period 1 and fed Period 2), and all females to the BA sequence (fed Period 1 and fasted Period 2) because a computer allocation schedule was not requested in error.

Bioanalytical Assay:

Plasma concentrations of suvorexant were determined using LC-MS/MS methods (method DM-909). The assay performance during the validation was acceptable; details of the validation are presented in Section 2.6.1 in QBR.
The assay performance during the analysis of the plasma samples was acceptable.

Pharmacokinetic Results:

The summary statistics for suvorexant PK parameters following administration of a single dose of 40 mg suvorexant with a standard Japanese breakfast or in the fasted state to Japanese healthy subjects is provided below. The geometric mean ratio (fed / fasted)

and 90% confidence intervals for $AUC_{0-\infty}$ and C_{max} were 1.10 (1.02, 1.19) and 1.23 (1.02, 1.49), respectively. Median T_{max} was 3.0 hours after a standard Japanese breakfast and 1.5 hours in the fasted state. Mean apparent terminal $t_{1/2}$ was generally unchanged after administration with a standard Japanese breakfast compared to administration in the fasted state.

Summary of Suvorexant Plasma PK Parameter Values and Ratios (Fed/Fasted) Following Administration of a 40 mg Single Oral Dose of Suvorexant to Japanese Healthy Subjects in the Fasted State and Following a Standard Japanese Breakfast (N=12)

	MK-4305 Fasted		MK-4305 Fed		Ratio (MK-4305 Fed MK-4305 Fasted)		Pseudo Within Subject % CV ‖
PK Parameter	GM	95 % CI	GM	95 % CI	GMR	90 % CI	
$AUC_{0-\infty}$(µM•hr)†	12.15	(10.97, 13.46)	13.37	(11.62, 15.40)	1.10	(1.02, 1.19)	10.1
C_{max} (µM)†	1.007	(0.858, 1.182)	1.244	(1.053, 1.470)	1.23	(1.02, 1.49)	25.7
T_{max} (hr)‡	1.5	[1.0, 3.0]	3.0	[1.0, 6.0]	1.0#	(0.0, 2.0)#	.
Apparent terminal $t_{1/2}$(hr)§	10.0	1.0	10.7	1.8	.		.

† Back-transformed least-squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
‡ Median; minimum, maximum.
# Hodges-Lehmann estimate and distribution-free 90% confidence interval for median difference (fed -fast).
§ Harmonic mean; jack-knife SD.
‖ Pseudo Within-Subject % CV = 100 * ($\sqrt{(\sigma^2_A + \sigma^2_B - 2\sigma_{AB})/2}$), where σ^2_A and σ^2_B are the estimated variances on the log scale for the two treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed effects model.
GM: Geometric Mean; CI: Confidence Interval; GMR= Least-Squares Geometric Mean Ratio

Since the study was not conducted as a randomized study (allocation was conducted with all males assigned to AB sequence and all females to BA sequence) (see section 9.4.3, the effects of gender and treatment sequence were completely confounded and could not clearly be separated in the statistical analysis. To evaluate the potential influence of the confounding, additional stratified analysis of $AUC_{0-\infty}$, C_{max} and T_{max} was conducted. The fed/fasted ratios between male and female subjects were largely comparable. The median difference in Tmax between administration with a standard Japanese breakfast or in the fasted state was 1.0 for both male and female subjects.

Summary of Pharmacokinetic Parameters of Suvorexant Following Administration of a Single Oral Dose of a 40 mg Single Oral Dose of Suvorexant to Japanese Healthy Subjects in the Fasted State and Following a Standard Japanese Breakfast by Gender

PK Parameter	Gender	MK-4305 Fasted			MK-4305 Fed			Ratio (MK-4305 Fed /MK-4305 Fasted)		Pseudo Within Subject % CV ‖
		N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI	
$AUC_{0-\infty}$ (μM•hr)†	Male	6	12.10	(9.67, 15.13)	6	12.59	(9.83, 16.14)	1.04	(0.93, 1.17)	9.8
	Female	6	12.21	(11.06, 13.49)	6	14.20	(11.29, 17.86)	1.16	(1.03, 1.32)	10.6
C_{max} (μM)†	Male	6	1.06	(0.852, 1.324)	6	1.25	(0.926, 1.678)	1.17	(0.92, 1.50)	21.0
	Female	6	0.96	(0.703, 1.299)	6	1.24	(0.957, 1.610)	1.30	(0.92, 1.83)	29.6
T_{max} (hr)‡	Male	6	1.0	[1.0, 3.0]	6	2.5	[2.0, 6.0]	1.0#	(0.0, 3.0)#	.
	Female	6	2.0	[1.0, 3.0]	6	3.0	[1.0, 4.0]	1.0#	(0.0, 2.0)#	.

† Back-transformed least-squares mean and confidence interval from mixed effects model performed on natural log-transformed values.

‡ Median; minimum, maximum.

Hodges-Lehmann estimate and distribution-free 90% confidence interval for median difference (fed -fast).

‖ Pseudo Within-Subject % CV = 100 * ($\sqrt{(\sigma^2_A + \sigma^2_B - 2\sigma_{AB})/2}$), where σ^2_A and σ^2_B are the estimated variances on the log scale for the two treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed effects model.

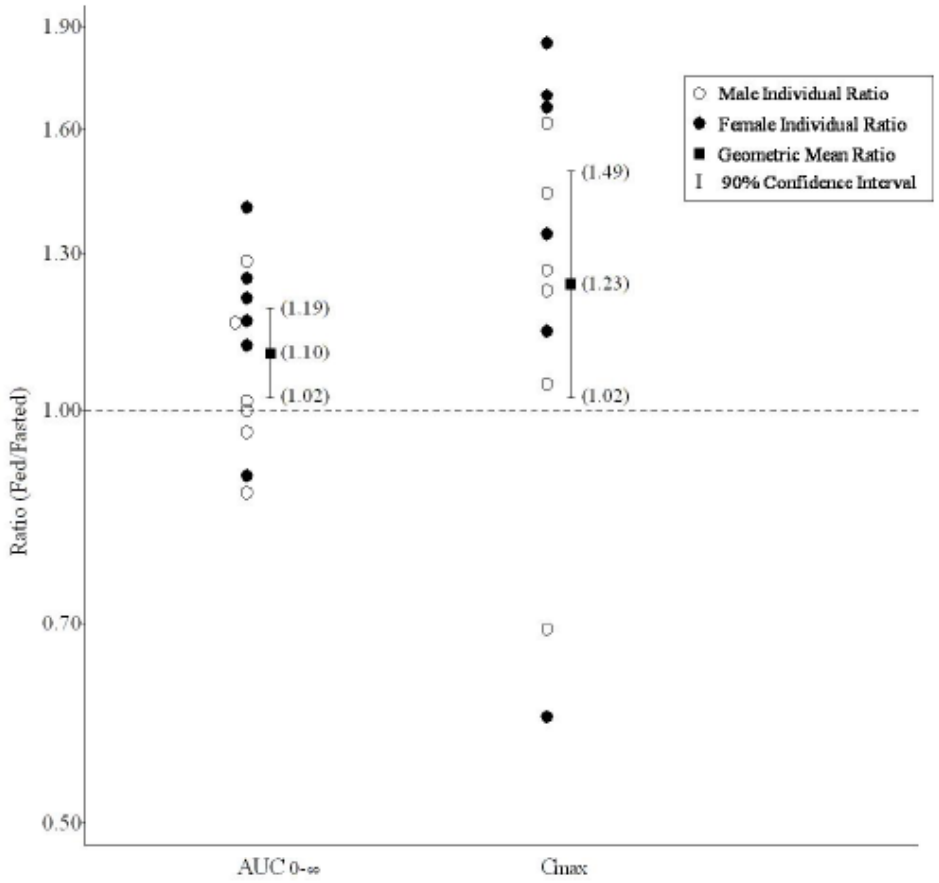
GM: Geometric Mean; CI: Confidence Interval; GMR= Least-Squares Geometric Mean Ratio

In addition, PSR (Proportion of Similar Responses) method was used to quantitatively assess the overlap between male and female subjects for $AUC_{0-\infty}$ and C_{max} after fed or fasted administration. PSR can range from 0 to 1, with a value of 0 indicating no overlap and a value of 1 indicating complete overlap of distributions. On $AUC_{0-\infty}$, the values of PSR were 0.97 for fasted and 0.79 for fed. On C_{max}, the values of PSR were 0.83 for fasted and 0.99 for fed, suggesting a largely overlapping distribution of data between males and females within a treatment.

PSR was also applied to assess the overlap between males and females on individual ratios of $AUC_{0-\infty}$ and C_{max}, the values of PSR were 0.70 for $AUC_{0-\infty}$ and 0.88 for C_{max}, suggesting high degree of overlap between males and females subjects.

According to the sponsor, although this study was not conducted in a randomized manner, the above analyses show that the GMs and GMRs of PK parameters are similar across gender, thus supporting the validity of the overall treatment comparison.

Individual Suvorexant $AUC_{0-\infty}$ and C_{max} Ratios (Fed/Fasted), Geometric Mean Ratios, and 90% Confidence Intervals Following Single Oral Doses of Suvorexant 40mg in Japanese Healthy Subjects (N=12)



Safety:

Suvorexant was generally well tolerated in the healthy young Japanese men and women in this study. No serious clinical, laboratory, other significant adverse experiences were reported during the study. There were no discontinuations due to an adverse experience. Mild somnolence (100% of subjects) was the most frequently reported adverse experience. Onset of the somnolence episodes generally occurred within 2 hours following suvorexant administration and resolved within 22 hours. The majority of the somnolence episodes had duration of less than 8 hours.
The incidence of somnolence was similar for both the fed and fasted treatments.

1.7 *IN VITRO* STUDIES

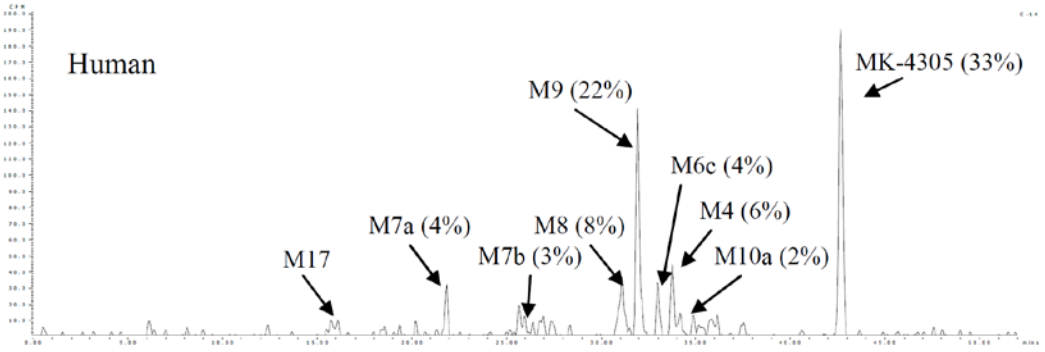
Study PK013: In Vitro Metabolite Profiling of MK-4305 in Rat, Dog, and Human
Objective: to compare the metabolic profiles of MK-4305 in different species
Method:
Microsomes: Pooled liver microsomes from male Sprague-Dawley rat (n=68), male beagle dog (n=8), and human (mixed gender; n=150) were used. [^{14}C]MK-4305 (10 µM) was incubated at 37°C in a final volume of 0.5 mL of 0.1 M potassium phosphate buffer (pH 7.4) containing 1 mg/mL (dog, human) or 0.25 mg/mL (rat) microsomal protein, and 1 mM NADPH. Reactions were terminated by the addition of ice cold acetonitrile at 30 minutes for rat and 60 minutes for dog and human. Samples were centrifuged and an aliquot of supernatant was injected for LC-RAM-MS (LC-MS/MS-Radiometric Analysis).
Hepatocytes: Cryopreserved pooled primary hepatocytes from male Sprague-Dawley rat (n=14), dog (n=3), and human (n=10) were used. [^{14}C]MK-4305 (10 µM) was incubated at 37°C for 1 hour with 1 million cells/mL (dog and human) or 0.5 million cells/mL (rat) hepatocytes in William's E medium fortified with L-glutamine (0.5 mL total volume). After incubation, samples were centrifuged and an aliquot of supernatant was analyzed by LC-RAM-MS analysis.

Results: Rat hepatocytes and liver microsomes displayed the highest rate of metabolism compared with dog and human. The major routes of metabolism in liver microsomes from all three species were oxidative, with metabolites formed through hydroxylation at the benzylic carbon of the triazolebenzyl moiety (M9, L-002015883), monooxidation of the chlorobenzoxazole group (M8) and hydroxylation at the diazapan moiety (M10a, L-002083792). Other metabolic pathways included further oxidation of M9 to a carboxylic acid (M4) and di- and tri-hydroxylation (M6a, c, M7a, b, and M13b).

Table 1. Summary of [^{14}C]MK-4305 Metabolites Formed in SD Rat, Dog, and Human Liver Microsomes

Metabolite	Microsomes		
	Rat	Dog	Human
M4	X		X
M6a	X		
M6c		X	X
M7a		X	X
M7b	X	X	X
M8	X	X	X
M9	X	X	X
M10a	X	X	X
M10b	X		
M13b	X		
M16	X	X	
M17		X	X

Figure 1. Representative Radiochromatograms of [^{14}C]MK-4305 (10 µM) Incubated in the Presence of Human Liver Microsomes



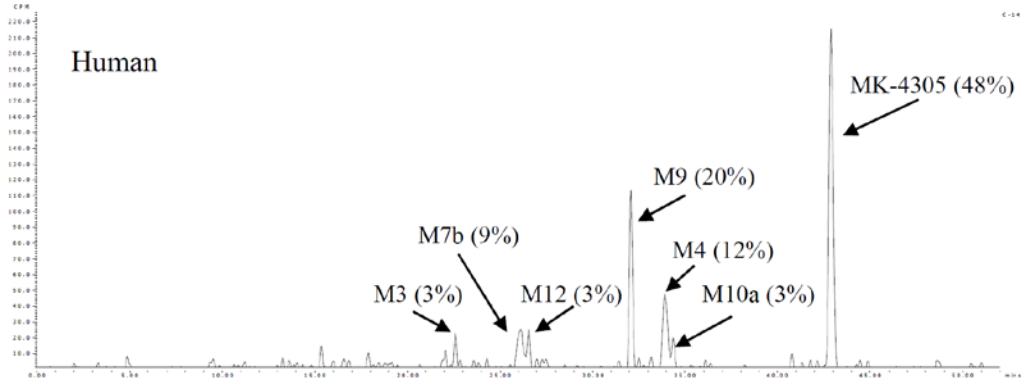
(The unit of y-axis is radioactivity (cpm), ranging from 10 to 200, with an increment step of 10. The unit of x-axis is minute, ranges from 5 to 50, with an increment step of 5.)

In human hepatocytes, the major metabolites observed were the oxidative metabolite M9, M4, and a di-oxidation (M7b). Additional metabolites detected in rat and dog hepatocytes included a glucuronide of M9 (M11) and an apparent water addition (M20).

Table 2. Summary of [^{14}C]MK-4305 Metabolites Formed in Sprague-Dawley Rat, Dog, and Human Hepatocytes

Metabolite	Hepatocytes		
	Rat	Dog	Human
M3		X	X
M4	X	X	X
M6a	X		
M6c	X		
M7b		X	X
M9	X	X	X
M10a	X	X	X
M11		X	
M12	X	X	X
M13b	X		
M20	X		

Figure 2. Representative Radiochromatograms of [^{14}C]MK-4305 (10 µM) Incubated in the Presence of Human Hepatocytes



(The unit of y-axis is radioactivity (cpm), ranging from 10 to 220, with an increment step of 10. The unit of x-axis is minute, ranges from 5 to 50, with an increment step of 5. M3 is a glucuronide conjugate of M8. M12 is a glucuronide conjugate of M10a.)

Study PK002: In Vitro Drug Metabolism Studies of MK-4305, L-002015883 (M9), and L-002440877 (M17)

Note: This study is composed of a number of sub-studies with diversified objectives and designs. Therefore, the review will be written separately for each sub-study.

1. CYP Reaction Phenotyping

Objective: To identify the human CYP isoforms mediating the metabolism of MK-4305

Methods:

Immuno-inhibition. Study was conducted with specific anti-CYP1A2, 3A4/5, 2C8/9/19, and 2D6 monoclonal antibodies. Human liver microsomes (0.5 or 0.1 mg/mL protein) were pre-incubated with the monoclonal antibodies for 15 minutes at room temperature. [^{14}C]MK-4305 (final concentrations at 2 and 20 µM) and NADPH (1 mM) were then added and the reactions were terminated after 15 and 30 minutes, respectively, by adding cold acetonitrile. The samples were centrifuged and the supernatants were analyzed by HPLC with simultaneous mass spectral and radiometric monitoring. The column effluent was mixed with scintillation cocktail for radiochemical detection. The parent and metabolite radioactive peaks were integrated for each sample and compared with the control (vector antibody).

Recombinant CYPs. Recombinant CYP enzymes (15 pmol/mL for CYP3A4 and 35 pmol/mL for 2C19, 2C9, 2C8, 2D6, and 1A2) were pre-incubated with 1 µM MK-4305 in 100 mM potassium phosphate buffer and 10 µM $MgCl_2$ (pH 7.4) at 37°C for 5 minutes before adding 1 mM NADPH. After the addition of NADPH, the reactions were stopped at 0, 5, 10, 20, and 40 minutes with the addition of acetonitrile containing labetalol (internal standard). The samples were centrifuged and the supernatants were subject to HPLC-MS/MS analysis by determining the peak area ratios of MK-4305 to the internal standard.

Chemical Inhibitors. Human liver microsomes (0.5 mg/mL) were pre-incubated with ketoconazole (1 µM, CYP3A4 inhibitor) or N-3-benzyl-phenobarbital (5 µM, CYP2C19 inhibitor) and 2 or 20 µM MK-4305 at 37°C for 5 minutes before the addition of 1 mM NADPH. After the addition of NADPH, the reactions were stopped at 40 minutes with the addition of acetonitrile containing labetalol. The samples were analyzed by HPLC-MS/MS. Peak area ratios of metabolites M9 (L-002015883) and M10a (L-002083792) to the internal standard were determined.

Formation of M9. Enzyme kinetic studies were conducted using pooled human liver microsomes (HLM), recombinant CYPs 3A4, 3A5, and 2C19. A serial of MK-4305 concentrations, ranging from 0.02 µM to 100 µM, were used. The rate of M9 formation was linear with regards to both the enzyme concentration and incubation time. The enzyme concentrations for HLM, rCYPs 3A4, 3A5, and 2C19 were 0.04 mg/mL, 20, 20,

and 120 pmol/mL, respectively. The incubation time was 10 min for HLM, rCYPs 3A4 and 3A5, and 20 min for rCYP2C19. 1 mM NADPH was used in the incubations. The formation of M9 was monitored using the HPLC-MS/MS method as described above.

Results:
Immuno-inhibition. Three oxidative metabolites (M8, M9, and M10a) were formed in human liver microsomes, with M9 (L-0021015883) being the predominant one. Anti-CYP3A4/5 monoclonal antibody inhibited formation of M8 and M10a by 82-100% at 2 and 20 µM MK-4305 concentrations. Formation of M9 was inhibited 80% and 65% by anti-CYP3A4/5 antibody at 2 and 20 µM MK-4305 concentrations, respectively, while anti-CYP2C8/9/19 antibody inhibited M9 formation by up to 30% at the two substrate concentrations. The anti-CYP1A2 and 2D6 antibodies had little effect.

Table 3. Inhibition of [^{14}C]MK-4305 (20 µM) Metabolite Formation (mean ± SD, n=3) in Human Liver Microsomes (0.5 mg/mL) in the Presence of Inhibitory Antibodies

Inhibitory Antibodies	% Inhibition (% Control ± SD)		
	M8	M9	M10a
Anti-CYP1A2	NI	NI	NI
Anti-CYP2C	8 ± 10	31 ± 9	13 ± 22
Anti-CYP2D6	NI	NI	NI
Anti-CYP3A	82 ± 11	65 ± 6	92 ± 5

NI: no inhibition.

Table 4. Inhibition of [^{14}C]MK-4305 (2 µM) Metabolite Formation (mean ± SD, n=3) in Human Liver Microsomes (0.1 mg/mL) in the Presence of Inhibitory Antibodies

Inhibitory Antibodies	% Inhibition (% Control ± SD)		
	M8	M9	M10a
Anti-CYP1A2	NI	6 ± 1	10 ± 9
Anti-CYP2C	NI	NI	11 ± 9
Anti-CYP2D6	NI	NI	NI
Anti-CYP3A	100 ± 0	80 ± 4	92 ± 7

Recombinant CYPs. To identify the specific CYP isoforms responsible for the oxidation of MK-4305, the substrate turnover in several recombinant CYP enzymes was measured. Only CYP3A4 and 2C19 demonstrated measurable turnover of MK-4305. No measurable turnover was observed with CYP2C8, 2C9, 2D6, or 1A2.

Chemical inhibitors. Ketoconazole inhibited formation of M9 and M10a by 82-85% at 2 µM of MK-4305 concentration and 70-74% at 20 µM. N-3-benzyl-phenobarbital inhibited the formation of M9 and M10a by 2-6% at 2 µM, and 20-28% at a 20 µM concentration of MK-4305.

Table 5. Inhibition of MK-4305 Metabolite Formation (mean ± SD, n=3) in Human Liver Microsomes (0.5 mg/mL) in the Presence of Chemical Inhibitors

Chemical Inhibitors	MK-4305 Concentration	% Inhibition (% Control ± SD)	
		M9	M10a
Ketoconazole	2 µM	82 ± 4	85 ± 2
	20 µM	70 ± 4	74 ± 3
N-3-benzyl-phenobarbital	2 µM	NI	NI
	20 µM	28 ± 4	20 ± 3

Taken together, these results indicate that MK-4305 is primarily metabolized by CYP3A4/5 with some contribution from CYP2C19 at higher MK-4305 concentrations.

Formation of M9 Kinetic analysis (Eadie-Hofstee plots) revealed that the formation rates of M9 were not consistent with a Michaelis-Menton kinetics model, but were better described using a substrate inhibition model for HLM, rCYP3A4, and rCYP2C19, and an auto-activation (Hill) model for rCYP3A5. Based on these models, the Km values for M9 formation was 1.7, 0.9, 2.5, and 8.0 µM for HLM, rCYPs 3A4, 3A5, and 2C19, respectively. The substrate inhibition constant Ks,i ranged from 19 to 600 µM for HLM, rCYPs 3A4, and 2C19, and the inhibition is unlikely to have *in vivo* consequences at the clinically efficacious dose.

2. Inhibition of CYP Mediated Reactions in Human Liver Microsomes

Objective: To investigate the inhibition potential of MK-4305 and its metabolites on major CYP isoforms

Methods:

Reversible Inhibition Studies with MK-4305 The studies were conducted in pooled human liver microsomes (0.25 mg/mL) at 37°C in a 0.2 mL reaction mixture containing the appropriate CYP probe substrate and MK-4305 (0.05 to 100 µM), 100 mM potassium phosphate buffer (pH 7.4), 3 mM $MgCl_2$, and an NADPH-generating system (3 mM glucose 6-phosphate, 1 mM NADP, and 1.4 units/mL glucose 6-phosphate dehydrogenase). The substrate concentrations (near to their Km values) and incubation times were as follows: phenacetin *O*-deethylation (100 µM, 10 min), bupropion hydroxylation (180 µM, 10 min), paclitaxel 6α-hydroxylation (10 µM, 10 min), diclofenac 4'-hydroxylation (10 µM, 10 min), *S*-mephenytoin 4'-hydroxylation (30 µM, 20 min), dextromethorphan *O*-demethylation (10 µM, 20 min), and testosterone 6β-hydroxylation (50 µM, 10 min). The resulting samples were subjected to LC-MS/MS analysis after sample preparation by acetonitrile precipitation.

CYP Isoform	Substrate	Maker Metabolite	Internal Standard
CYP1A2	phenacetin	acetaminophen	4′-hydroxybutyranilide
CYP2B6	bupropion	hydroxybupropion	propranolol
CYP2C8	paclitaxel	6α-hydroxypaclitaxel	baccatin III
CYP2C9	diclofenac	4′-hydroxydiclofenac	flufenamic acid
CYP2C19	S-mephenytoin	4′-hydroxymephenytoin	phenytoin
CYP2D6	dextromethorphan	dextrorphan	levallorphan
CYP3A4	testosterone	6β-hydroxytestosterone	cortisone

Reversible Inhibition Studies with L-002015883 (M9) The IC_{50} values were determined after incubation with a single concentration of isoform-selective substrate and varying concentrations of positive control inhibitor or M9. The substrate concentrations used were similar to published Michaelis constants (Km) for each of the respective reactions. The reaction mixtures (200 µL final volume) contained approximately 100 mM potassium phosphate buffer (pH 7.4), 3.14 mM $MgCl_2$, 2.82 mM G6P, 1.25 mM NADP, 1.34 units G6PDH/mL, and 0.25 mg microsomal protein/mL.

Assay	Substrate	Substrate Concentration (µM)	Reaction Time (min)
CYP1A2-P	Phenacetin	100	10
CYP2B6-B	Bupropion	180	10
CYP2C8-A	Amodiaquine	4	3
CYP2C9-D	Diclofenac	10	10
CYP2C19-M	(*S*)-Mephenytoin	30	20
CYP2D6-D	Dextromethorphan	10	20
CYP3A4-M	Midazolam	3	3
CYP3A4-T	Testosterone	50	10

The samples were analyzed by LC-MS/MS as below.

Assay	Analyte	Ionization Mode	Transition (*m/z*)→(*m/z*)	Internal Standard	Transition (*m/z*)→(*m/z*)
CYP1A2-P	Acetaminophen	Positive	152.1→110.1	Acetaminophen-d_4	156.1→114.1
CYP2B6-B	Hydroxybupropion	Positive	256.1→139.0	Hydroxybupropion-d_6	262.1→139.0
CYP2C8-A	*N*-Desethylamodiaquine	Positive	328.1→283.1	*N*-Desethylamodiaquine-d_5	333.2→283.1
CYP2C9-D	4′-Hydroxydiclofenac	Negative	310.0→266.0	4′-Hydroxydiclofenac-d_4	316.0→272.0 (A+2 isotope)
CYP2C19-M	4′-Hydroxymephenytoin	Positive	235.1→150.1	4′-Hydroxymephenytoin-d_3	238.1→150.1
CYP2D6-D	Dextrorphan	Positive	258.2→157.1	Dextrorphan-d_3	261.2→157.1
CYP3A4-M	1′-Hydroxymidazolam	Positive	342.1→203.1	1′-Hydroxymidazolam-$^{13}C_3$	347.1→208.1 (A+2 isotope)
CYP3A4-T	6β-Hydroxytestosterone	Positive	305.3→269.2	6β-Hydroxytestosterone-d_3	308.3→272.2

Reversible Inhibition Studies with L-002440877 (M17) The studies were conducted in pooled human liver microsomes (0.2 mg/mL) at 37°C in a 50 µL reaction mixture containing the appropriate CYP probe substrate and L-002440877 (0.05 to 100 µM), 100 mM potassium phosphate buffer (pH 7.4), 3.25 mM $MgCl_2$, and an NADPH-generating system (3 mM glucose 6-phosphate, 1.3 mM NADP, and 1.4 units/mL glucose 6-phosphate dehydrogenase). The substrate concentrations (close to their Km values) and incubation times were as follows: diclofenac (20 µM, 10 min), dextromethorphan (40 µM, 10 min), and testosterone (100 µM, 10 min). The resulting samples were subjected to LC-MS/MS analysis after sample preparation by acetonitrile precipitation.

CYP Isoform	Substrate	Maker Metabolite	Internal Standard
CYP2C9	diclofenac	4′-hydroxydiclofenac	$^2H_4$-4′-hydroxydiclofenac
CYP2D6	dextromethorphan	dextrorphan	$^2H_3$-dextrorphan
CYP3A4	testosterone	6β-hydroxytestosterone	$^2H_7$-6β-hydroxytestosterone

Time-Dependent Inhibition of CYP3A4 with MK-4305 and L-002015883 (M9) Pooled human liver microsomes (1 mg/mL) were pre-incubated at 37°C with 2, 5, 10, 20, 30, 50, and 100 µM of MK-4305 or 10 and 50 µM L-002015883 in 100 mM potassium phosphate buffer (pH 7.4) with 1 mM EDTA, 6 mM $MgCl_2$, and an NADPH-generating system for a duration ranging from 5 to 30 min. The incubation mixtures were diluted 10-fold with the same buffer containing 250 µM testosterone and an NADPH-generating system. The incubation was continued for an additional 10 min. The resulting samples were subjected to LC-MS/MS analysis to measure the formation of 6β-hydroxy testosterone. The first order rate constants (*kobs*) for inactivation at various concentrations were calculated from the negative slope of the lines by using linear regression analysis of the logarithm of the remaining activity as a function of time. The *kinact* and K_I values for MK-4305 were calculated by nonlinear regression analysis.

Results:
MK-4305 showed weak reversible inhibition of CYP1A2, 2B6, 2C8, 2C9, and 2D6 mediated reactions with IC_{50} values of 74, 64, 15, 15, and 17 µM, respectively. MK-4305 was a moderate inhibitor of CYP2C19 and 3A4 with IC_{50} values of 5.3 and 4.0 µM, respectively.

Table 6. Effect of MK-4305 on Cytochrome P450 Marker Enzyme Activities in Pooled Human Liver Microsomes (Reversible Inhibition)

CYP	Reaction	Absolute IC_{50} (µM)[a]	
		Control Inhibitor	MK-4305
1A2	Phenacetin *O*-Deethylation	0.015 (7,8-benzoflavone)	74
2B6	Bupropion Hydroxylation	0.11 (MBA[b])	64
2C8	Paclitaxel 6α-Hydroxylation	0.101(montelukast)	15
2C9	Diclofenac 4'-Hydroxylation	0.59 (sulfaphenazole)	15
2C19	*S*-Mephenytoin 4'-Hydroxylation	0.12 (NBPB[c])	5.3
2D6	Dextromethorphan *O*-Demethylation	0.099 (quinidine)	17
3A4	Testosterone 6β-Hydroxylation	0.031 (ketoconazole)	4.0

a. IC_{50} values represent the average value from duplicate determinations.
b. MBA: *N*-(α-methylbenzyl)-1-aminobenzotriazole.
c. NBPB: (-)-*N*-3-Benzyl-phenobarbital.

Similarly, M9 (L-002015883) was a weak reversible inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6, with IC_{50} values of >100, 44, 37, 47, 35, and 39 µM, while it was a moderate reversible inhibitor of CYP3A4 (IC_{50} = 11 µM for testosterone and 26 µM for midazolam).

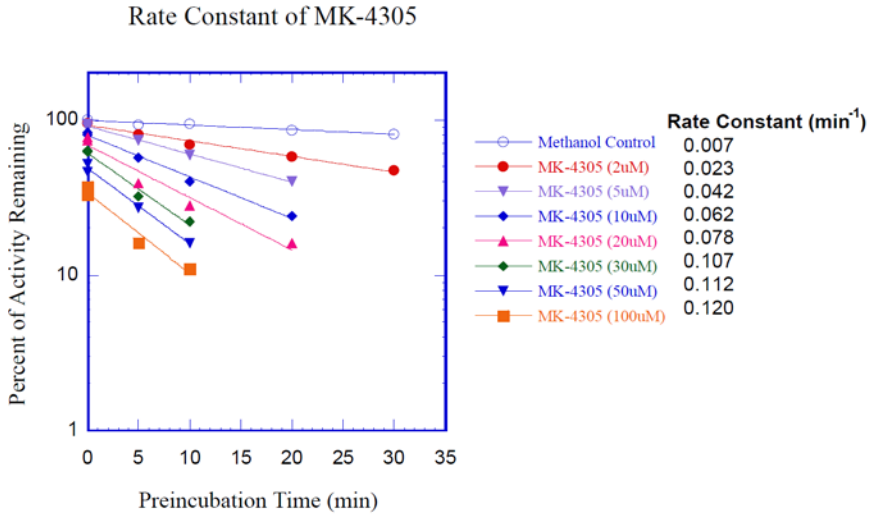
Table 7. Effect of L-002015883 on Cytochrome P450 Marker Enzyme Activities in Pooled Human Liver Microsomes (Reversible Inhibition)

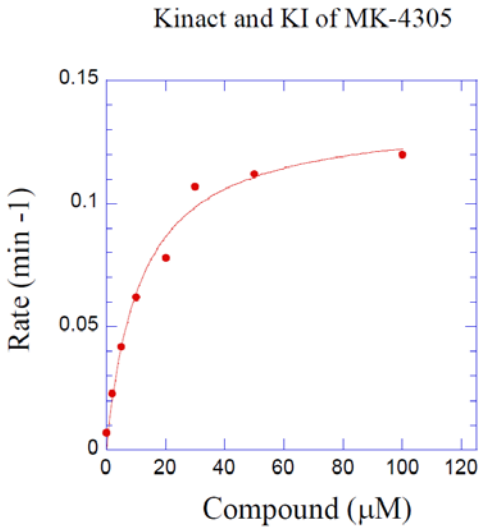
CYP	Reaction	Absolute IC_{50} (μM)[a]	
		Control Inhibitor	L-002015883
1A2	Phenacetin *O*-Deethylation	0.0073 α-Naphthoflavone	>100 (7.2 ± 2.3%)[b]
2B6	Bupropion Hydroxylation	0.77 Ticlopidine	44
2C8	Amodiaquine *N*-Deethylation	0.14 Montelukast	37
2C9	Diclofenac 4′-Hydroxylation	0.80 Sulfaphenazole	47
2C19	*S*-Mephenytoin 4′-Hydroxylation	0.20 Benzylnirvanol	35
2D6	Dextromethorphan *O*-Demethylation	0.088 Quinidine	39
3A4	Midazolam 1′-Hydroxylation	0.030 Ketoconazole	26
3A4	Testosterone 6β-Hydroxylation	0.026 Ketoconazole	11

M17 was a weak inhibitor of CYP2C9, 2D6 and 3A4, with IC_{50} values of > 50 μM for CYP2C9 and 2D6, and 28 μM for CYP3A4.

In addition, MK-4305 was shown to be a time-dependent inhibitor of CYP3A4 with *kinact* and K_I values of 0.136 ± 0.007 min^{-1} and 11.6 ± 1.9 μM, respectively. M9 was also a time-dependent inhibitor of CYP3A4 with *kobs* values of 0.052 and 0.078 min^{-1} obtained at 10 and 50 μM, respectively. *kinact* and K_I values were not calculated for M9.

Figure 3. Time-Dependent Inhibition of Testosterone 6β-Hydroxylation by MK-4305 in Human Liver Microsomes





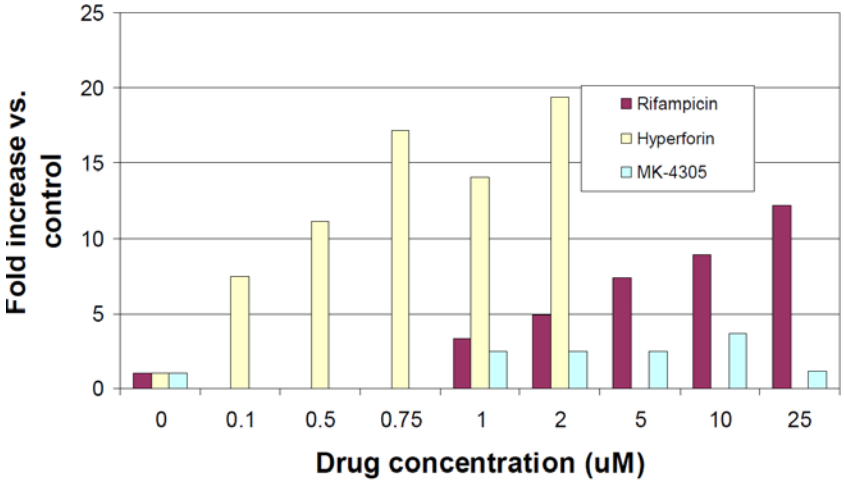
3. PXR Transactivation

Objective: to evaluate to induction potential of MK-4305 mediated by activation of a nuclear receptor – PXR

Method: The species specific PXR (Pregnane X receptor) receptors and pFR-UASLUC reporter constructs were transiently transfected into HepG2 cells. After overnight recovery, the transfected cells were split into 24-well plates (300,000 cells/well) and treated with test compounds or DMSO vehicle (0.1%) for 48 hours. In the case of human, rhesus, and dog PXR, rifampicin and hyperforin served as controls. For rat PXR, dexamethasone and dexamethasone-t-butyl acetate were employed as positive controls. After the incubation, the cells were lysized, with the lysates tested with Luciferase assay and measured for the luminescence.

Results: MK-4305 displayed a concentration-dependent activation of rat, monkey, and human PXR. At 10 μM, the response to MK-4305 was ~33% of rifampicin.

Figure 4. Assessment of MK-4305 in Human PXR Transactivation Assay



4. Human Hepatocyte Induction (CYP3A4, 1A2, and 2B6)

Objective: to evaluate the induction potential of MK-4305 on CYP1A2, CYP2B6 and CYP3A4

Method: Cryopreserved human hepatocytes were cultured for 24 or 48 hours prior to initiation of the study. The hepatocytes were then treated for 48 hours with vehicle control 0.1% (v/v) DMSO, MK-4305 (0.1-20 µM, or 0.1-100 µM for the "RIS calibrated" hepatocyte lots), or the positive control inducers rifampicin (10 µM), omeprazole (50 µM), or phenobarbital (1000 µM), with all solutions being replaced with fresh solutions at 24 hours. At the end of the 48-hour incubation, whole cell-based CYP3A4, CYP1A2, or CYP2B6 enzyme activity was determined using HPLC-MS/MS, and total RNA was isolated for quantitative PCR analysis of CYP3A4, CYP1A2, or CYP2B6 mRNA expression. Changes in the measured responses following treatment with test compounds were reported as fold changes (response to test compound relative to vehicle control) and as percent positive control, using the following relationship:

$$\% \text{ positive control} = \frac{(\text{response to test compound} - \text{response to vehicle control}) \times 100}{(\text{response to positive control} - \text{response to vehicle control})}$$

Results:

CYP1A2 The highest increase (4.8-fold) in CYP1A2 mRNA after the 48-hour incubation occurred at 5 µM MK-4305 and averaged 20% of the omeprazole (positive control) response. An accompanying increase (up to 2.7-fold) in CYP1A2 activity was observed with increasing concentrations of MK-4305, which was up to 11% of the omeprazole response.

Table 8. Assessment of MK-4305 as a Potential Inducer of CYP1A2 in Human Hepatocytes (Average from n=3 Donors)

Treatment	Dose (µM)	CYP1A2 mRNA		Phenacetin *O*-dealkylation Activity	
		Fold[a] Increase	% PC[b] Response	Fold Increase	% PC Response
Omeprazole	50	23.9 ± 10.0	100	16.7 ± 3.0	100
MK-4305	0.1	0.8 ± 0.0	NR[c]	0.9 ± 0.1	NR
	0.5	1.0 ± 0.2	0.4 ± 0.5	1.2 ± 0.2	2.6 ± 1.1
	1	2.2 ± 0.1	6.5 ± 4.1	1.2 ± 0.3	2.2 ± 2.5
	5	4.8 ± 0.5	20.4 ± 12.7	2.3 ± 0.7	8.5 ± 4.6
	10	4.5 ± 0.7	19.8 ± 15.3	2.7 ± 1.4	10.8 ± 8.5
	20	3.8 ± 2.3	16.2 ± 15.1	2.7 ± 1.7	10.7 ± 10.1

a. Fold – represents the mean fold change of treated samples compared to vehicle control samples.
b. % PC – represents the percent of induction relative to positive control omeprazole corrected for vehicle control.
c. NR - not reported since response was less than vehicle control.

CYP2B6 CYP2B6 mRNA showed the highest increase (2.4-fold) at 5 µM MK-4305 and was 19% of the phenobarbital (positive control) response. An increase in CYP2B6 activity (up to 2.3-fold) was also observed, corresponding to 23% of the phenobarbital response.

Table 9. Assessment of MK-4305 as a Potential Inducer of CYP2B6 in Human Hepatocytes (Average from n=3 Donors)

Treatment	Dose (μM)	CYP2B6 mRNA		Bupropion Hydroxylation Activity	
		Fold[a] Increase	% PC[b] Response	Fold Increase	% PC Response
Phenobarbital	1000	11.7	100.0	5.9	100.0
MK-4305	0.1	0.8 ± 0.2	NR[c]	1.0 ± 0.2	1.9*
	0.5	0.9 ± 0.1	NR	1.1 ± 0.1	3.0*
	1	1.2 ± 0.4	14.1*	1.5 ± 0.4	9.7 ± 9.5
	5	2.4 ± 0.6	18.6 ± 2.2	2.3 ± 1.4	23.1 ± 12.9
	10	2.0 ± 1.1	18.8*	1.7 ± 1.1	20.8*
	20	0.2 ± 0.2	NR	0.0*	NR

a. Fold – represents the mean fold change of treated samples compared to vehicle control samples.
b. % PC – represents the percent of induction relative to positive control phenobarbital corrected for vehicle control.
c. NR - not reported since response was less than vehicle control.
* Value represents average of two values, or only one value, as at least one donor was reported as NR.

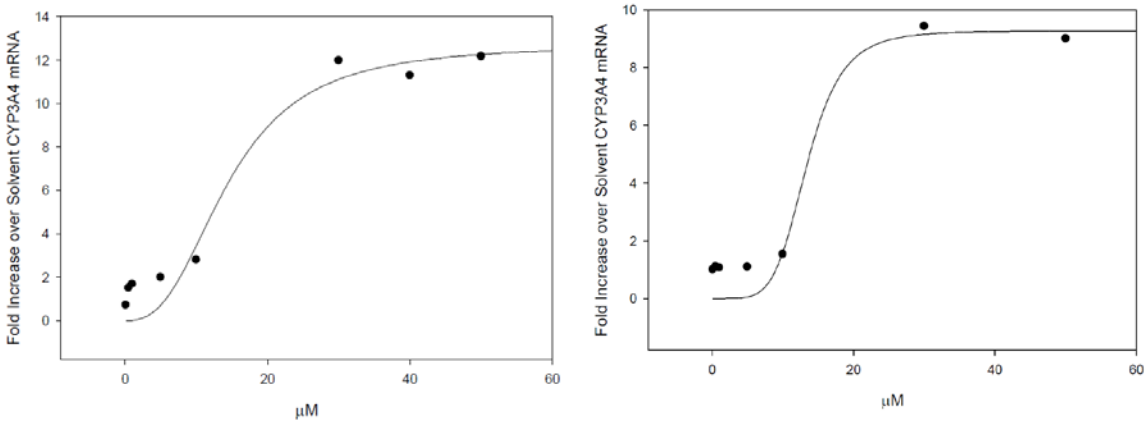
CYP3A4 The highest increase (22-fold) in CYP3A4 mRNA occurred at 5 μM and averaged 43% of the rifampicin (positive control) response. A decrease in CYP3A4 enzyme activity was observed with increasing MK-4305 concentrations, most likely due to concurrent time-dependent inhibition.

Table 10. Assessment of MK-4305 as an Inducer of CYP3A4 in Human Hepatocytes (Average from n=3 Donors)

Treatment	Dose (μM)	CYP3A4 mRNA		Testosterone 6β Hydroxylation Activity	
		Fold[a] Increase	% PC[b] Response	Fold Increase	% PC Response
Rifampicin	10	48.4 ± 10.4	100	9.1 ± 6.0	100
MK-4305	0.1	1.6 ± 0.4	1.4 ± 1.0	0.8 ± 0.2	NR[c]
	0.5	3.3 ± 1.8	5.5 ± 5.3	0.7 ± 0.2	NR
	1	10.3 ± 13.3	23.5 ± 35.6	0.6 ± 0.3	NR
	5	22.0 ± 10.9	42.7 ± 13.1	0.4 ± 0.3	NR
	10	13.9 ± 7.0	26.3 ± 8.5	0.3 ± 0.1	NR
	20	9.3 ± 8.1	16.6 ± 14.3	0.4 ± 0.1	NR

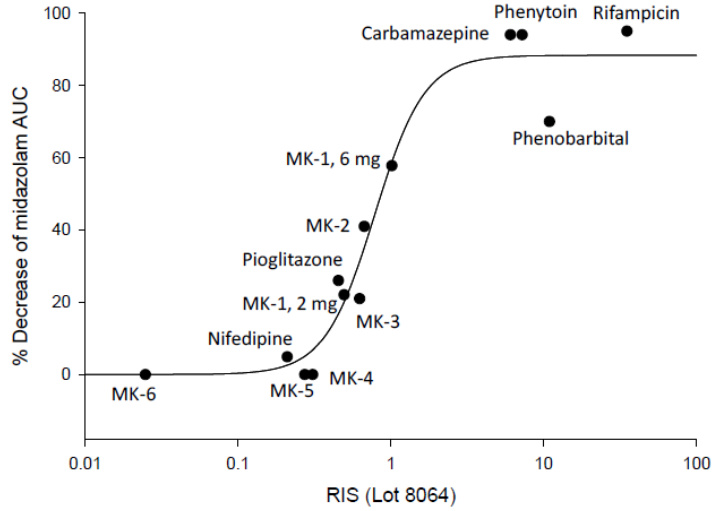
Additionally, MK-4305 caused a concentration-dependent induction response of CYP3A4 mRNA in both donors of the "RIS calibrated" cell lots (RIS: the relative induction score) with the maximal effect observed at 20 μM. An EC_{50} of 14.5 μM and an E_{max} of 12.7-fold over the solvent control was obtained with Lot HIE, with Lot Hu8064 yielding an EC_{50} of 13.4 μM and an E_{max} of 9.3-fold over the solvent control (Figure 5). Similar to the above experiment, a decline in enzyme activity was observed in both cell lots.

Figure 5. Induction Titration Curve of MK-4305 in Cyropreserved Human Hepatocytes (Left panel: Donor HIE; Right panel: Donor Hu8064)



The relative induction score (RIS) model was established using a total of 12 known CYP3A inducers (including rifampicin, phenytoin, carbamazepine, pioglitazone, nifidipine, and phenobarbital, and 6 internal compounds from the sponsor) where clinical induction DDI results with midazolam were available. Using human hepatocytes and CYP3A mRNA as the readout, induction Emax and EC50 for each of the calibrator compounds were determined using a Hill equation. The RIS was then calculated by incorporating the free Cmax (Cmax,u) for each compound, with RIS = (Emax x Cmax,u)/(EC50 + Cmax,u). A calibration curve that is described by a 3-parameter Hill model was then established between the RIS value of each calibrator compound and the corresponding decrease in midazolam AUC observed in clinical DDI studies. A representative calibration curve is shown below. This was similar as what shown in a literature paper (Drug Metab Dispos. 2008 Sep;36(9):1971-4. Left panel of Figure 1.)

Figure 6. A Representative Calibration Curve Showing the Relationship Between RIS Values and Clinically Observed Midazolam AUC Decreases for 12 Calibrator Compounds in Hepatocyte Lot 8064



For MK-4305, the RIS values were 0.003 and 0.004 for the two lots of hepatocytes studied (Donors HIE and Hu8064). Using the RIS calibration curve, the modeled AUC decrease for midazolam was predicted to be 0% for both lots of hepatocytes.

Table 11. RIS Modeling of MK-4305 as Potential CYP3A4 mRNA Inducer in Cryopreserved Human Hepatocytes

Donor	Treatment	C_{max}	fu,p	$C_{max,u}$	EC50 (μM)	E_{max} (fold increase over solvent control)	RIS	Projected Decrease MDZ AUC (%)
HIE	MK-4305	1	0.005	0.005	14.51 ± 2.80	12.71 ± 1.59	0.004	0
	Rifampicin	10	0.22	2.2	1.16 ± 0.76	24.49 ± 3.54	16.04	97
Hu8064	MK-4305	1	0.005	0.005	13.4 ± 2.02	9.28 ± 0.69	0.003	0
	Rifampicin	10	0.22	2.2	0.11 ± inf	13.51 ± 0.75	12.86	88

Induction potential of M9 was not evaluated separately. As shown in Study PK013, M9 was present as a predominant metabolite in human hepatocytes after incubation with MK-4305 (Figure 2). M9 represented the major metabolite in the incubation media, with the level reaching 42% of MK-4305. Thus, the observed induction effects on CYP isoforms in the hepatocytes treated with MK-4305 may include the contribution (if any) of M9.

5. In Vitro P-Glycoprotein Transport and Inhibition Studies

Objective: To investigate whether MK-4305 and its metabolites are substrates of P-gp and whether they are P-gp inhibitors

Methods:

In Vitro Transcellular Transport Studies. LLC-PK1 (porcine renal epithelial cells), L-MDR1 (LLC-PK1 transfected with human P-gp), L-mdr1a (rat P-gp), and Mdr1 (cynomologous P-gp) cells were plated at a density of 9.0 x 10^4 cells/0.15 mL/well on porous (0.4 μm) polycarbonate membrane filters in a feeder tray with 25 mL of culture medium. Cells were used for the transport study on the 4th day after plating. About 1 hour before the start of the transport experiment, the medium was aspirated and the cells were washed with 0.15 mL transport buffer (serum-free Hanks' balanced salt solution, HBSS, containing 10 mM Hepes (pH=7.4)) added to both cell culture insert (apical; A) and reservoir (basal; B) sides. The transport experiment was then initiated by replacing the medium in each compartment with 0.15 mL of transport buffer with and without test compounds (0.1, 0.5, 1, or 5 μM). Directional transport of [^{3}H]verapamil (1 μM) was run in parallel as a positive control for P-gp activity.

For [^{14}C]MK-4305, after 3-hour incubation at 37°C, 50 μL aliquots were taken from the apical and basolateral sides and the radioactivity was measured by liquid scintillation. For L-002015883 and L-002440877, the aliquots were analyzed by HPLC-MS/MS.

The apparent permeability coefficient (Papp in x 10^{-6} cm/s) was calculated:

Papp = Transported amounts (pmol/well) /sum of the concentration in the donor and receiver compartments after 3-hrs incubation (nM) /surface area (0.11 m^2/well) /incubation time (3 hrs).

The basal-to-apical (BA) versus apical-to-basal (AB) ratio (BA/AB) was calculated as follows:

BA/AB ratio = mean Papp (BA) / mean Papp (AB)

P-gp Inhibition Studies. The LLC-MDR1 and LLC-PK1 cell lines were cultured in 24-well transwell culture plates. [^{3}H]Digoxin (0.1 µM) and the inhibitors were prepared in transport buffer (Hanks buffer with 10 mM HEPES, pH 7.4). MK-4305 was tested at 0, 1, 5, 10, 25, 50, 100 µM and L-002015883 at 0, 1, 5, 10, 30, 100, and 300 µM. Prior to each transport study, cells were washed three times with transport buffer. Substrate solution (500 µL) was added to either the A or B compartment of the culture plate, and buffer (500 µL) was added to the compartment opposite to that containing the compound. The inhibitor at various concentrations was added to both compartments. At t=3 hr, 50 µL of sample was taken out from both sides and the radioactivity was determined by liquid scintillation. IC_{50} values for inhibition of P-gp-mediated digoxin transport by MK-4305 and L-002015883 were obtained by fitting the data to equation 1:

$$\% \text{ Control} = 100 / (1 + I / IC_{50}) \qquad \text{Eq. (1)}$$

Where I was the inhibitor concentration; percent control was calculated according to equation 2:

$$\% \text{ Control} = (R_I / R_0) \times 100 \qquad \text{Eq. (2)}$$

Where R_I represents net transport of digoxin measured in the presence of various concentrations of inhibitor; R_0 represents the net transport of digoxin in the absence of inhibitor. Where net digoxin transport in LLC-MDR1 was calculated according to equation 3:

$$\text{Net digoxin transport} = (\% \text{ Transport B-A}) - (\% \text{ Transport A-B}) \qquad \text{Eq. (3)}$$

Percentage of transport was calculated by dividing the concentration of compound measured in the receiver compartment by the sum of the concentrations measured in the receiver and donor compartments (x 100%).

$$\text{Percent Transport A to B} = A \rightarrow B \times 100\% / (A + A \rightarrow B)$$
$$\text{Percent Transport B to A} = B \rightarrow A \times 100\% / (B + B \rightarrow A)$$

The apparent permeability (Papp) was calculated by the following formula for samples taken at t = 3 hr:

$$P_{app} = \frac{\text{Volume of Receptor Chamber (mL)}}{[\text{Area of membrane (cm}^2)][\text{Initial Concentration } (\mu\text{M})]} x \frac{\Delta \text{ in Concentration } (\mu\text{M})}{\Delta \text{ in Time (s)}}$$

Where volume of Receptor Chamber is 0.5 ml; Area of membrane is 0.7 cm2; Δ in concentration is concentration in the receiver compartment at 3 hr; and Δ in Time is the incubation time (3 x 60 x 60 = 10800 s).

The B-A/A-B ratio was calculated by dividing the Papp from B to A by the Papp from A to B at t = 3 hr:

$$B - A/A - B \text{ Ratio} = \frac{P_{app}(B \rightarrow A)}{P_{app}(A \rightarrow B)}$$

Results:

Substrate Assessments At concentrations of 0.5, 1, and 5 µM, MK-4305 was not a substrate for either rat or human P-gp, as shown by net efflux ratios ranging from 0.8 to 1.5. In contrast, the positive control, verapamil (a known P-gp substrate), showed net efflux ratios of 3.4 or 3.9 for human P-gp, and 4.8 or 6.0 for rat P-gp, confirming the P-gp activity in the cell systems used. The net efflux ratio is calculated in the following equation:

$$(R) = (R_T) / (R_W)$$

where (R_T) and (R_W) are the permeability ratios (i.e., BA/AB ratio) for the transfected and the non-transfected lines (i.e., LLC-PK1 cells), respectively.

In addition, the passive permeability for MK-4305 was high (P_{app} = 22.8 – 34.6 x 10^{-6} cm/s in LLC-PK1 cells), suggesting that passive permeation may be predominant in the transport process of MK-4305 across cell membranes and transporters may only play a limited role.

Table 12. Assessment of [^{14}C]MK-4305 as a Substrate for Rat (LLC-Mdrla) and Human (LLC-MDR1) P-gp

A: with 0.1% BSA

Compound	Papp BA/Papp AB Ratio			Papp x 10^{-6} (cm/s) LLC-PK1	% Transport (t=3h) LLC-PK1
	LLC-PK1[a]	LLC-MDR1	LLC-Mdr1a		
MK-4305 5 µM	1.3	1.6	1.5	30.4	17
MK-4305 1 µM	1.1	1.3	1.5	28.3	22
MK-4305 0.5 µM	1.0	1.5	1.1	34.6	35
Verapamil 1 µM	1.0	3.4	4.8	31.7	25

B: without 0.1% BSA

0.1% BSA Compound	Papp BA/Papp AB Ratio			Papp x 10^{-6} (cm/s) LLC-PK1	% Transport (t=3h) LLC-PK1
	LLC-PK1[a]	LLC-MDR1	LLC-Mdr1a		
MK-4305 5 µM	1.6	1.6	1.7	22.8	18
MK-4305 1 µM	1.3	1.5	1.5	23.6	19
MK-4305 0.5 µM	1.2	1.0	1.2	25.9	21
Verapamil 1 µM	0.8	3.1	4.8	28.2	22

In contrast to MK-4305, M9 was a substrate for human and rat P-gp. M9 (L-002015883) showed net efflux ratios of 3.7-5.4 in human and 3.4-4.3 in rat, which were similar to verapamil (with net efflux ratio of 4.2 for human P-gp and 3.7 for rat P-gp). M17 (L-002440877) was transported by both human and cynomologous monkey P-gp, with net efflux ratios of 3.8-4.8 and 7.8-9.9, respectively, which were comparable or higher than those of verapamil (with net efflux ratio of 3.2 and 3.7 for human and monkey P-gp, respectively). These data indicate that neither M9 nor M17 are likely to have good brain penetration in humans. This was also supported by findings in P-gp knock-out mice study (PK011) as described later.

Table 13. Assessment of L-002015883 as a Substrate for Rat (LLC-Mdrla) and Human (LLC-MDR1) P-gp

Compound	Papp BA/Papp AB Ratio			Papp x 10^{-6} (cm/s) LLC-PK1
	LLC-PK1	LLC-MDR1 human	LLC-Mdr1a rat	
L-002015883 1 µM	0.8	3.2	2.7	28.4
L-002015883 0.5 µM	1.0	3.7	3.6	30.8
L-002015883 0.1 µM	0.8	4.3	3.4	26.7
Verapamil 1 µM	1.2	5.0	4.4	28.4

Table 14. Assessment of L-002440877 as a Substrate for Rat (LLC-Mdr1a), Human (LLC-MDR1), and Cynomologous Monkey (LLC-MDR1) P-gp

Compound	Papp BA/Papp AB Ratio				Papp x 10^{-6} (cm/s) LLC-PK1
	LLC-PK1	LLC-MDR1 human	LLC-Mdr1a rat	LLC-MDR1 cyno	
L-002440877 1 µM	2.8	10.5	4.0	27.8	4.0
L-002440877 0.1 µM	2.4	11.4	3.8	18.8	3.9
Verapamil 1 µM	1.1	3.5	3.3	4.1	28.5

Inhibition Potential Assessments

Digoxin showed a significant P-gp-mediated efflux transport with net efflux ratios of 3.9 and 3.4. MK-4305 inhibited human P-gp mediated digoxin transport with a calculated IC_{50} of 18.7 ± 3.3 µM. M9 (L-002015883) inhibited human P-gp an IC_{50} of 73 ± 16 µM.

Table 15. Effect of MK-4305 on Bi-Directional Transport of [^{3}H]Digoxin (0.1 µM) in LLC-MDR1 Cells

MK-4305 concentration (µM)	Papp BA/Papp AB Ratio		% Net Transport
	LLC-PK1	LLC-MDR1 human	
0	3.1	12.2	100 ± 6
1	2.3	10.4	91 ± 3
5	1.6	9.0	91 ± 13
10	1.4	3.9	73 ± 4
25	ND	2.0	33 ± 4
50	ND	1.4	20 ± 2
100	ND	1.2	18 ± 5

Table 16. Effect of L-002015883 on Bi-Directional Transport of [^{3}H]Digoxin (0.1 µM) in LLC-MDR1 Cells

L-002015883 Concentration (µM)	Papp BA/Papp AB Ratio		% Net Transport
	LLC-PK1	LLC-MDR1 human	
0	4.4	14.8	100 ± 5
1	4.0	12.9	86 ± 10
5	2.6	10.7	92 ± 7
10	1.5	7.4	85 ± 9
30	ND	5.1	84 ± 6
100	ND	1.8	37 ± 21
300	ND	1.2	14 ± 11

6. Blood to Plasma Distribution Ratio

Objective: To determine the blood to plasma ratio of suvorexant (MK-4305)

Method:

MK-4305. The distribution of [^{14}C]MK-4305 between red blood cells and plasma of rats, dogs, monkeys, and humans was determined in freshly drawn blood. The concentration in plasma was measured by adding [^{14}C]MK-4305 as a stock solution in 50% acetonitrile to pre-warmed rat, dog, monkey, and human blood to give final concentrations of 1, 10, and 25 µM (final organic concentration was 0.5%). After 30 minutes incubation at 37°C, plasma was obtained by centrifugation for 5 minutes at 4000 rpm. Aliquots of plasma were then added to scintillation cocktail and counted using a liquid scintillation counter. As a surrogate to experimentally determine the initial whole blood concentration, [^{14}C]MK-4305 was added to pre-warmed rat, dog, monkey, and human plasma for final concentrations of 1, 10, and 25 µM. Aliquots of plasma were transferred to scintillation vials and counted to represent the whole blood concentration. The blood to plasma ratio was calculated by dividing the "whole blood" concentration by the plasma concentration.

L-002015883 (M9). Similarly, the distribution of L-002015883 between red blood cells and plasma of humans was determined at a concentration of 1 µM. Samples were analyzed by HPLC-MS/MS. Peak area ratios of L-002015883 to internal standard (labetalol) were determined. The blood to plasma ratio was calculated by dividing the "whole blood" peak area ratio by the plasma peak area ratio.

Results:

The blood to plasma ratios for [^{14}C]MK-4305 in rat, dog, monkey, and human blood were ~0.6 for all species over the concentration range of 1 to 25 µM, indicating that MK-4305 was distributed to red blood cells but not bound extensively to blood components. Similar results were obtained in human blood for metabolite M9 (L-002015883), in which the B/P ratio was 0.6 at a concentration of 1 µM.

Table 17. Blood-to-Plasma Concentration Ratios of [^{14}C]MK-4305 and L-002015883 in Human, Rat, Dog, and Monkey

Compound	Concentration (µM)	Human	Rat	Dog	Monkey
MK-4305	1	0.59	0.60	0.51	0.55
	10	0.68	0.60	0.54	0.54
	25	0.61	0.60	0.57	0.64
L-002015883	1	0.60	ND	ND	ND

The blood to plasma ratios are obtained using an average of n=3 measurements of blood concentration and an average of n=3 measurements of plasma concentration.

7. Plasma Protein Binding

Objective: To determine the protein binding of MK-4305 in plasma of different species

Method:

MK-4305. The binding of [^{14}C]MK-4305 to plasma proteins was determined by ultracentrifugation. The plasma samples spiked with [^{14}C]MK-4305 were incubated for 30 minutes at 37°C. Triplicate aliquots of each sample were taken and counted by liquid scintillation counting (LSC) to determine the total plasma concentration. The remaining plasma was divided into triplicate samples and centrifuged for 18 hours at 37°C at 58000 rpm (180,000 x g). After 18 hours, the centrifuge was allowed to stop without braking to minimize the sample turbulence. Successive 100 µL aliquots were pipetted from the top to the bottom of each sample and counted. The aliquots containing the lowest levels of radioactivity were considered to be protein-free sections. The fraction of [^{14}C]MK-4305 unbound was calculated as:
% f_u = [dpm/mL in protein-free section] / [dpm/mL in plasma] x 100%

L-002015883 (M9). The procedures were the same as those described above, except that L-002015883 samples were analyzed by HPLC-MS/MS. A standard curve was prepared at concentrations of L-002015883 ranging from 0.005 µM to 2 µM. Labetalol was used as internal standard. The aliquots containing the lowest levels of L-002015883 were considered to be protein-free sections. The fraction L-002015883 unbound was calculated as: % f_u = [L-002015883] in free section / [L-002015883] in plasma x 100%

L-002440877 (M17). The binding of L-002440877 to plasma proteins was determined by equilibrium dialysis. L-002440877 was added as a stock solution in DMSO to rat and human plasma to produce a final concentration of 2.5 µM. The plasma samples were transferred to the top half of the wells of a Dialysis plate. Phosphate buffer was added into all the bottom half locations. The plate was then covered and incubated at 37°C for 20 hours. After equilibration, samples were analyzed by HPLC-MS/MS. A standard curve was prepared at concentrations ranging from 0.0025 µM to 2.5 µM L-002440877. The fraction L-002440877 unbound was calculated as:
% f_u = 100 * (Fc/Tc)
Tc = Total compound concentration as determined by the calculated concentration on the plasma side of the membrane.
Fc = Free compound concentration as determined by the calculated concentration on the buffer side of the membrane

Results:
MK-4305 was extensively bound to rat, dog, monkey, mouse, rabbit, and human plasma proteins. The protein bound of MK-4305 in human plasma was 99.5% or more. Metabolites M9 (L-002015883) and M17 (L-002440877) exhibited even higher protein bound, with unbound fraction of 0.2% in human plasma.

Table 18. Protein Binding (mean ± SD, n=3) of [^{14}C]MK-4305, L-002015883, and L-002440877 in Rat, Dog, Monkey, Mouse, Rabbit, and Human Plasma

Compound	Species	Unbound Fraction in Plasma, %				
		1 µM	2.5 µM	5 µM	10 µM	25 µM
MK-4305	Rat	1.1 ± 0.1	ND	1.4 ± 0.1	ND	1.7 ± 0.2
	Dog	0.9 ± 0.1	ND	1.0 ± 0.0	ND	1.7 ± 0.1
	Monkey	1.0 ± 0.0	ND	1.4 ± 0.1	ND	1.9 ± 0.0
	Mouse	ND	ND	1.8 ± 0.1	ND	ND
	Human	0.3 ± 0.0	ND	0.5 ± 0.1	ND	0.5 ± 0.1
	Rabbit	3.7 ± 0.2	ND	ND	4.4 ± 0.2	ND
L-002015883	Rat	ND	ND	2.9 ± 0.2	ND	ND
	Dog	ND	ND	1.9 ± 0.2	ND	ND
	Monkey	ND	ND	4.9 ± 0.2	ND	ND
	Mouse	ND	ND	1.8 ± 0.1	ND	ND
	Human	ND	ND	0.2 ± 0.0	ND	ND
	Rabbit[a]	7.8	ND	ND	10.4	ND
L-002440877	Rat	ND	6.2 ± 0.5	ND	ND	ND
	Human	ND	0.2 ± 0.0	ND	ND	ND

Study PK009: In Vitro Protein Binding of MK-4305 in Plasma from Healthy and Hepatic Insufficient Human Subjects, Human Serum Albumin and α1-Acid Glycoprotein

Methods: Ultracentrifugation was utilized to measure protein binding of MK-4305 in plasma from patients with moderate hepatic insufficiency and matching healthy controls (Protocol MK-4305-017). Pre-dose plasma sample from each subject (0001-0016) was spiked with [^{14}C]MK-4305 and incubated at 37°C for 30 minutes followed by procedures as described in Study PK002. Same method was also used to determine the binding of MK-4305 with 40 mg/mL human Serum Albumin (HSA) or 1 mg/mL α1-Acid Glycoprotein (AAG).

Results:
At a MK-4305 concentration of 2 µM, the mean unbound fraction in plasma from the patients with moderate hepatic insufficiency was 0.77±0.18%, slightly lower than that in the healthy matched subjects (1.00 ± 0.41%).

Table 19. Human Plasma Protein Binding of 2µM [^{14}C] MK-4305 (Fraction Unbound %)

Subjects (Hepatic Insufficient)	Fraction Unbound%	Subjects (Healthy)	Fraction Unbound%
1	0.84	9	0.80
2	1.14	10	1.30
3	0.68	11	0.87
4	0.61	12	0.66
5	0.83	13	0.81
6	0.78	14	0.71
7	0.62	15	0.95
8	0.63	16	1.94

At a MK-4305 concentration of 2 µM, the mean unbound fraction in HSA and AAG was 2.80 ± 0.05% and 0.40 ± 0.007%, respectively, indicating MK-4305 is highly bound to both types of proteins.

Study PK010: In Vitro Protein Binding of MK-4305 in Plasma from Healthy and Renal Insufficient Human Subjects

Methods: Ultracentrifugation was utilized to measure protein binding of MK-4305 in plasma from patients with severe renal insufficiency and matching healthy controls (Protocol MK-4305-023). Pre-dose plasma sample from each subject (0001-0016) was spiked with [^{14}C]MK-4305 and incubated at 37°C for 30 minutes followed by procedures as described in Study PK002.

Results: At a MK-4305 concentration of 2 µM, the mean unbound fraction in plasma from the patients with severe renal insufficiency was 1.1 ± 0.2%, similar to that in the healthy matched subjects (1.1 ± 0.2%).

Table 20. Human Plasma Protein Binding of 2 µM [^{14}C]MK-4305 (fraction unbound %)

Subjects (Renal Insufficient)	Fraction Unbound%	Subjects (Healthy)	Fraction Unbound%
0001	1.0	0009	0.9
0002	1.3	0010	0.9
0003	1.2	0011	1.1
0004	1.3	0012	1.0
0005	0.9	0013	1.3
0006	1.0	0014	1.5
0007	1.0	0015	1.2
0008	1.0	0016	1.2

Study PK015: In Vitro Studies of MK-4305 and L-002015883 (M9) on Inhibition of human BCRP, OATP1B1, and OCT2

Objective: To evaluate the inhibition potential of MK-4305 and its metabolite M9 on transporters, BCRP, OATP1B1, and OCT2

Method:
BCRP The inhibitory effect of MK-4305 and L-002015883 on ATP-dependent uptake of methotrexate by BCRP was conducted in Sf9 membrane vesicles containing BCRP. 20 µg BCRP containing membrane vesicles (2 mg protein/mL) were pre-incubated for 3 minutes at 37°C with 10 µM [^{3}H] methotrexate with the presence of various concentrations of MK-4305 or L-002015883 (0.1–15 µM for both compounds), or 1 µM Ko143 (prototypic BCRP inhibitor), which were dissolved in transport buffer (0.25 M sucrose, 10 mM Tris-HCl buffer (pH 7.4), 10 mM $MgCl_2$). Uptake was initiated by the addition of ATP regenerating reagent (5 mM ATP, 10 mM creatine phosphate and 100

µg/mL creatine phosphokinase) or transport buffer, followed by incubation at 37°C for 5 minutes. After stopping the incubation, the reaction mixture was transferred to filter plate and washed with ice-cold stop buffer for five times. The filter plate containing the membrane vesicles was counted with radioactivity determined by liquid scintillation counting. ATP-dependent uptake was calculated by subtracting the uptake in the absence of ATP from that in the presence and data were normalized to % control, where uptake in the absence of test compound was 100%.

OATP1B1 The inhibitory effect of MK-4305 and L-002015883 on OATP1B1-mediated pitavastatin uptake was conducted in MDCKII cells and MDCKII cells stably transfected with OATP1B1. Cells were treated with 10 mM sodium butyrate 24 hours prior to the experiment to increase expression of OATP1B1. On the day of experiment, cells were suspended at a density of 0.4 x 10^6 cells/well in 96-well plates. Uptake was initiated by the addition of 0.1 µM [^{3}H] pitavastatin containing various concentrations of MK-4305, L-002015883 (0.1–15 µM for both compounds), or 5 µM cyclosporin A (prototypic OATP1B1 inhibitor) dissolved in HBSS buffer with 10 mM Hepes, pH 7.4. Cells were then incubated for 5 minutes at 37°C and uptake was stopped by the addition of ice cold PBS. Cells were centrifuged, followed by washing of the cell pellets for 4 times. Cell pellets were resuspended in 50% acetonitrile and the radioactivity was determined by liquid scintillation counting. OATP1B1-mediated pitavastatin uptake was calculated by subtracting the uptake of pitavastatin into MDCKII cells from that observed in MDCKII-OATP1B1 cells and data were normalized to % control, where uptake in the absence of test compound was 100%.

OCT2 The inhibitory effect of MK-4305 and L-002015883on OCT2-mediated metformin uptake was conducted in CHO-K1 cells and CHO-K1 cells stably transfected with OCT2. Cells were suspended at a density of 0.4 x 10^6 cells/well in 96-well plates. Uptake was initiated by the addition of 1 µM [^{14}C] metformin containing various concentrations of MK-4305, L-002015883 (0.1–15 µM for both compounds), or 5 µM decynium 22 (prototypic OCT2 inhibitor) dissolved in HBSS buffer with 10 mM Hepes, pH 7.4. Cells were then incubated for 5 minutes at 37°C and uptake was stopped by the addition of ice cold PBS. Cells were centrifuged, followed by washing of the cell pellets for 4 times. Cell pellets were resuspended in 50% acetonitrile and the radioactivity was determined by liquid scintillation counting. OCT2-mediated metformin uptake was calculated by subtracting the uptake of metformin into CHO-K1 cells from that observed in CHO-OCT2 cells and data were normalized to % control, where uptake in the absence of test compound was 100%.

Results:

Inhibition of BCRP In the absence of inhibitors, [^{3}H] methotrexate (10 µM) showed significant uptake transport in BCRP-expressed vesicles at rate of ~120 pmol/mg/min. At 10 µM and 15 µM, MK-4305 inhibited 45% and 62% of ATP-dependent methotrexate uptake, respectively, suggesting that the IC_{50} is in the range of 10-15 µM. Similarly, at 15 µM, M9 inhibited 46% of ATP-dependent methotrexate uptake, suggesting the IC_{50} to be ~15 µM. Near complete inhibition of BCRP by 1 µM Ko143 (a known BCRP inhibitor) was observed, confirming functionality of the vesicles in both MK-4305 and M9 assays.

The steady-state plasma C_{max} of MK-4305 following 40 mg once-daily dosing in non-elderly subjects is predicted to be 1.17 μM based on a population PK analysis. Thus, the C_{max} /IC_{50} ratio will be less than or just around 0.1, suggesting that MK-4305 is unlikely to inhibit BCRP at its systemic circulation level. However, MK-4305 has the potential to inhibit BCRP present on the gut wall, since the [I_2[/IC_{50} ratio (I_2= Dose/250 mL) with 40-mg dose is about 28, higher than the cut-off value of 10. It should be noted that such inhibition potential decreases when lower dose of MK-4305 is administered. For a dose of 15 mg, the [I_2[/IC_{50} ratio is 10.6, just on the margin of the cut-off value, indicating that at this dose level, MK-4305 is less likely to result in clinically significant inhibition on BCRP.

Table 21. Summary of IC_{50} Values of MK-4305 and Metabolite M9 (L-002015883) as Inhibitors of Human BCRP, OATP1B1, and OCT2

Transporter	Substrate	Positive Control Inhibitor	MK-4305	L-‘883 (M9)
BCRP	Methotrexate (10 μM)	Ko143 (1 μM)	10-15 μM	Approximately 15 μM
OATP1B1	Pitavastatin (0.1 μM)	Cyclosporine A (5 μM)	Approximately 10 μM	>15 μM
OCT2	Metformin (1 μM)	Decynium 22 (5 μM)	1.3 ± 0.3 μM	>15 μM

Inhibition of OATP1B1 In the absence of inhibitors, [^{3}H] pitavastatin (0.1 μM) showed significant uptake transport in MDCKII-OATP1B1 cells at a rate of approximately 0.3 pmol/million cells/min. At 10 μM, MK-4305 inhibited 48% of OATP1B1-mediated pitavastatin uptake. L-002015883 (M9) showed less inhibitory effect with ~40% inhibition observed at 15 μM. Near complete inhibition of OATP1B1 by 5 μM cyclosporine A (a known OATP1B1 inhibitor) was observed, confirming functionality of the cells in both MK-4305 and M9 assays.

Inhibition of OCT2 In the absence of inhibitors, [^{14}C] metformin (1 μM) showed uptake transport in CHO-K1-OCT2 cells at a rate of approximately 0.3-0.4 pmol/million cells/min. MK-4305 showed concentration-dependent inhibition on OCT2-mediated uptake with an IC_{50} of 1.3 ±0.3 μM. On the contrary, L-002015883 (M9) showed minimal inhibitory effect of OCT2 activity, where ~30% inhibition was observed at 15 μM. Near complete inhibition of OCT2 by 5 μM Decynium 22 (a known OCT2 inhibitor) was observed, confirming functionality of the cells in both MK-4305 and M9 assays.

Study PK011. In Vitro Evaluation of MK-4305 Metabolite M9 (L-002015883) as a Substrate of Mouse P-gp and In Vivo Brain Penetration of M9 in CF-1 Mice

Method:
In Vitro: M9 was evaluated as a P-gp substrate in LLC-PK1 cells overexpressing mouse (Mdr1a) P-gp. The procedures were the same as described in Study PK002.
In Vivo: Groups of P-glycoprotein competent (+/+) and deficient (-/-) CF-1 mice received an IV dose of 3 mg/kg M9 via the tail vein. Animals (n=3 at each time point) were sacrificed at 0.25, 0.5, and 1 hr post-dose. The concentration of M9 in plasma, CSF, and brain homogenate was determined by LC-MS/MS.

Results:

Transport of M9 At concentrations of 0.1, 0.5, and 1 µM of M9, the net efflux ratios ranged from 5.8 to 7.2, higher than that (5.1) for verapamil (positive control), indicating M9 is a substrate of mouse P-gp.

Table 22. Assessment of M9 (L-002015883) as a Substrate for Mouse (LLC-Mdrla) P-gp

Compound	P_{app} BA/ P_{app} AB Ratio		P_{app} x 10^{-6}
	LLC-PK1	LLC-Mdr1a	LLC-PK1 (cm/s)
1 µM verapamil	1.1	5.6	39
0.1 µM L-002015883	0.9	6.4	40.5
0.5 µM L-002015883	0.9	6.5	39.6
1 µM L-002015883	1.0	5.8	37.7

Brain Penetration The plasma concentrations of M9 were similar in the two types of mice. In the P-gp (+/+) mice, brain concentrations ranged from 0.05 to 0.27 µM, while in the P-gp deficient (-/-) mice brain concentrations ranged from 0.66 to 2.96 µM, which were about 10-fold more than those in the (+/+) mice. Consistently, the average brain to plasma ratio of M9 was about 0.07 in the (+/+) mice, and increased to approximately 0.9 in (-/-) mice, suggesting that P-gp limits brain penetration of M9 in wild-type mice. Moreover, the CSF concentrations ranged from 0.01 to 0.03 □M in the (+/+) mice, in the (-/-) mice, the CSF levels were 2-3 fold higher. In the P-gp (-/-)mice, the M9 CSF concentrations are ~2% of those in plasma, which is similar to the M9 free fraction in mouse plasma (1.8%, see Table 18), indicating that there is no apparent efflux of M9 in the absence of P-gp.

Table 23. Concentrations of MK-4305 Metabolite M9 (L-002015883) in Plasma, Brain Homogenate, and CSF from P-Glycoprotein Competent (+/+) CF-1 Mice Following an IV Dose of M9

Time (hr)	Plasma (µM)		Brain Homogenate (µM)		CSF (µM) Pool of n=3
	Mean	SD	Mean	SD	
0.25	4.15	0.72	0.27	0.15	0.03
0.5	2.13	0.40	0.14	0.05	0.01
1.0	0.62	0.33	0.05	0.03	BLQ

Table 24. Concentrations of MK-4305 Metabolite M9 (L-002015883) in Plasma, Brain Homogenate, and CSF from P-Glycoprotein Deficient (-/-) CF-1 Mice Following an IV Dose of M9

Time (hr)	Plasma (µM)		Brain Homogenate (µM)		CSF (µM) Pool of n=3
	Mean	SD	Mean	SD	
0.25	4.00	0.45	2.96	0.86	0.08
0.5	1.51	0.81	1.44	0.57	0.02
1.0	0.61	0.10	0.66	0.11	0.01

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/s/

HRISTINA DIMOVA
06/21/2013

XINNING YANG
06/21/2013

YUXIN MEN
06/21/2013

DRAFT BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-569 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DNP		
Applicant:	Merck Sharp & Dohme Corp.	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D	
Trade Name:	(b) (4) Tablets	**Acting Biopharmaceutics Supervisor:** Richard Lostritto, Ph.D	
Generic Name:	Suvorexant Film-Coated IR Tablets	**Date Assigned:**	Sep 14, 2012
Indication:	Treatment of Insomnia	**Date of Review:**	April 10, 2013
Formulation/strength	Immediate Release Tablet/15 mg, 20 mg, 30 mg, and 40 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**Final ONDQA recommendations in DARRTS**
Aug 29, 2012 Dec 22, 2012 March 29, 2013	Sep 05, 2012	May 5, 2013
Type of Submission:	Original NDA	
Biopharmaceutics Review Focus:	• Dissolution information (method and acceptance criterion) • IVIVC Model • Role of dissolution on the construction of Design Space for the proposed product	

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Submission: NDA 204-569 is a 505(b)(1) submission for a New Molecular Entity, suvorexant (MK-4305). (b) (4) Tablets contain suvorexant, an orexin receptor antagonist being proposed for the treatment of insomnia. The proposed dosing regimen for non-elderly adults is 40 mg once daily immediately before bed time and 30 mg once daily for elderly adults. A lower dose (*20 mg and 15 mg*) may be appropriate for some patients based on individual tolerability.

(b) (4) is an immediate release film-coated tablet for oral administration available in four strengths: 15 mg, 20 mg, 30 mg, and 40 mg. (b) (4) Suvorexant drug substance (b) (4) has very low aqueous solubility across the physiological pH range (b) (4) and has very low oral bioavailability.

(b) (4)

Some aspects of the drug substance, drug product and process development were conducted under a

Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy. Dissolution was identified as one of the Critical Quality Attributes (CQAs) for the drug product and was used as a response parameter to support the design space of the drug product. An IVIVC model was developed to support the Applicant's proposed dissolution acceptance criterion and to establish in-process controls (b) (4)

Review: This Biopharmaceutics review focuses on the evaluation of: **1)** the acceptability of the dissolution method and acceptance criterion; **2)** The acceptability of the (b) (4) limits derived from the IVIVC model[1]; and **3)** The role of dissolution as a response parameter (b) (4) ; and **4)** The role of dissolution in the selection of a design space (DS) (b) (4)

1) Dissolution Method and Acceptance Criterion:
The following dissolution method and acceptance criterion are being proposed for all strengths of (b) (4) Tablets.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	75 rpm	900mL QLA sinker	37°C	0.4% SDS in water	Q = (b) (4) in 30 min

The dissolution method was evaluated and found acceptable under the IND submission[1]. The data show that the method is able to discriminate for batches with different hardness and other process parameters. There was not dissolution data included in the submission to determine the discriminating ability of the dissolution method (b) (4) The Applicant proposes (b) (4) . However, the CMC review team's position is that the control strategy implemented is sufficient to ensure adequate control (b) (4) and its monitoring is not warranted provided that the Applicant follows the FDA recommendation (see CMC review for more details).

The dissolution acceptance criterion of Q = (b) (4) at 30 minutes is also acceptable. Following the FDA's recommendation during the review cycle, this criterion was set based on the performance of batches tested in phases 3 clinical trials and on the results of BE study PN051 which showed that 2x15 mg vs. 30 mg tablets and 2x20mg vs. 40 mg tablets were bioequivalent despite observed differences in dissolution profiles between the 15 mg vs. the 30 mg and the 20 mg vs. the 40 mg strengths.

2) (b) (4) Limits Derived from the IVIVC Model
A QbD approach was implemented for the development of the drug substance and manufacturing process that according to the Applicant provides a final drug product of acceptable and consistent quality and stability for the patient's safety and efficacy. The Applicant states that the drug product was designed to meet the drug product critical quality attributes (CQAs) of content uniformity, assay, impurities/degradates, drug substance phase and form stability, appearance, elegance, identity, and dissolution.

A relationship was established between the tablet's quality attributes and dissolution, in order to help in the determination of the appropriate (b) (4) from the IVIVC dissolution borderline predicted profiles. According to the Applicant, (b) (4) was selected as the tablet attribute used for this

[1] Biopharmaceutics review for IND 101847/SDN-175 by Dr. John Duan entered in DARRTS on Jan 2012.

analysis, predicted (b) (4) were also used (b) (4) Subsequently, the IVIVC (b) (4) Dissolution at (b) (4) time point was selected (b) (4)

(b) (4)

3) The role of dissolution as a response parameter in the selection of the DS for other COA

(b) (4)

(b) (4)

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed NDA 204-469 submitted on Aug 30, 2012, and its amendments received on Dec 22, 2012, March 12. 2013 for (b) (4) (suvorexant) IR tablets, 15 mg, 20 mg, 30 mg and 40 mg.

From Biopharmaceutics perspective, NDA 204-469 is recommended for approval.

The following dissolution method and acceptance criterion for all the strengths of Suvorexant IR Tablets have agreed upon:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	75 rpm	900mL QLA sinker	37°C	0.4% SDS in water	Q = (b) (4) in 30 min

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. RLostritto

BIOPHARMACEUTICS ASSESSMENT

INTRODUCTION

Suvorexant, also known as MK-4305 is a New Molecular Entity (NME). It is an orally active, potent, and reversible orexin receptor antagonist (ORA) and is anticipated to be the first in class ORA for the treatment of patients with insomnia. The proposed dosing regimen for non-elderly adults is 40 mg once daily immediately before bed time and 30 mg once daily for elderly adults. A lower dose (15 and 20 mg) may be appropriate for some patients based on individual tolerability [(b) (4)] drug product is an immediate release film-coated tablet for oral administration available in four strengths: 15 mg, 20 mg, 30 mg, and 40 mg.

Drug Substance

Suvorexant is a white [(b) (4)] powder which [(b) (4)] has very low aqueous solubility across the physiological pH range [(b) (4)] (Table 1) and has very low oral bioavailability. [(b) (4)]

The chemical structure of Suvorexant IR Tablets is shown in Figure 1.

Table 1. Equilibrium Solubility of Suvorexant (MK-4305)in Aqueous Buffer Solution (72 hours)

[(b) (4)]

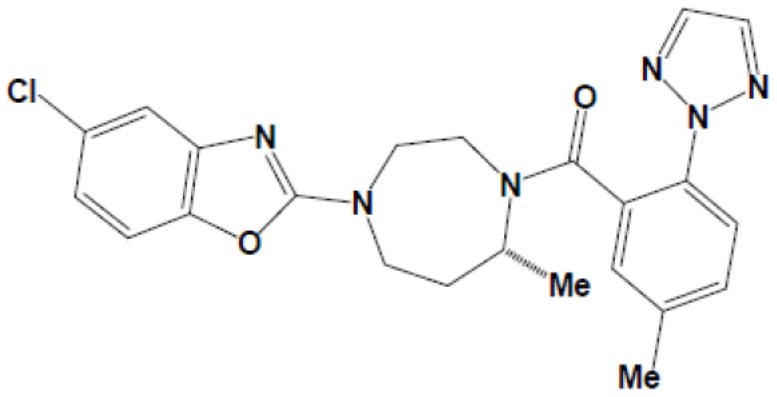

Figure 1. Chemical Structure of Suvorexant.

Drug Product

(b) (4)

Table 2. Target Product Profile (TPP) for Suvorexant Drug Product*

Clinical Attributes	
Indication	Sleep disorder
Mechanism	Dual Orexin Antagonist (DORA)
Route of Administration	Oral/Immediate Release
Dose Frequency	QD before sleep
Treatment	Chronic
Safety and Efficacy	
Impurities and Degradates	Controlled below ICH Q3 or qualified levels
Dose Range	15-40 mg (Final proposed strengths are 15, 20, 30 , 40 mg)
Pharmacokinetic Target	Fast Onset (Short T_{max})
Patient Compliance Requirements	
Subjective Properties	Suitable for global market
Dosage Form/Size	Tablet
Food Effect Consideration	Lack of food effect desirable

*Source: 3.2.P.2.1, Table 1.

The components and composition of Suvorexant IR tablets are summarized in Table 3.

Table 3. Composition of Suvorexant Tablet. (b) (4)

Strength:			15 mg	20 mg
Components	Quality Reference	Function	Amount per tablet (mg)	Amount per tablet (mg)
(b) (4)				
Suvorexant (MK-4305)	----	Active	15.00	20.00
Polyvinylpyrrolidone/Vinyl Acetate Copolymer (Copovidone)	USP-NF, Ph. Eur., JPE			
Lactose Monohydrate	USP-NF, Ph. Eur., JP			
Microcrystalline Cellulose	USP-NF, Ph. Eur., JP			
Croscarmellose Sodium	USP-NF, Ph. Eur., JP			
Magnesium Stearate (b) (4)	USP-NF, Ph. Eur., JP			
(b) (4)				
Total Tablet Weight			195.5	258.8
(b) (4)				

(b) (4)

Reviewer's Comments

(b) (4)

Formulation Development

The formulations used throughout the clinical development of the proposed product and the biopharmaceutics data used for bridging are summarized in Figure 2.

Figure 2. Summary of drug product formulation development

The changes implemented to the phase 3/commercial formulation were as follows:

(b) (4)

These changes are considered minor changes according to the SUPAC-IR guidance and since PK data are available for the highest strength (40 mg) tablet and all the strengths were tested in the phase 3 clinical trials, no additional biopharmaceutics data are needed to support these changes. In addition, differences from FSS/Reference batches to the proposed commercial process include changes in tooling embossing and scale-up batch sizes, which were shown not to impact product quality or performance

DISSOLUTION METHOD

The following dissolution method is proposed for all strengths of (b) (4) Tablets:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	75 rpm	900mL QLA sinker	37°C	0.4% SDS in water

The dissolution method was found acceptable under the IND submission[1]. The following summarizes the dissolution method development data included in the submission:

1. Effect of Media: The following surfactants were evaluated:

(b) (4)

- SDS

2. Effect of Paddle Speed: The following paddle speeds were evaluated:
   [redacted]
   - 75 rpm
   [redacted]
3. Effect of Surfactant Concentration: The following surfactant concentrations were evaluated:
   - [redacted] 0.4%

In addition, the data show that the method is able to discriminate for batches [redacted] (Figure 4).

Figure 3. Effect of Suvorexant Tablet [redacted] on Dissolution (Source: 3.2.P.2.2, Figure 15).

Figure 4. Dissolution (b) (4) (Source: 3.2.P.2.2, Figure 120).

Figure 5. Dissolution curves for MK-4305 (b) (4)
(source: Figure 9, ref. 00002, dissolution method development report).

Reviewer's Comments

The physical stability of the tablet and adequate solubility of the drug substance are considered as TPP and have a high impact on the drug product's dissolution (Figure 5) and bioavailability. According to ICH Q6A guidance, (b) (4) *setting an*

adequate acceptance criteria (b) (4) *is recommended;* (b) (4) *Therefore, the following comments were sent to the Applicant as part of the 74-day letter:*

> ***You have not provided sufficient information to support control at batch release and upon stability*** (b) (4) ***, then provide a limit for the maximum percent*** (b) (4) ***allowable in the drug product (at release and on stability). Also provide the analytical procedure (including their capability of quantitative limit) used to determine*** (b) (4) ***along with appropriate validation data.***
>
> ***In addition, you may use dissolution testing to monitor for the amount*** (b) (4) ***If you choose this alternative path, provide information showing that your proposed dissolution testing methodology and proposed acceptance criterion are able to reject for batches (at release and on stability) with an adequate amount*** (b) (4) ***In addition, an acceptable amount*** (b) (4) ***needs to be supported by clinical information (i.e. ,bioavailability, exposure-response, etc.). Provide dissolution profiles*** (b) (4)

Reviewer's Comments

On December 22, 2012, the Applicant submitted their responses to the above requests. According to the Applicant, the proposed manufacturing process and (b) (4) *controls are sufficient* (b) (4) *However, the CMC reviewer considers that the Applicant has not provided appropriate analytical procedure for quantitative determination* (b) (4) *in the drug product at any given time and therefore the response is inadequate (refer to Dr. Akm Khairuzzaman's CMC review).*

The Applicant also stated that the use of dissolution methodology to monitor the amount (b) (4) *is currently not being pursued.* (b) (4)

(b) (4)

(b) (4) *Therefore, the following comments were conveyed to the Applicant as part of the IR midcycle letter:*

> ***Your proposal*** (b) (4) ***is not acceptable. We have the following recommendations and requests:***
>
> ***a) In consistency with the ICH Q6A guidance*** (b) (4) ***we recommend the use of dissolution testing to monitor for the amount*** (b) (4) ***at release and on stability. For this purpose, provide information/data showing that your proposed dissolution testing methodology and proposed acceptance criterion are able to reject batches*** (b) (4) ***Submit dissolution profiles*** (b) (4) ***In addition, the setting of the acceptable amount*** (b) (4) ***allowed by the dissolution acceptance criterion should be supported by clinical information (i.e., bioavailability, exposure-response, etc.).***
>
> ***b) Alternatively, monitor*** (b) (4) ***at release and on stability using a sensitive analytical method*** (b) (4) ***. In addition, the setting of the acceptable amount*** (b) (4) ***allowed by*** (b) (4) ***specification should be supported by clinical information (i.e., bioavailability, exposure-response, etc.).***

DISSOLUTION ACCEPTANCE CRITERION

The following dissolution acceptance criterion is being proposed by the Applicant as a QC for all the strengths of Suvorexant IR, tablets:

Acceptance Criterion
Q= (b) (4) at 30 min

The Applicant's justification for their proposal is based on a Multiple "Level C" IVIVC model, which was reviewed and found acceptable under IND submission (Refer to Dr. Duan's review for 101847/SDN-175[1]). According to the Applicant, the IVIVC will be used to manage the product lifecycle across various scales and batch sizes, including continuous improvement in process robustness that will ensure product supply, quality, and performance *(see section* (b) (4) *for applicability of the IVIVC in the present NDA submission).*

Briefly, a dedicated PK study was conducted to establish the relationship between dissolution, (b) (4), and PK parameters. A multiple "Level C" IVIVC was developed

using data from different IR formulations which were manufactured to exhibit different dissolution profiles (b) (4) as shown by the in vitro dissolution testing using the proposed QC dissolution method (Figure 7). The IVIVC model correlated dissolution at different time points with Cmax (Table 4), but NOT with AUC, given that all the batches were found BE to the target profile formulation in terms to AUC (Table 5).

(b) (4)

The Cmax of the target formulation was predicted by the model and an interval was generated between ±10% of the target value, represented by the green dash horizontal lines in Figure 7.

Figure 7. Model Predicted Cmax values overlapped with observed values (*Source: Dr. Duan's review for IND 101847/SDN-175[1]).

Based on the IVIVC model, a dissolution profile can be generated representing the border line for bioequivalence to the targeted formulation as shown in the Figure 8, which is the purple thick dashed line overlapped with the profiles of the other 4 batches.

Figure 8. Predicted (purple dashed-line) dissolution profiles based on IVIVC Model to be within 10% of the Mean Cmax Relative to Reference (Source: Adapted from Dr. Duan's review for IND 101847/SDN-175[1]).

Reviewer's Comments

The Applicant proposed dissolution acceptance criterion is based on the IVIVC model predictions. However, since the model is ***NOT*** *a "Level A" correlation and AUC is not part of the correlation, it is uncertain if the proposed dissolution specifications will be able to screen for batches that are not BE containing inadequate amount of* (b) (4) (b) (4)*. Figure 5 indicates that the proposed acceptance criterion of Q=* (b) (4)*% at 30 min is not able to reject for batches containing* (b) (4)*, suggesting a lack of discriminating ability of the dissolution specifications (method and acceptance criterion) in terms of* (b) (4) *content. This reviewer is of the opinion that by tightening the acceptance criterion the discriminating power could be increased. Therefore, the following requests were conveyed to the Applicant as part of the mid-cycle IR letter:*

Your proposed dissolution acceptance criterion is based on IVIVC model predictions. However, since the model is NOT based on a "Level A" correlation and AUC is not part of the correlation, it is uncertain if the proposed dissolution specifications will be able to reject batches that are not bioequivalent because they (b) (4) ***Figure 9, (ref. 00002, dissolution method development report) clearly indicates that your proposed acceptance criterion of Q=*** (b) (4)***% at 30 min is not able to reject batches containing*** (b) (4)***, suggesting the lack of discriminating ability of the dissolution method in terms of*** (b) (4) ***content. Since*** (b) (4) ***content is likely to be a major factor affecting dissolution and therefore the bioavailability of your product, we recommend that one of the following approaches be used for the setting of the dissolution acceptance criterion of your product:***

- ***a) If you select to monitor*** (b) (4) ***content*** (b) (4) ***set the dissolution acceptance criterion based on the performance of the pivotal phase 3 clinical trial batches only. A wider dissolution acceptance criterion should be supported by BE studies.***
  - ***Submit the dissolution profile data (individual and mean values in tabulated and graphical form) from the pivotal phase 3 clinical batches.***

- ***b) If you select to monitor*** (b) (4) ***using dissolution testing, set the dissolution acceptance criterion based on the ability of the dissolution test to reject batches*** (b) (4) ***(refer to our comments in 1a).***

  Also, when setting the dissolution acceptance criterion you need to take into consideration that Tmax plays an important role in the onset of action for this drug product. Since Tmax is dependent on the rate of in vitro an in vivo drug release, setting a specification at 30 min may allow for higher variability on the onset of action.

The following response (summarized) was received on March 12, 2013:

In their response the Applicant proposed the new dissolution acceptance criterion shown below. Note that the Applicant proposes [redacted] in the product (refer to Dr. Khairuzaman for details on the acceptability of the Applicant's proposal).

Acceptance Criterion
Q=[redacted] at 30 min

The newly proposed criterion for dissolution is acceptable, based on the supporting information summarized in the following two points and further described below:

1. Dissolution data with the proposed release method of pivotal clinical batches used in PN028/PN029
2. Dissolution data with the proposed release method of clinical supplies utilized in PN051 "A Two-Part, Single-Dose, Comparative Bioavailability Study of Four Dose Strengths of MK-4305 Tablets under Fasting Conditions"

Table BP-Q2-1 below summarizes the average dissolution profiles of batches used in clinical trial PN028/PN029.

Table BP-Q2-1. Average (% RSD in parenthesis) Dissolution for Clinical Supplies used in PN028/PN029

[redacted]

[redacted]

Table BP-Q2-3. Bioequivalence assessment (AUC and Cmax, GMR with 94.12% CI in parenthesis) for PN051.

	AUC0-t	AUC0-inf	Cmax
2x20 (n=59) vs 1x40 mg (n=60)	102.52%(99.08%-106.07%)	102.33%(98.80%-105.99%)	96.58% (90.96%-102.55%)
2x15 (n=60) vs 1x30 mg (n=59)	99.71% (96.66%-102.85%)	99.66%(96.52%-102.91%)	108.74%(101.10%-116.95%)

Table BP-Q2-2. Average (% RSD in parenthesis) Dissolution for Clinical Supplies used in PN051

(b) (4)

(b) (4)

Figure BP-Q2-2. Average Dissolution profiles for tablets used in PN051 (n=18)

Reviewer's Comments

The following comment was communicated to the CMC review team during an internal meeting dated April 10, 2013:

(b) (4)

Despite the findings presented

by the Applicant (b) (4) *this reviewer is of the opinion that monitoring* (b) (4) *at release and upon stability is warranted. This is because there was no dissolution data included in the submission to demonstrate that the dissolution specifications (method and acceptance criterion) are able to screen for batches* (b) (4) *beyond that present in batches evaluated in phase 3 clinical trials and bioequivalence studies.* (b) (4)

The CMC team responded that the control strategy implemented is sufficient to ensure adequate control (b) (4) *and its monitoring is not warranted provided that the Applicant follows the FDA recommendation (see CMC review for more details).*

QUALITY-BY-DESIGN FOR SUVOREXANT IR TABLETS

The QbD approach summarized in Figure 9 was utilized for the selected formulation to develop the manufacturing processes to consistently provide a final product of acceptable quality.

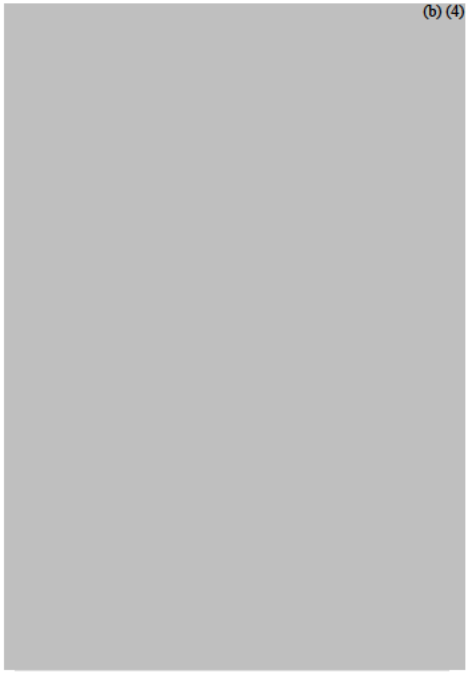

Figure 9. QbD Approach for Suvorexant Drug Product Development.

(b) (4)

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/s/

SANDRA SUAREZ
04/30/2013

ANGELICA DORANTES
04/30/2013

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Suvorexant (MK-4305)
PRODUCT (Brand Name):	Pending
NDA:	204569
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	15 mg, 20 mg, 30 mg and 40 mg
INDICATION:	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
NDA TYPE:	Standard
SUBMISSION DATE:	Aug 29, 2012
SPONSOR:	Merck Sharp & Dohme Corp.
PRIMARY REVIEWER:	Hristina Dimova, Ph.D.
REVIEWER (in vitro studies)	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
PHARMACOMETRICS REVIEWERS:	Joo-Yeon Lee, Ph.D. Satjit Brar, Pharm.D., Ph.D.
PHARMACOMETRICS TEAM LEADER:	Atul Bhattaram, Ph.D.
OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

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1.0 EXECUTIVE SUMMARY

The sponsor is seeking an approval of suvorexant, an orally active, reversible antagonist for orexin receptors, for the treatment of insomnia. By transiently blocking the binding of the wake-promoting neurotransmitters orexin A and orexin B to orexin receptors OX1R and OX2R, suvorexant inhibits activation of wakefulness-promoting neurons of the arousal system. This binding facilitates the physiological process by which the brain transitions from wake to sleep.

The proposed dosing regimen is 40 mg in non-elderly and 30 mg in elderly patients. Suvorexant is formulated for oral administration as an immediate-release tablet (15 mg, 20 mg, 30 mg, and 40 mg).

Thirty one Phase 1 studies have been conducted to evaluate the initial safety and tolerability, PK and PD of suvorexant in healthy subjects and special populations as well as drug-drug interaction (DDI) potential studies (a total of 802 subjects).

Four Phase 2b/3 program in patients with primary insomnia (a total of 2809 patients) have been completed to support the insomnia indication: one Phase 2b dose-finding clinical trial, one Phase 3 Long Term Safety Trial and two Phase 3 efficacy and safety trials in patients with primary insomnia. The Phase 3 trials (P028/P029) were double-blind, placebo-controlled, parallel group trials in patients with primary insomnia. Patients aged 18 to <65 years (non-elderly) were randomized to receive suvorexant 20 mg (low dose) or 40 mg (high dose) QD. Patients aged ≥65 years (elderly) were randomized to receive suvorexant 15 mg (low dose) or 30 mg (high dose) QD. In the primary efficacy analyses on the objective (polysomnography [PSG]) measures of sleep onset and sleep maintenance (Latency to onset of Persistent Sleep [LPS] and Wakefulness after persistent sleep onset [WASO]), both dose groups showed statistically significant effectiveness compared to placebo in both elderly and non-elderly patients on days 1, 28 and 90. No clear dose/exposure-response relationship was observed for the objective measures of sleep and there was no significant difference in exposure between elderly (15 mg) and non-elderly patients (20 mg). Based on the reviewer's analyses, the dose of 15 mg would be reasonable starting dose for both elderly and non-elderly patients.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 204569. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided the sponsor agrees with the Agency's dosing and labeling recommendations.

Post-Marketing Commitment:

1) Develop lower strengths tablets: 7.5 mg and 10 mg.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

Exposure-Response for Effectiveness:
Data obtained from two Phase 3 studies in patients with primary insomnia were used for E-R analysis. A total of 2809 non-elderly and elderly patients with chronic insomnia participated in the phase 3 program (1784 patients treated with suvorexant, including 160 patients treated for at least one year).
In the phase 3 trials, patients aged 18 to <65 years (non-elderly) randomized to suvorexant received 20 mg (low dose) and 40 mg (high dose) QD. Patients aged ≥65 years (elderly) randomized to suvorexant received 15 mg (low dose) or 30 mg (high dose) QD. In the primary efficacy analyses on the objective measures of sleep (LPS and WASO), both dose groups showed statistically significant effectiveness compared to placebo in both elderly and non-elderly patients on days 1, 28 and 90. No clear dose/exposure-response relationship was observed for the objective measures of sleep. Therefore, the high dose did not provide additional benefits relative to the low dose for both elderly and non-elderly patient, based on the objective sleep maintenance (WASO) and onset (LPS) measures.
There was no significant difference in exposure between elderly (15 mg) and non-elderly patients (20 mg). Based on the reviewer's analyses, the dose of 15 mg would be reasonable starting dose for both elderly and non-elderly patients, although 15 mg was not studied in non-elderly patients.

Exposure-Response for Safety:

- The risk of somnolence increases with suvorexant concentrations
- Non-elderly patients showed higher probability of somnolence than elderly patients
- The results from the highway driving studies suggested that elderly subjects may be less sensitive than non-elderly subjects to the impairment on driving performance

General Pharmacokinetics (ADME characteristics) of suvorexant
Absorption:
Suvorexant is a Class 2 drug substance according to the Biopharmaceutics Classification System (high permeability, low solubility).
After oral administration of suvorexant median peak plasma concentrations occur approximately 2 hours (range: 0.5 to 6.0 hours) after dosing of 40 mg under fasted conditions. The estimated absolute bioavailability (F) for 40 mg is approximately 47%.
Distribution:
The absolute volume of distribution was estimated to be 48.6 L following a 20-mg suvorexant IV dose. The total V/F was estimated to be 105.9 L following oral administration of suvorexant.

Plasma protein binding for suvorexant is high (99.5%) and is independent of concentration over the range of 1 to 25 μM. Suvorexant is highly bound to both human serum albumin and to α1-acid glycoprotein.

Metabolism:

Suvorexant is eliminated almost entirely through metabolism in humans, primarily by cytochrome P450 3A (CYP3A), with less contribution by CYP2C19. The predominant metabolic pathway of suvorexantin human is hydroxylation (formation of M9) followed by further oxidation to the carboxylic acid derivative (M4).

M9 was the major circulating metabolite, present to approximately equal concentrations to parent under steady-state conditions. However, unlike suvorexant, M9 is a substrate of P-gp and does not penetrate the brain. M9 is not expected to be active *in vivo* based on results from *in vitro* and EEG studies in dogs.

Elimination:

Suvorexant was eliminated primarily in the form of metabolites.

The primary route of excretion is through feces, approximately 66% of the suvorexant dose recovered in the feces and 23% recovered in the urine.

The mean terminal half-life ($t_{1/2}$) for suvorexant is 12.2 hours. The terminal half-life for M9 is similar to that observed for suvorexant.

Steady-state of suvorexant was reached by 3 days of once-daily dosing, consistent with its terminal half-life. Estimates of suvorexant AUC and C_{max} accumulation, based on the increase from single to multiple-dose, approximates 1.2 to 1.6.

Single dose and multiple dose pharmacokinetics:

Suvorexant pharmacokinetics has been characterized in healthy men and women over a single-dose range of 4 mg to 240 mg. Additionally, the pharmacokinetics of suvorexant has been assessed in clinical trials of patients with insomnia following administration of multiple doses up to 80 mg administered once daily at bedtime.

A population approach was used to evaluate the pharmacokinetics of suvorexant in healthy subjects from 16 Phase 1 studies (12 single-dose and 4 multiple-dose) with dense pharmacokinetic sampling following doses ranging from 10 to 80 mg administered under fasted conditions. The population PK model that best characterized the Phase 1 data was a 3-compartment model with dose-dependent F1, sigmoidal absorption (with lag time), linear distribution into the first peripheral compartment (Vp1/F) and and first-order elimination from the central compartment (Vc/F). The plasma clearance of suvorexant was estimated to 2.92 L/hour following an IV dose of 20 mg. Following oral administration of suvorexant, the typical CL/F is in general agreement with that following IV dosing adjusting for absolute bioavailability.

Dose proportionality:

Suvorexant pharmacokinetics are less than dose proportional over the 10 to 80-mg range, likely due to absorption limitations.

Pharmacokinetics in patients:

The systemic exposure to suvorexant in patients is similar to that in healthy subjects.

Intrinsic Factors:

Gender

Suvorexant exposure was higher in females than in males. The apparent oral clearance of suvorexant was 20.5% lower in females compared to males. No dose adjustment for suvorexant is needed based on gender only.

Weight and Body Mass Index (BMI)

Apparent oral clearance of suvorexant was inversely related to BMI. Obese females have ~ 1.5-1.6 fold higher exposure compared to the majority population studied in the pivotal Phase 3 trials.

Suvorexant dose in obese females should be reduced, e.g. 10 mg starting dose if the recommended suvorexant dose is 15mg.

As the lowest proposed marketed strength is 15 mg, the sponsor needs to develop a lower strength tablet for this patient population. (PMC)

Age

The lower doses for the elderly in the phase 3 trials were selected based on the belief that elderly subjects may be more sensitive to hypnitics than non-elderly subjects. However, data from the phase 1 suvorexant driving studies and the sponsor's PK/PD Analysis of Adverse Effects (AEs) from the Phase 2 and 3 trials did not indicate that age has an effect on suvorexant PK and PD. Elderly patients are predicted to have ~15% increased C_{9hr} relative to non-elderly. In addition, the results from the highway driving studies suggested that elderly subjects may be slightly less sensitive than non-elderly subjects to the impairment on driving performance. No dose adjustment for suvorexant is recommended based on age.

Pediatrics

The safety and effectiveness of suvorexant in pediatric patients under 18 years of age have not been established.

Race:

There is no significant impact of race on the PK of suvorexant obsereved.

No dose adjustment for suvorexant is recommended based on race.

Hepatic impairment

Systemic exposure (expressed as unbound and bound) to suvorexant in subjects with moderate hepatic impairment was similar to that in matched healthy subjects. However, suvorexant half-life was increased (from 14.7 to 19.1 h) in subjects with moderate hepatic impairment. Suvorexant pharmacokinetics were not evaluated in subjects with severe hepatic impairment.

Suvorexant is not recommended in subjects with severe hepatic impairment.

No dose adjustment for suvorexant is needed in subjects with mild and moderate hepatic impairment.

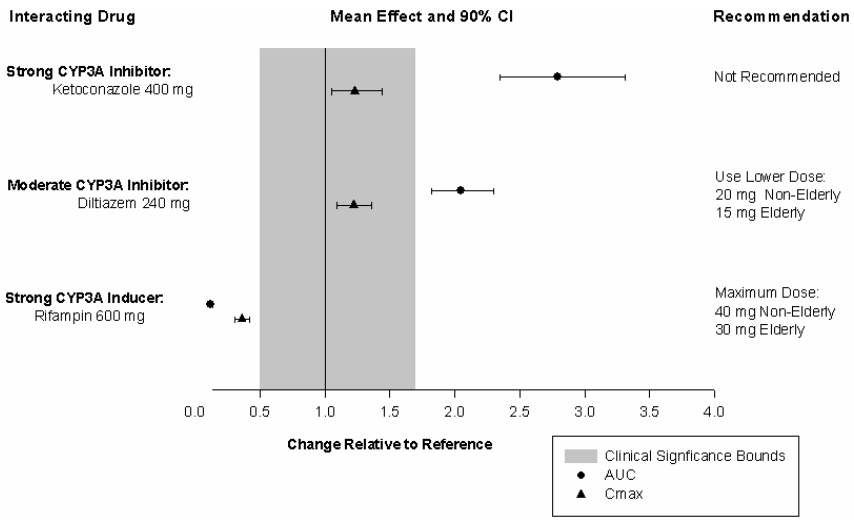
Renal impairment:

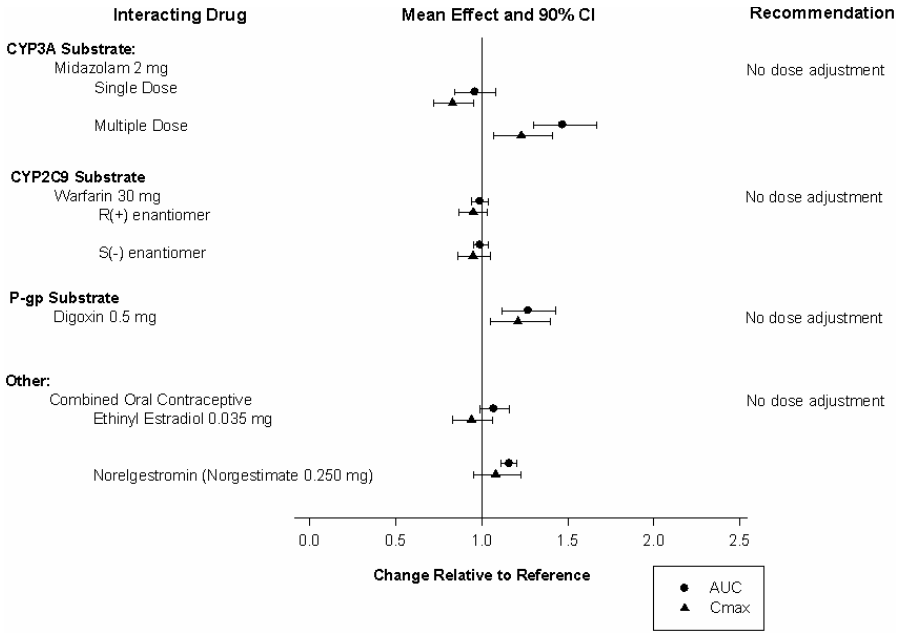
Severe renal impairment does not have significant impact on the PK of suvorexant.

No dose adjustment is required in patients with renal impairment.

Extrinsic Factors:
In Vitro Studies: *In vitro* metabolism studies demonstrate that suvorexant has a potential to inhibit CYP3A, intestinal P-gp and BCRP; however, suvorexant is unlikely to cause clinically significant inhibition of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. In addition, no clinically meaningful inhibition of OATP1B1 and OCT2 transporters is anticipated. At clinically recommended doses, suvorexant does not exhibit an induction potential for CYP3A4, CYP1A2, and CYP2B6. M9 did not show in vitro inhibition potential for any of the CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A). M9 is a P-gp substrate.

In Vivo Studies:
In Vivo drug-drug interaction (DDI) studies have been conducted with ketoconazole (strong CYP3A and/or P-gp inhibitor), diltiazem (moderate CYP3A inhibitor) and rifampin (strong CYP3A inducer) to evaluate the DDI potential of other drugs on suvorexant PK. In addition, clinical PK studies were conducted to determine the DDI potential of suvorexant on midazolam (sensitive CYP3A substrate), oral contraceptives (CYP3A, UGT and SULT substrate), warfarin (CYP2C9 substrate), and digoxin (P-gp substrate). The results from these studies and the dose adjustments proposed by the sponsor are presented below.





Due to potential additive CNS effects, clinical studies have been conducted to evaluate the potential for PK and PD drug-drug interactions between suvorexant and CNS-active agents, including alcohol and paroxetine, a commonly prescribed selective serotonin reuptake inhibitor (SSRI).
The co-administration of suvorexant with alcohol produced additive impairment on on psychomotor performance. There was no PK interaction between alcohol and suvorexant. There was no PK or PD interaction between suvorexant and paroxetine.

OPC Recommendations:

- Suvorexant should not be co-administered with strong CYP3A inhibitors.
- The suvorexant dose in subjects receiving moderate CYP3A4 inhibitors should be reduced by half. If the recommended suvorexant dose is 15 mg, the sponsor needs to develop a lower strength tablet for dose adjustment in patients receiving moderate CYP3A4 inhibitors. (PMC)
- The efficacy of suvorexant dose in subjects receiving CYP3A4 inducers may be decreased.
- No dose adjustment is needed for CYP3A substrates, however patients on sensitive CYP3A substrates with narrow therapeutic range (e.g., alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) should be closely monitored.
- No dose adjustment is needed for oral contraceptives when given in combination with suvorexant.
- No dose adjustment is needed for warfarin when given in combination with suvorexant.
- No dose adjustment is needed for digoxin when co-administered with suvorexant, however serum digoxin concentrations should be monitored as clinically indicated.

- Alcohol should not be co-administered with suvorexant due to the additive CNS effects.
- A general precaution should be advised when suvorexant is co-administered with drugs that produce CNS depressant effects due to potential additive effects.

Biopharmaceutics:
BCS Class:
Suvorexant can be considered a Biopharmaceutical Classification System (BCS) Class II drug (low solubility, high permeability).
Bioequivalence:
The Final Market Image (FMI), which is the intended commercial formulation, was used in the Phase 3 trials, therefore no bioequivalence study is required.
Food Effect:
Suvorexant can be administered without regards to meals or meal types. For faster onset of sleep suvorexant should not be administered with or immediately after a meal as Tmax is delayed ~1 hour by food.

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form/Strengths: immediate-release tablet (15 mg, 20 mg, 30 mg, and 40 mg)

Indication: Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance

Pharmacologic Class: selective antagonist for orexin receptors OX_1R and OX_2R

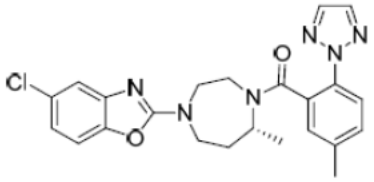
Chemical Name: [(7R)-4-(5-Chloro-2- benzoxazolyl)hexahydro-7-methyl-1H-1,4-diazepin-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl] methanone.

Company or laboratory code(s): suvorexant

Molecular formula: $C_{23}H_{23}ClN_6O_2$

Molecular mass: 450.92

Chemical structure:



Physical Characteristics: Suvorexant is a white to off-white powder, (b) (4) The aqueous solubility for (b) (4) drug substance found in the drug product formulation is (b) (4)

(b) (4)

Formulation: Suvorexant has been formulated as immediate release tablets: 15 mg, 20 mg, 30 mg and 40 mg. The composition of suvorexant tablets is presented below:

(b) (4)

		Strength:	15 mg	20 mg
Components	Quality Reference	Function	Amount per tablet (mg)	Amount per tablet (mg)
(b) (4)				
Suvorexant (MK-4305)	----	Active	15.00	20.00
Polyvinylpyrrolidone/Vinyl Acetate Copolymer (Copovidone)	USP-NF, Ph. Eur., JPE			(b) (4)
Lactose Monohydrate	USP-NF, Ph. Eur., JP			
Microcrystalline Cellulose	USP-NF, Ph. Eur., JP			
Croscarmellose Sodium	USP-NF, Ph. Eur., JP			
Magnesium Stearate (non-bovine)	USP-NF, Ph. Eur., JP			
				(b) (4)
		Total Tablet Weight	195.5	258.8

(b) (4)

2.1.2 Mechanism of action and therapeutic indication:

Suvorexant is a selective antagonist for orexin receptors OX_1R and OX_2R, indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. By blocking the binding of the wake-promoting neurotransmitters orexin A and orexin B to orexin receptors OX_1R and OX_2R, suvorexant inhibits activation of wakefulness-promoting neurons of the arousal system, and thereby facilitates the physiological process by which the brain transitions from wake to sleep, enabling sleep to occur. Suvorexant has no pharmacological affinity for receptors that bind to gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, melatonin, histamine, acetylcholine, or opiates.

2.1.3 Proposed dosages and route of administration:

Suvorexant is orally-administered as an immediate-release tablet. Four strengths (15 mg, 20 mg, 30 mg and 40 mg) are proposed to match the intended daily dosage based on age and tolerability/efficacy considerations.

Sponsor's proposed dosages: Non-elderly Adults: 40 mg once daily immediately before bedtime, can decrease to 20 mg in case of tolerability issues. Elderly Adults: 30 mg once daily immediately before bedtime, can decrease to 15 mg in case of tolerability issues.

Reviewer's proposed dosages: 15 mg starting dose for both elderly and non-elderly patients, if tolerable, can increase to 30 mg in case of lack of efficacy.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

Four Phase 2b/3 program in patients with primary insomnia have been completed to support the insomnia indication: a Phase 2b dose-finding clinical trial (Protocol 006), one Phase 3 Long Term Safety Trial (Protocol 009), and two Phase 3 efficacy and safety trials in patients with primary insomnia (Protocols 028 and 029). A total of 2809 non-elderly and elderly patients with chronic insomnia participated in the phase 3 program (1784 patients treated with suvorexant, including 160 patients treated for at least one year).

In the two confirmatory efficacy trials (P028 and P029), efficacy and safety of suvorexant were evaluated in replicate core 3-month Treatment Phases. These trials were similarly designed as combined-age (with enrollment of both non-elderly and elderly adults) and combined-measure studies (with data collected for both objective and subjective efficacy measures) placebo-controlled, parallel group, multi-center/multi-national trials.

Based on the results of the Phase 2b dose-ranging clinical trial (P006), the Phase 3 dose of primary focus in non-elderly patients (< 65 years) was 40 mg (referred to as high dose [HD]). Based on initial evidence for slightly higher exposures in elderly patients in Phase 1 studies, suvorexant HD in elderly patients was 30 mg. A lower dose (LD) of 20 mg in non-elderly and 15 mg in elderly was also evaluated in these two trials, but with a smaller sample size than HD with intention of pooling sample across the two studies for more precise estimation of LD effects. Exposure-response analyses were performed by the sponsor (and the pharmacometrics reviewer) based on the Phase 2/3 studies.

Summary of Design Features of Phase 2b/3 Clinical Trials With Suvorexant

Trial ID	Design Control Type	Duration	Trial Objective	Trial and Control Drugs Dose, Route & Regimen	No. Patients Treated (Total, by Treatment Arm), and Completed
PHASE 2b					
Dose Finding (PN006)	Phase 2b, multicenter, randomized, double-blind placebo- controlled, 2-period adaptive crossover PSG trial	4-week treatment phase in each period	- Evaluate Efficacy at Night 1 and Week 4 by endpoints of SE. - Evaluate the safety and tolerability of MK-4305 in patients with chronic insomnia	Suvorexant • MK-4305 10 mg • MK-4305 20 mg • MK-4305 40 mg • MK-4305 80 mg Placebo	Total: 254 • MK 10 mg: 62 • MK 20 mg: 61 • MK 40 mg: 59 • MK 80 mg: 61 • PBO: 249 Completed: 228
PHASE 3 PIVOTAL STUDIES					
Pivotal Efficacy 1 (PN028)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group, trial	3-month Treatment Phase followed by 3-month Extension Phase	- Evaluate the safety and tolerability of MK-4305 in patients with chronic insomnia - Evaluate efficacy at Week 1, Month 1, and Month 3 by patient-reported outcomes of sTST, sTSO, and sWASO; and at Night 1, Month 1, and Month 3 by PSG endpoints of LPS and WASO.	Suvorexant HD • MK-4305 40 mg (non-elderly) • MK-4305 30 mg (elderly) Suvorexant LD • MK-4305 20 mg (non-elderly) • MK-4305 15 mg (elderly) Placebo	Treatment Phase (P028) Total: 1021 • LD: 254 • HD: 383 • PBO: 384 Completed: 916 Extension Phase Total: 423 • LD: 100 • HD: 172 • PBO: 151 Completed: 377
Pivotal Efficacy 2 (PN029)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group trial	3-month Treatment Phase			Treatment Phase (P029) Total: 1009 • LD: 239 • HD: 387 • PBO: 383 Completed: 881
Long Term Safety (PN009)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, long term safety trial	12-month double-blind Treatment Phase followed by a 2-month Randomized Discontinuation Phase	Evaluate long term safety of MK-4305 in patients with chronic insomnia	Suvorexant HD • MK-4305 40 mg (non-elderly) • MK-4305 30 mg (elderly) Placebo	Treatment Phase Total: 779 • MK: 521 • PBO: 258 Completed: 484 Randomized Discontinuation Phase Total entered: 484 • MK/MK: 156 • MK/PBO: 166 • PBO/PBO: 162 Completed: 470

HD= high dose, LD= low dose, PBO= placebo; MK/MK= MK / MK, MK / PBO, PBO / PBO = therapy received during Treatment phase / therapy received during Randomized Discontinuation phase.
.PSG= polysomnography, PRO= patient-reported outcomes, SE= sleep efficiency, sTST = subjective total-sleep-time, sTSO= subjective time-to-sleep-onset , sWASO= subjective wake-time-after-sleep-onset , LPS=Latency-to-onset-of-Persistent-Sleep, WASO= Wakefulness-After-persistent-Sleep-Onset

Suvorexant pharmacokinetics has been characterized in healthy men and women over a single-dose range of 4 mg to 240 mg and over a multiple-dose range of 10 to 100 mg/day. The clinical pharmacology program includes thirty one Phase 1 studies to evaluate the initial safety and tolerability, PK and PD of suvorexant in healthy subjects and special populations (a total of 802 subjects).
Additionally, the pharmacokinetics of suvorexant has been assessed in clinical trials of patients with insomnia following administration of doses up to 80 mg administered once daily at bedtime.
An overview of all clinical pharmacology studies is presented below.

List of Suvorexant Clinical Pharmacology Studies

Module 5/2.7 Section	Module 5 Study Type	PN	Protocol Short Title	Dosing	N
Biopharmaceutics in Module 2.7.1	Comparative BA/BE	P007	Biocomparison Study	AM	18
		P041	Biocomparison Study	AM	12
	Bioavailability	P020	FMI Food Effect	AM	14
		P042	Japanese Food Effect	AM	12
Human PK In Module 2.7.2	Healthy Subject PK and Initial Tolerability	P001	FIM SD Young	AM (two panels have PM)	40
		P003	MD Young	PM	40
		P011	SD Young Extension	AM	17
		P012	ADME	AM	6
		P018	Dose Proportionality	AM	Part 1: 32 Part 2: 16
	Intrinsic Factors	P004	SD Elderly	AM	20
		P005	Japanese SD PK	AM/PM	32 (Part II data only is N=16)
		P017	Hepatic Insufficiency	AM	8 moderate; 8 healthy
		P023	Renal Insufficiency	AM	8 severe; 8 healthy
		P027	MD Elderly	PM	75
	Extrinsic Factors	P008	Ketoconazole DDI	AM	10
		P013	OCP DDI	PM	20
		P015	Midazolam DDI	AM	12
		P016	Digoxin DDI	AM	20
		P024	Warfarin DDI	AM	14
		P026	Paroxetine DDI	PM	24
		P038	Rifampin and Diltiazem DDI	AM	Part I: 10 Part II: 20

Module 5/2.7 Section	Module 5 Study Type	PN	Protocol Short Title	Dosing	N
Human PD In Module 2.7.2	Healthy Subject PD and PK/PD	P002	Healthy Subject PSG	PM	22
		P010	Alcohol Interaction	AM	31
		P021	Elderly PM Safety	PM	12
		P022	Thorough QTc	AM	53
		P025	Abuse Liability Part I – Qualifying Phase Part II – Treatment Phase	AM	73
		P035	Car Driving Study (Non-Elderly)	PM	28
		P039	Car Driving Study (Elderly)	PM	24
		P040	Healthy Subject Respiratory Safety	PM	12
	Patient PD and PK/PD	P032	Respiratory Safety Study in COPD Patients	PM	25
		P036	Respiratory Safety Study in OSA Patients	PM	26
			Total N in suvorexant safety database		802
N is the number of subjects enrolled in each study					

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

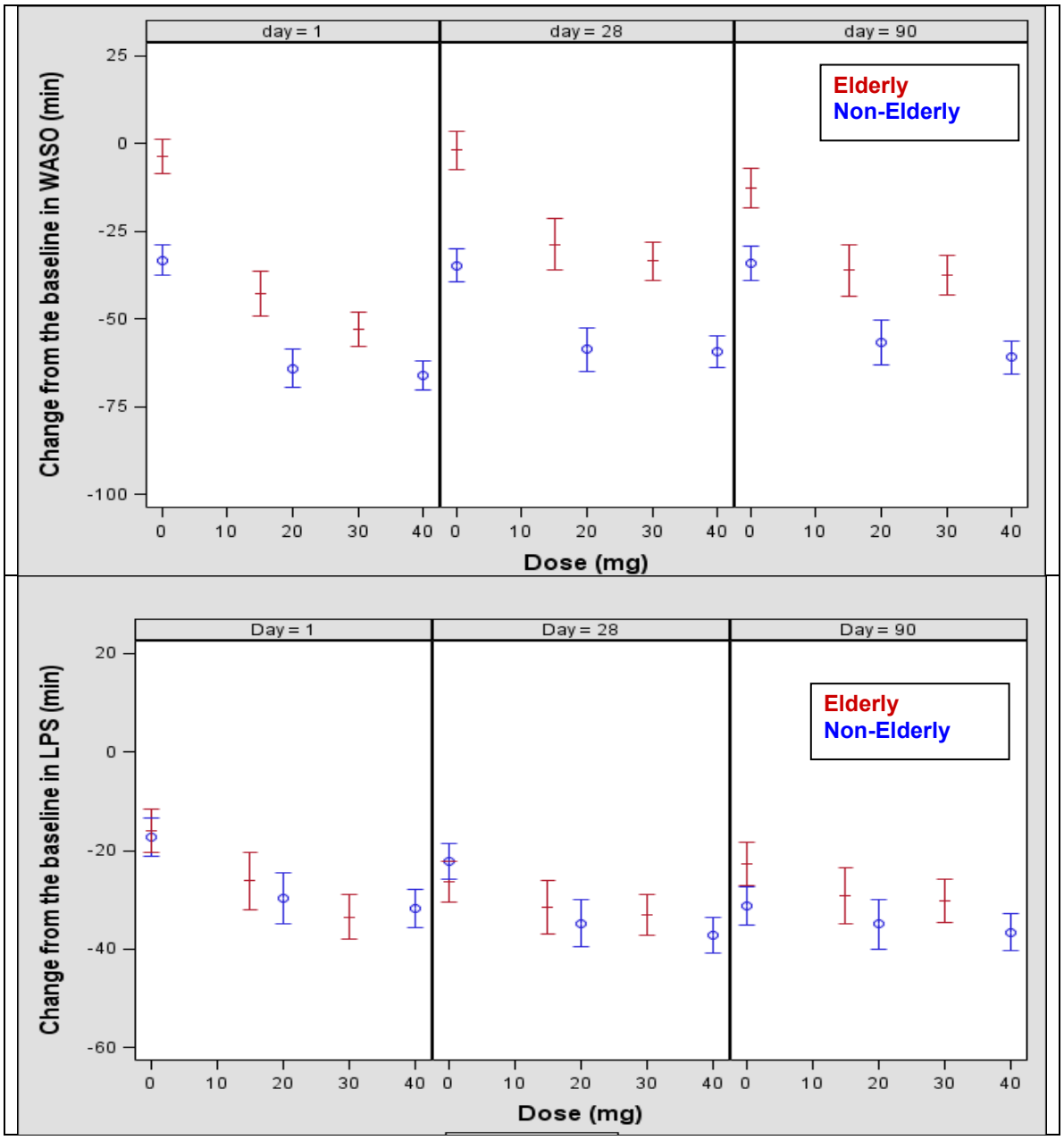
The efficacy evaluation included analyses of improvement in sleep maintenance and sleep onset as evidenced by both objective assessments by polysomnography (PSG) and subjective patient reports. Wakefulness after persistent sleep onset (WASO) and latency to onset of persistent sleep (LPS) are considered the primary endpoints for the objective evaluation of sleep maintenance and onset, respectively, while weekly means (of the daily e-diary) for mean subjective total sleep time (sTSTm) and mean subjective time to sleep onset (sTSOm) are considered the primary endpoints for the subjective evaluation of sleep maintenance and onset, respectively. Supportive analyses of mean subjective wake time after sleep onset (sWASOm) were also provided, as further evidence for the efficacy of suvorexant in sleep maintenance.
Key safety evaluations included Adverse Effects (AEs) analysis, next-day effects on digital symbol substitution test (DSST), an objective measure in Phase 3 studies.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

Dose-response analyses were conducted on pooled data from the phase 3 trials 028 and 029. Both LD and HD showed significant effectivelness compared to placebo group. No apparent exposure-dependent improvement was observed in both sleep maintenance and onset measurements over the dose range of 15 mg to 40 mg, based on the independent analyses performed by the pharmacometrics reviewer.

Figure 1 presents the dose-response relationship for sleep maintenance (ΔWASO) and onset (ΔLPS) from the phase 3 trials. It shows little difference in effectiveness between the two dose groups for both elderly and non-elderly patients.

Figure 1: LS mean with 95% CI for Δ WASO (top) and Δ LPS (bottom) vs. Dose by day. LS means were adjusted by baseline value, age group, region and gender

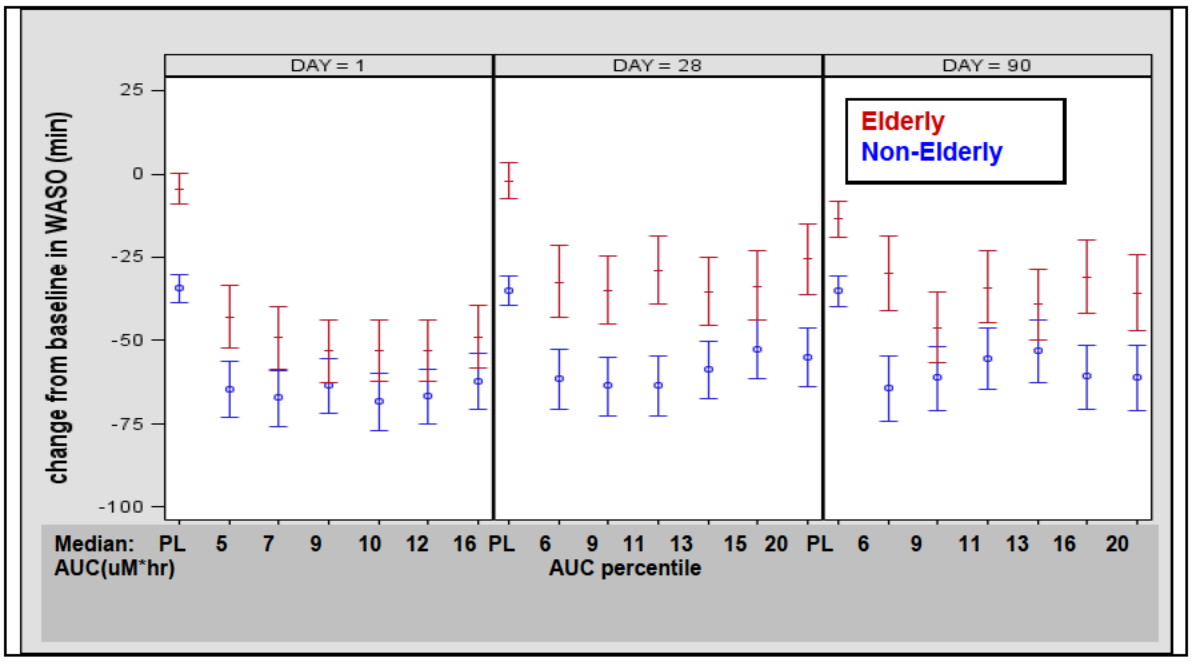


The pharmacometrics reviewer further looked into the same endpoints related to AUC_{0-24} which was predicted from the sponsor's model. AUC_{0-24} was categorized by 6 bins with same number of patients at each bin. All placebo patients were grouped in the first bin.

Figure 2 presents the exposure-response relationship for ΔWASO, which shows no clear exposure-dependent improvement over the dose range of 15 mg to 40 mg.
The top panel of Figure 3 shows the results by elderly and non-elderly patients where non-elderly patients seems to get better benefit in ΔWASO compared to elderly patients but there appears to be still no clear exposure-dependent relationship in both populations. Note that the reviewer could not fit the model due to the flat exposure-response relationship.
The bottom panel of Figure 3 displays the exposure-response relationship for ΔLPS for by elderly and non-elderly patients. No exposure dependent changes in sleep onset endpoint were observed.

In conclusion, based on the reviewer's analyses, the dose of 15 mg would be reasonable starting dose for both elderly and non-elderly patients, although 15 mg was not studied in non-elderly patients. It is expected that 5 mg lower dose in non-elderly patients will not make much difference in suvorexant exposure based on population PK results and distribution of exposure at 10mg and 20mg from Study 006 (see Figure 3).

Figure 2: LS mean with 95% CI for Δ WASO (top) and Δ LPS (bottom) vs. exposure (AUC_{0-24}) by day by elderly and non-elderly patients. LS means were adjusted by baseline value, age group, region and gender to be consistent with dose-response analysis.



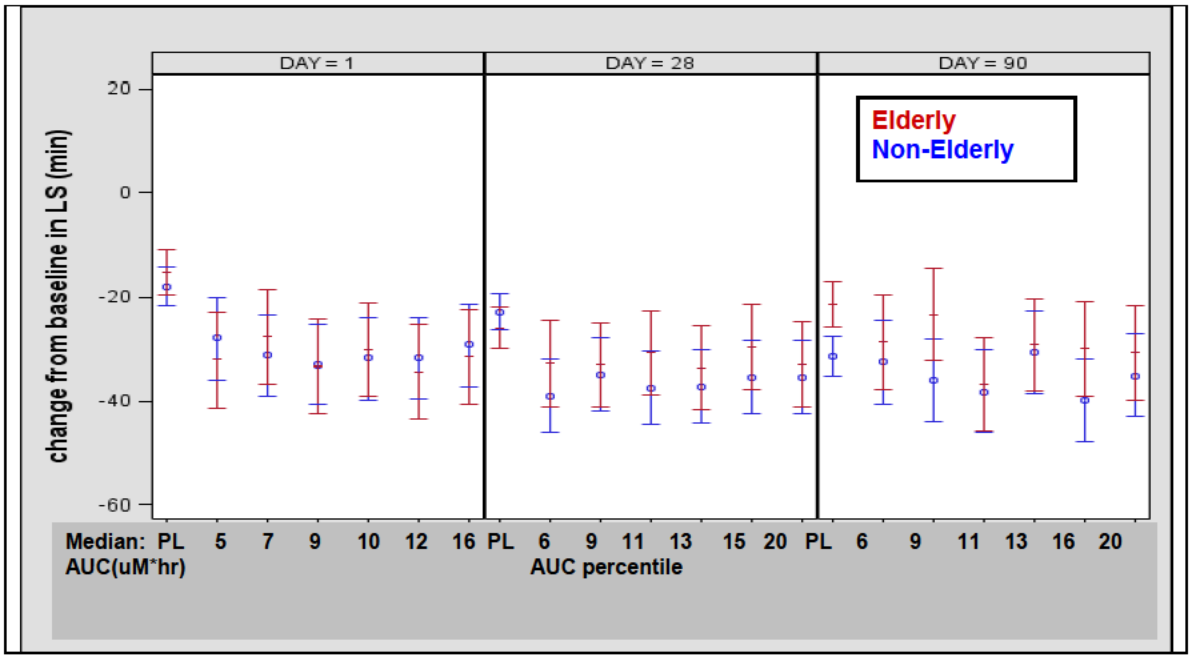
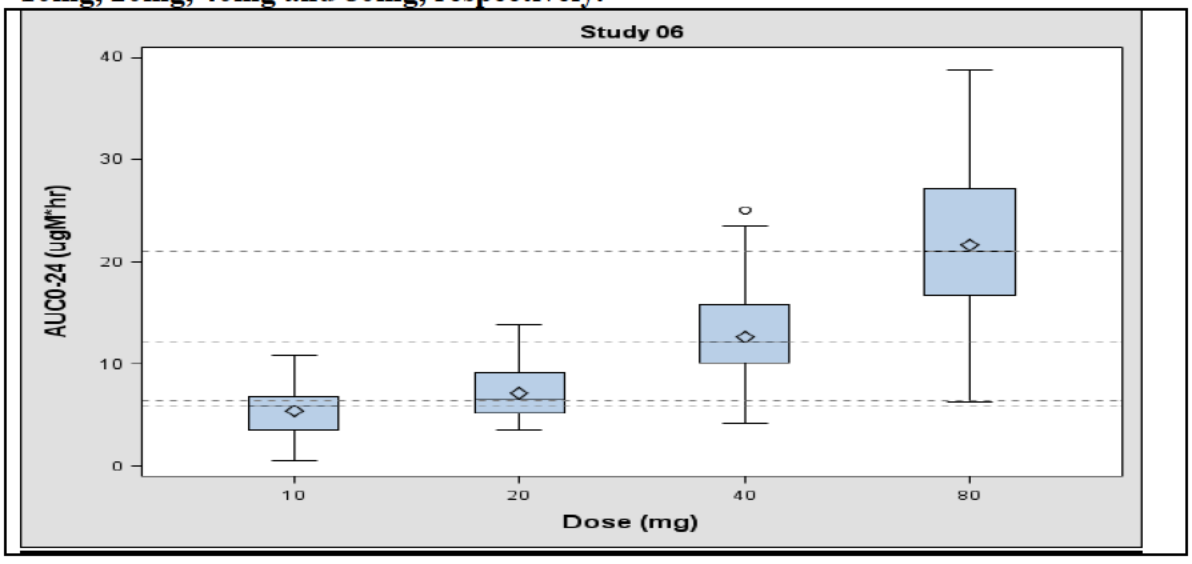


Figure 3: Distribution of $AUC_{0\text{-}24}$ (µM*hr) at each dose (data from 1st period of Study 006). The dotted horizontal lines on the top indicate the median $AUC_{0\text{-}24}$ at each dose: The median $AUC_{0\text{-}24}$ are 5 µM*hr, 6 µM*hr, 12 µM*hr and 21 µM*hr at 10mg, 20mg, 40mg and 80mg, respectively.

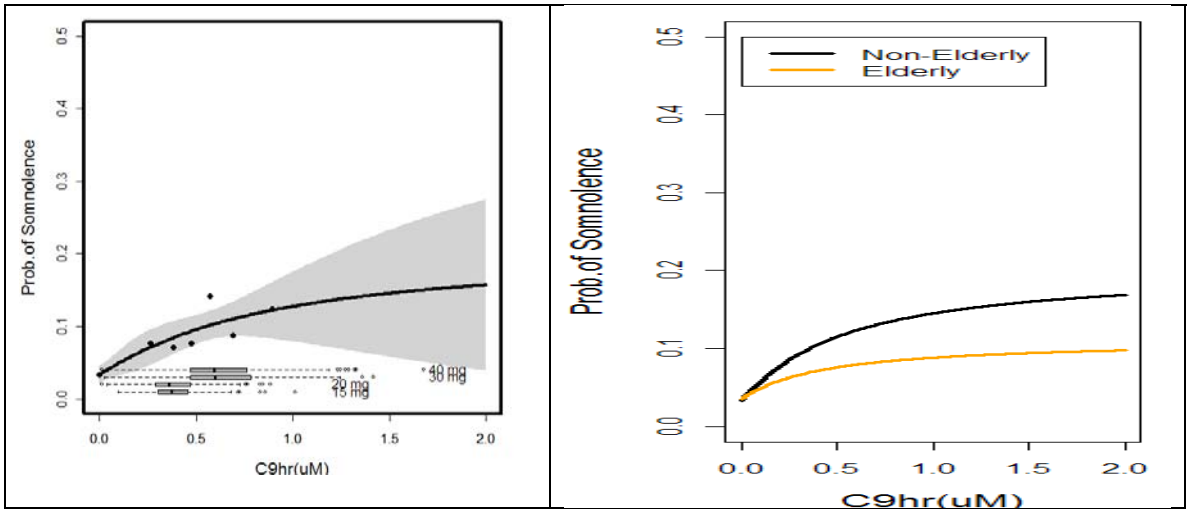


2.2.4 What are the characteristics of exposure-safety relationships?

For the safety analysis, the pharmacometrics reviewer analyzed the relationship between C_{9hr} (Surovexant concentrations at 9h post-dose) and incidence of somnolence (the most frequently reported AE) and digital symbol substitution test (DSST) score. The DSST was used to evaluate the next-day effects of suvorexant on psychomotor performance.

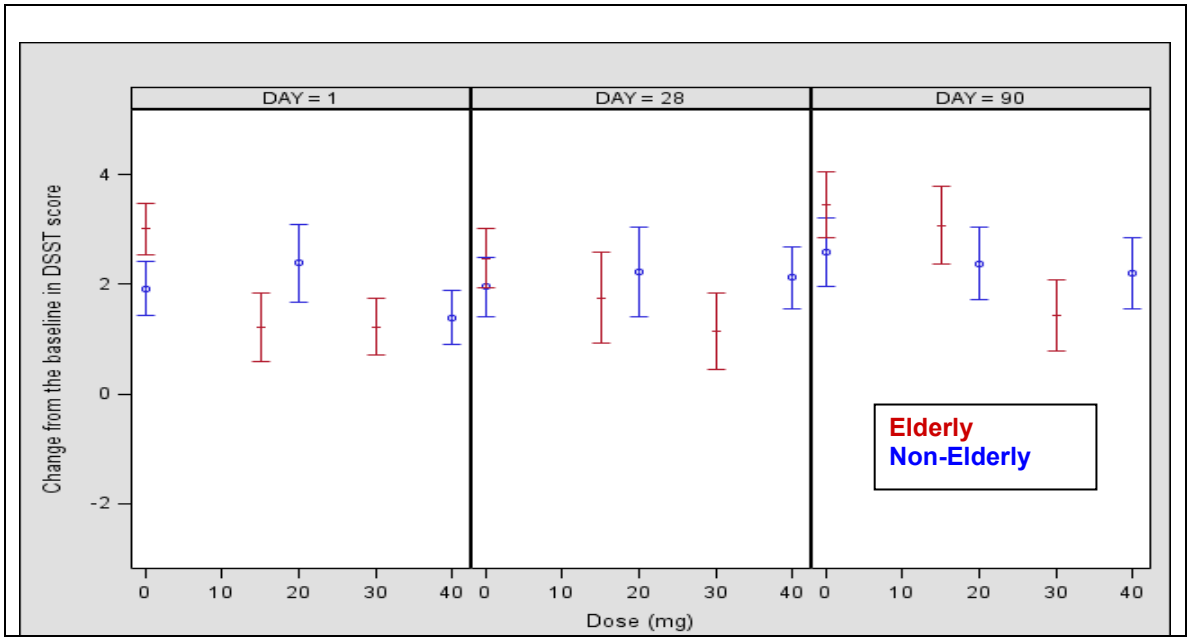
As shown in Figure 4, the probability of somnolence increases with increase of suvorexant concentrations. In addition, non-elderly patients showed higher risk of somnolence at the same concentration compared to elderly patients.

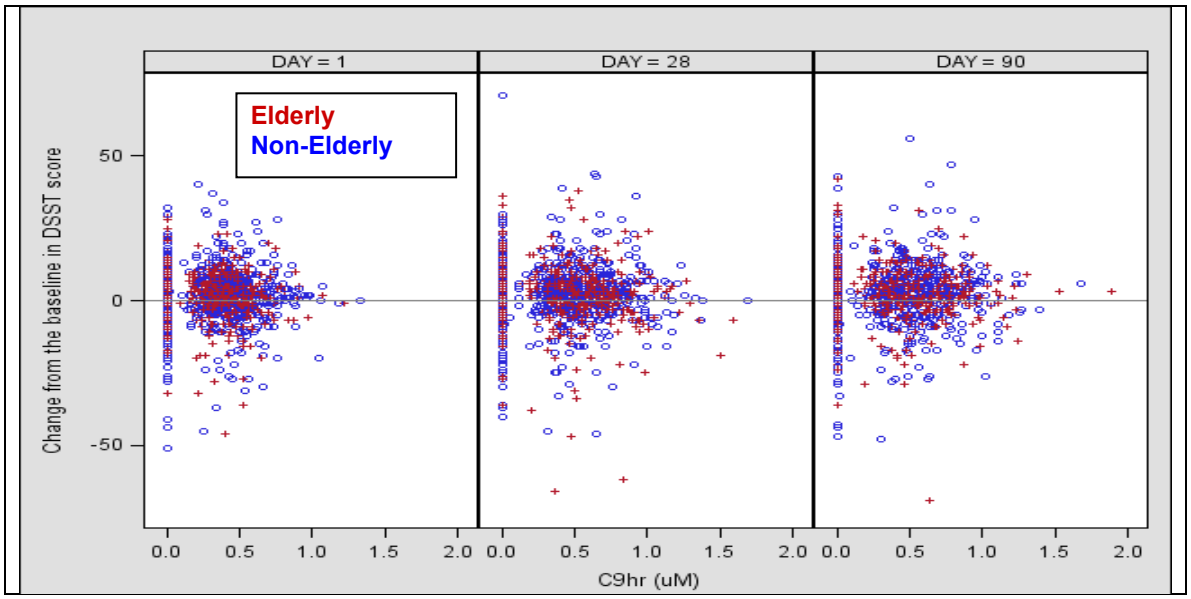
Figure 4: Left: Overall model-predicted relationship for probability of somnolence and suvorexant concentration (C_{9hr}). Right: model-predicted relationship for probability of somnolence and suvorexant concentration (C_{9hr}) by elderly and non-elderly patients



In elderly patients dose dependent (30 mg vs. 15 mg relative to placebo) decrease in DSST was observed (Figure 5). However, the magnitude of difference did not seem to be noticeable, and DSST score did not show clear concentration-dependent relationship.

Figure 5: Dose vs. ΔDSST (top) and C_{9hr} vs. ΔDSST (bottom) relationship by elderly and non-elderly patients





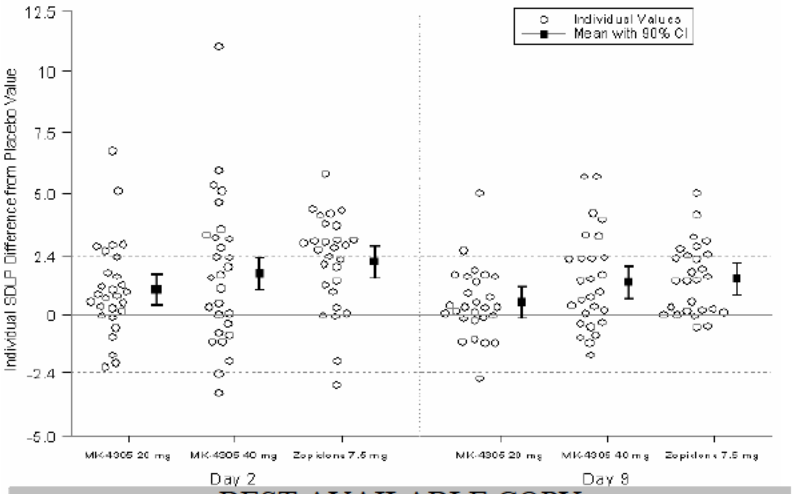
The potential for next day residual effects of suvorexant was also evaluated in two Highway Car Driving Studies in healthy non-elderly and elderly subjects (P035 and P039).

Both studies had a similar design: randomized, double-blind, placebo- and positive-controlled, 4 period crossover studies. Zopiclone 7.5 mg, administered double-blind as a single dose on Day 1 and again on Day 8, was included as an active control. The primary endpoint was standard deviation of lane position (SDLP), a measure of road tracking error or "weaving," on Day 2 (after a first, ie. single dose) and Day 9 (after 8 consecutive doses). An increase in SDLP of 2.4 cm or greater is considered clinically meaningful, based on literature data indicating a blood alcohol concentration of 0.05% increases SDLP by 2.4 cm. Twenty-eight healthy non-elderly male and female subjects (21 to 64 years old, inclusive) received two dose levels of suvorexant (20 mg and 40 mg) or placebo consecutively for 8 days in Study P035; twenty-four healthy elderly male and female subjects (65 to 80 years) received 15 mg and 30 mg suvorexant in Study P039. The primary endpoint was standard deviation of lane position (SDLP) from the driving test. SDLP was analyzed both by mean analysis and symmetry analysis. The symmetry analysis was conducted to evaluate potential effects on the population distribution: for each treatment comparison it was determined if there was a significant difference in the number of individuals with an increase in SDLP >2.4 cm (worsening) vs. the number of subjects who had a decrease in SDLP below -2.4 cm (improvement). Standard deviation of speed (SDS), memory, balance, psychomotor tests and PK were also assessed.

Highway Car Driving Study P035 Results:

Based on mean SDLP analysis, suvorexant did not impair highway driving performance following single- and multiple- 20 mg and 40 mg doses. However, the symmetry analysis of SDLP revealed that there was a statistically greater number of subjects with SDLP treatment difference of >2.4 cm than those with SDLP <-2.4 cm on

Day 2 for both suvorexant doses and for zopiclone. On Day 9 (following 8 consecutive days dosing), there was a significantly greater number of subjects with SDLP treatment difference of >2.4 cm than those with SDLP <-2.4 cm after 40 mg but not after 20 mg suvorexant.



The treatment difference of SDLP was generally larger with the high dose (40 mg) than low dose (20 mg). The treatment difference on Day 9 was smaller for both suvorexant doses as compared to Day 2, suggesting tolerance effects.

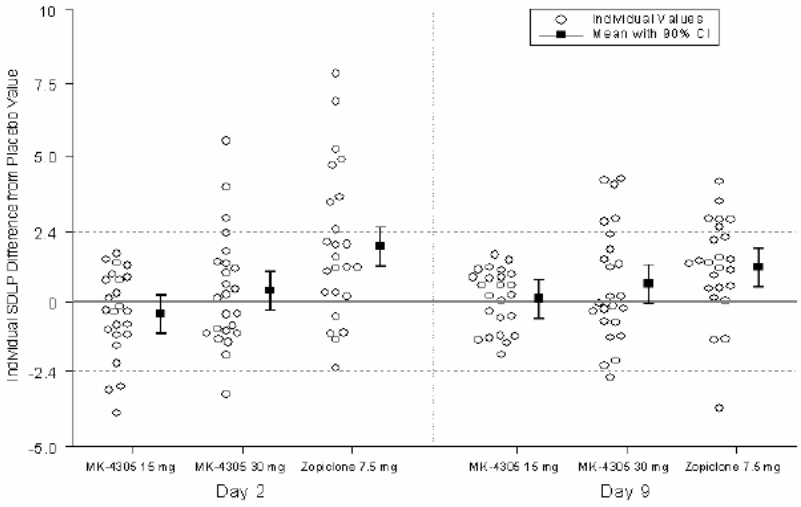
In addition, there was a statistically significant increase in standard deviation of speed (SDS) on Day 2 for zopiclone, 20 mg suvorexant and 40 mg suvorexant compared to placebo, suggesting impairment on driving performance. On Day 9, only 40 mg suvorexant had a statistically significant effect on SDS compared with placebo.

Statistically significant decreases in delayed recall were observed on Day 2 for zopiclone and 40 mg suvorexant, but not on Day 9.

Four female subjects prematurely stopped the driving test due to somnolence after driving for 29 to 57 minutes: three subjects following 40 mg suvorexant on Day 2 (AN0006, AN0007 and AN0016); two subjects following 20 mg suvorexant, one each on Day 9 (AN0007) and on Day 2 (AN0021). Among them, AN0016 had the highest C_{11h} levels in the group, Subjects AN0006 and AN021 had comparable C_{11h} levels with the other subjects in the group and subject AN0007 had no PK samples collected.

Highway Car Driving Study P039 Results:

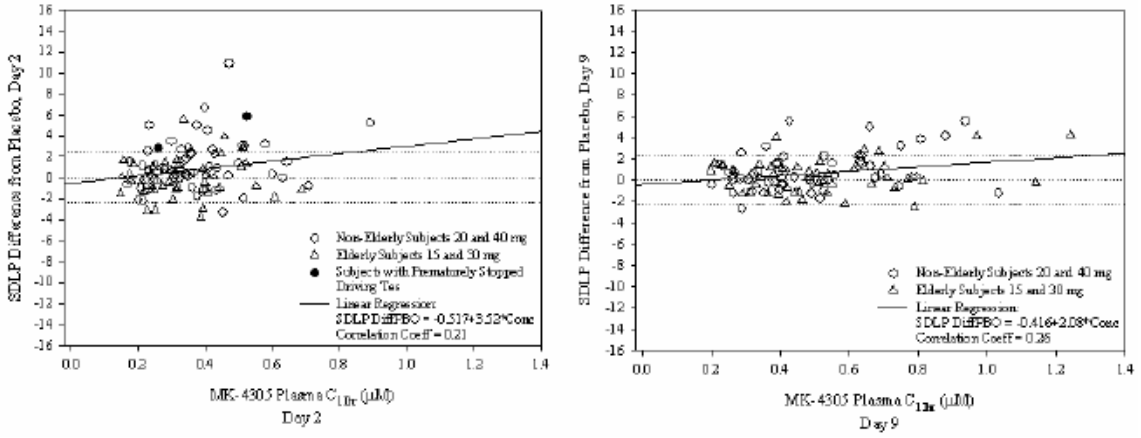
Based on mean SDLP analysis, suvorexant at did not impair highway driving performance in elderly subjects following single- and multiple- 15 mg and 30 mg doses. However, based on symmetry analysis of SDLP, it appears that there was a greater number of subjects with SDLP treatment difference of >2.4 cm than those with SDLP <-2.4 cm on Day 2 for the high (30 mg) suvorexant dose and for zopiclone.



Suvorexant (15 mg and 30 mg) did not show any statistically significant effect on SDS, word recall and body sway area, following single and multiple dose administration.

Plasma concentrations at 11 hr postdose were measured in both driving studies and the PK/PD relationship was explored for SDLP. There was a dose response on SDLP (especially for the non-elderly study), but a weak correlation between C_{11hr} and treatment difference on SDLP.

SDLP Differences From Placebo vs Suvorexant Plasma Concentrations (C_{11hr}) in Non-Elderly and Elderly Subjects on Day 2 (left panel) and Day 9 (right panel). Subjects whose driving was prematurely stopped due to somnolence were identified (no PK sample was available for AN007, AN016 repeat period data is shown)



Conclusion: Based on the results of the highway driving studies, the only suvorexant dose, which did not cause next-day impairment on driving performance, is 15 mg.

2.2.5 Are the proposed dosage regimens adequately supported by the clinical trials and consistent with the dose-response relationship?

No. All objective measures of sleep maintenance and onset (e.g. WASO, LPS) the dose (exposure) -response relationship was flat in the 15-40 mg range (see Figure 1) although there was a dose-dependent improvement in some subjective measures of sleep maintenance (e.g., sWASO).
Based on the sponsor's PK/PD analyses, suvorexant ED_{50} was estimated in the 10-20 mg range for sTSOm, WASO, and sTSTm consistent with a value at the lower end of the dose range evaluated clinically. The maximal drug effect was greatest on Night 1/Week 1 with approximately 2/3rd of the maximal response maintained at Month 1 and Month 3. For LPS, the ED_{50} could not be estimated, consistent with a flat response curve within the clinical dose range, suggesting the maximal drug effect is observed at the lowest dose studied (i.e., 10 mg).
Therefore, no additional efficacy is expected for suvorexant doses higher than 15-20mg.

In addition, the lower doses for the elderly in the phase 3 trials were based on the belief that elderly subjects may be more sensitive to sleep medicationss than non-elderly subjects.
However, the data from the phase 1 suvorexant PK and driving studies and the PK/PD analysis of AEs from the Phase 2 and 3 trials did not indicate that age has an effect on suvorexant PK and PD:

- Age was not shown to have an effect on suvorexant PK (elderly patients are predicted to have ~15% increased C_{9hr} relative to non-elderly patients based on a combination of covariate effects of age, BMI, and creatinine clearance),
- In addition, the results from the highway driving studies suggested that elderly subjects may be slightly less sensitive than non-elderly subjects to the impairment on driving performance.
- The PK/PD analysis of AEs from the Phase 2 and 3 trials performed by the sponsor did not identify patient age (elderly vs. non-elderly) as a statistically significant covariate indicating that elderly patients are not more sensitive to somnolence than non-elderly [Section 5.3.5.3.4.4]. At the Phase 3 doses studied in elderly, somnolence incidence is predicted to be 9.4% and 6.9% at 30 and 15 mg respectively. Thus, the lower doses given to elderly in Phase 3 resulted in lower somnolence rates in elderly relative to 40 and 20 mg doses in non-elderly (10.6% and 7.9%).

Considering that age did not show an effect on suvorexant PK (elderly patients are predicted to have ~15% increased C_{9hr} relative to non-elderly patients) and PD (elderly patients are not more sensitive to somnolence than non-elderly), there is no justification for recommending different doses for the elderly.

2.2.6 Does Suvorexant prolong QT or QTc interval?

A double-blind, randomized, placebo-controlled, 4-period, crossover study in healthy male and female volunteers was conducted to evaluate the potential effects of a 60 mg dose and supratherapeutic doses (150 mg and 240 mg combined) of suvorexant on

ventricular repolarization by quantitative analysis of corrected QT intervals in healthy subjects.
Interdisciplinary Review Team Summary: The largest upper bounds of the 2-sided 90% CI for the mean difference between Suvorexant and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

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

Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using a validated liquid chromatography-tandem mass spectrometric detection (LC-MS/MS) method. The method was linear in the range of 1.0 – 1000 ng/mL for both analytes. Bioanalytical stability studies were of sufficient scope and duration to assure the concentration values determined for pharmacokinetic samples collected during the development program are valid for all conditions experienced. A method report was also generated for each clinical study.
Details pertaining to assay methodology, assay validation, acceptance criteria, and stability are provided in Section 2.6 and the individual study reviews.
Several drug-drug interaction studies were conducted with medications that were coadministered with suvorexant. Information regarding the analytical methods used to support the analysis of co-administered compounds can be found in the individual study reviews (P008, P013, P015, P016, P024, P026 and P038).

2.2.8 What are the general ADME characterstics of Suvorexant?

Absorption:

Suvorexant is a low solubility drug substance that is highly permeable across biological membranes. Therefore, this drug substance is a Class 2 according to the Biopharmaceutics Classification System (high permeability, low solubility).
After oral administration of suvorexant median peak plasma concentrations occur approximately 2 hours (range: 0.5 to 6.0 hours) after dosing of 40 mg under fasted conditions. The estimated absolute bioavailability (F) for 40 mg is approximately 47% (5th to 95th percentile: 41% to 53%) based on IV and oral administration data.
The results of a crossover study (P018) suggest that suvorexant pharmacokinetics are less than dose proportional over the 10 to 80-mg range, likely due to absorption limitations (dose-dependent reduction in suvorexant plasma exposure with increasing doses; whereas, similar terminal elimination slopes were observed across all doses, suggesting reduction in relative bioavailability with higher doses). The relative bioavailability is predicted to be 83.9%, 98.4%, 69.9%, and 52.0% for 20-mg, 30-mg, 40-mg, and 60/80-mg doses in relation to a 10-mg suvorexant oral dose, which is set as a reference (100% BA).

The extent of suvorexant absorption following administration with either a high-fat or low-fat meal is similar to that following administration in the fasted state. Suvorexant may be administered without regard to food and this is consistent with the dosing instructions for Phase 2 and pivotal Phase 3 studies. However, for faster sleep onset, suvorexant should not be administered with or immediately after a meal as Tmax is delayed ~1 hour. The food effect study results are listed in Section 2.5.3.

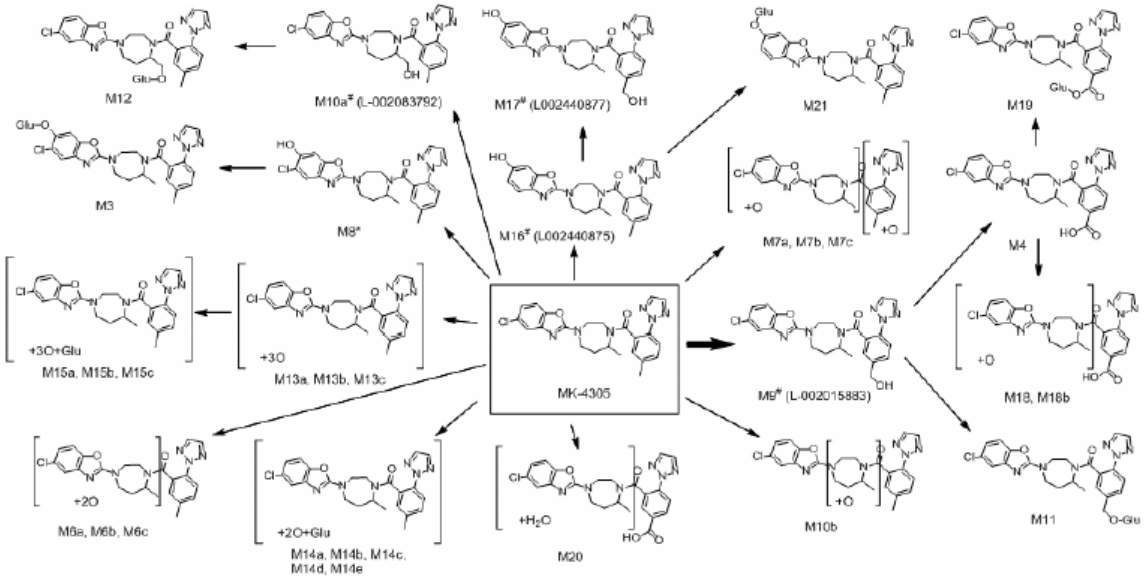
Distribution:

The absolute volume of distribution was estimated to be 48.6 L following a 20-mg suvorexant IV dose. Following oral administration of suvorexant, the total V/F was estimated to be 105.9 L. These data are consistent with extensive distribution of suvorexant beyond the extracellular fluid space (~10-14 L).
Plasma protein binding for suvorexant is high (99.5%) and is independent of concentration over the range of 1 to 25 μM. Suvorexant is highly bound to both human serum albumin and to α1-acid glycoprotein and is not preferentially distributed into red blood cells (blood/plasma concentration ratio of 0.59). Similarly, the in vitro human plasma protein binding of the major circulating metabolite, M9, is high (99.8%) with a blood/plasma concentration ratio of 0.60.

Metabolism:

The metabolism and excretion of suvorexant were evaluated in six healthy male subjects who received [^{14}C] Suvorexant as a 50 mg oral dose containing 200 μCi of radioactivity. The mean (n=6) total recovery of radioactivity in the excreta was 90%, with biliary/fecal route as the main route of elimination of MK-4305- derived material. Similar to in animals, suvorexant was eliminated almost entirely through metabolism in humans, primarily by cytochrome P450 3A (CYP3A), with less contribution by CYP2C19. The predominant metabolic pathway of suvorexantin human is hydroxylation of the triazolebenzyl group (formation of M9) followed by further oxidation to the carboxylic acid derivative (M4).
M9 was the major circulating metabolite. The average metabolite/parent ratio was approximately 0.6 to 1.2, demonstrating that both suvorexant and its major metabolite are present to approximately equal concentrations under steady-state conditions. However, M9 is not expected to be active *in vivo* based on results from *in vitro* and EEG studies in dogs. The affinity of M9 for Orexin receptors 1 and 2 was approximately 10-fold lower than the affinity of MK-4305. The only other affinity of M9 was at the dopamine transporter (8 μM). In addition, the results from *in vitro* studies showed that, in contrast to suvorexant, M9 is a substrate of P-gp, suggestsing that M9 will not penetrate the brain. M9 was not found to be active in canine sleep studies.
Other hydroxylated metabolites of suvorexantand conjugated and oxidated derivatives of M9 were also identified (M4, M7A, M8, M10A, M12 and M17).

Proposed *In Vitro* and *In Vivo* Pathways of Metabolism for [^{14}C]Suvorexant



*Structure of M8 confirmed by NMR; #Synthetic standards of M9, M10a, M16, M17 are available
Bold arrows represent the major metabolic pathway in human

Circulating metabolites at steady-state of suvorexant were also evaluated semi-quantitatively using HPLC-HRMS. Day 3 and 14 plasma samples (0-24 hr pooled) from a multiple dose human study (PN003, healthy young male subjects, n=6, 40, 80, and 100 mg) were evaluated. Compared with the plasma profile after a single dose, in addition to M9 and suvorexant, metabolite M17 became prevalent in Day 3 and Day 14 plasma. The structure of M17 was determined to be a di-hydroxylated derivative of suvorexant based on NMR analysis. The level of M17 in Day 14 samples was estimated to be <10% of the total drug related material (ranging from 8.6 – 9.8% for the three dose levels). Circulating level of M17 approached steady-state by Day 14 following multiple daily dosing of suvorexant in human (based on the plasma total plasma radioactivity $t_{1/2}$ of 53 hr, M17 should have reached steady-state by Day 14), therefore its levels should not be expected to increase further. In addition, the *in vitro* potency of M17 was approximately 5-100-fold lower than that of suvorexant with Ki values of 355 and 46.5 nM for binding towards Orexin-1 and Orexin-2 receptors, respectively. Similar to M9, M17 was found to be a good P-gp substrate in human. Based on the information above, M17 is unlikely to be present sufficiently in the CNS to contribute to the pharmacological activity of MK-4305 in humans. M17 did not show any activities in the Panlabs screen (secondary pharmacology). Since M17 in day 14 samples was estimated to be less than 10% of the total drug related material and there were no notable findings in the primary and secondary pharmacology, M17 should not be considered a major human metabolite. M12, a glucuronide derivative of an oxidation product of suvorexant, was another human circulating metabolite (accounting for 12.2% of the total circulating suvorexant-derived material). However, M12 is a glucuronide and is a much more polar compound; therefore, M12 is unlikely to have intrinsic pharmacological activity or to be brain penetrant.

Elimination:

The primary route of excretion is through feces, with approximately 66% of the [^{14}C]-Suvorexant dose recovered in the feces and 23% recovered in the urine.
Suvorexant was eliminated primarily in the form of metabolites. There was no unchanged [^{14}C]- Suvorexant detected in human feces. Similarly, <1% of the dose excreted in urine was unchanged suvorexant, indicating negligible renal clearance.
The plasma clearance of suvorexant was estimated to be 2.92 L/hour following 20 mg IV dose. Following oral administration of suvorexant, the typical CL/F was in general agreement with that following IV dosing, adjusting for absolute bioavailability.
Based upon the mean CL/F value and the blood/plasma concentration ratio of 0.59, the corresponding blood CL/F was estimated to be 2.89 L/h, which is <5% of hepatic blood flow, indicating that suvorexant is a low hepatic clearance drug. Furthermore, the moderate DDI effect observed following coadministration with ketoconazole is consistent with suvorexant being a low clearance compound.
The mean terminal half-life ($t_{1/2}$) for suvorexant is 12.2 (95% CI: 12.0 to 13.1) hours following 40 mg administration. The terminal half-life for M9 is similar to that observed for suvorexant, suggesting that metabolite elimination is formation-rate limited.
Steady-state of suvorexant was reached by 3 days of once-daily dosing, consistent with its terminal half-life. Estimates of suvorexant AUC and C_{max} accumulation, based on the increase from single to multiple-dose, approximates 1.2 to 1.6 and consistent with that predicted based upon the $t_{1/2}$ of suvorexant. Negligible accumulation of M9 was observed following multiple-dose administration of suvorexant.

2.2.9 What are the basic pharmacokinetic parameters of Suvorexant after single and multiple doses?

Single Dose Pharmacokinetics:

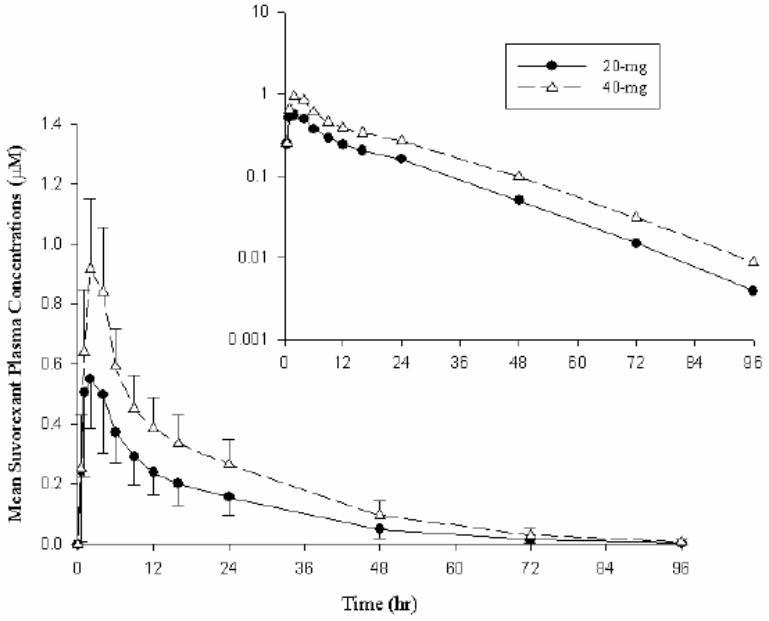
Suvorexant pharmacokinetics has been characterized in healthy men and women over a single-dose range of 4 mg to 240 mg. Additionally, the pharmacokinetics of suvorexant has been assessed in clinical trials of patients with insomnia following administration of doses up to 80 mg administered once daily at bedtime.
A composite analysis of conventional, non-compartmental pharmacokinetic data pooled from 10 clinical pharmacology studies including up to 116 healthy subjects was performed by the sponsor. These data are summarized below.

Descriptive Statistics of Pharmacokinetic Parameters Following Administration of 40-mg and 20-mg Single Oral Dose of Suvorexant Under Fed and Fasted Conditions from Composite Analysis

Dose	N‡	Parameter	Geometric Mean	95% CI
40 mg	120 (96)	$AUC_{0-\infty}$ (μM•hr)	14.26	(13.42, 15.12)
	140 (116)	C_{max} (μM)	1.09	(1.04, 1.15)
	140 (116)	T_{max} (hr)†	3.0§	(0.5, 6.0)
20 mg	52 (52)	$AUC_{0-\infty}$ (μM•hr)	9.20	(8.33, 10.17)
	52 (52)	C_{max} (μM)	0.68	(0.62, 0.74)
	52 (52)	T_{max} (hr)†	1.0‖	(0.5, 4.0)

† Median, minimum, maximum.
‡ N= number of observations (number of unique subjects).
§ Both fed and fasted data were included.
‖ Only fasted data available and included.

Mean (SD) Plasma Concentration Profiles for Suvorexant Following Administration of Single Oral Doses to Healthy Fasted Male and Female Subjects, Study P018 (N=16) (Inset: Semi-Log Scale)



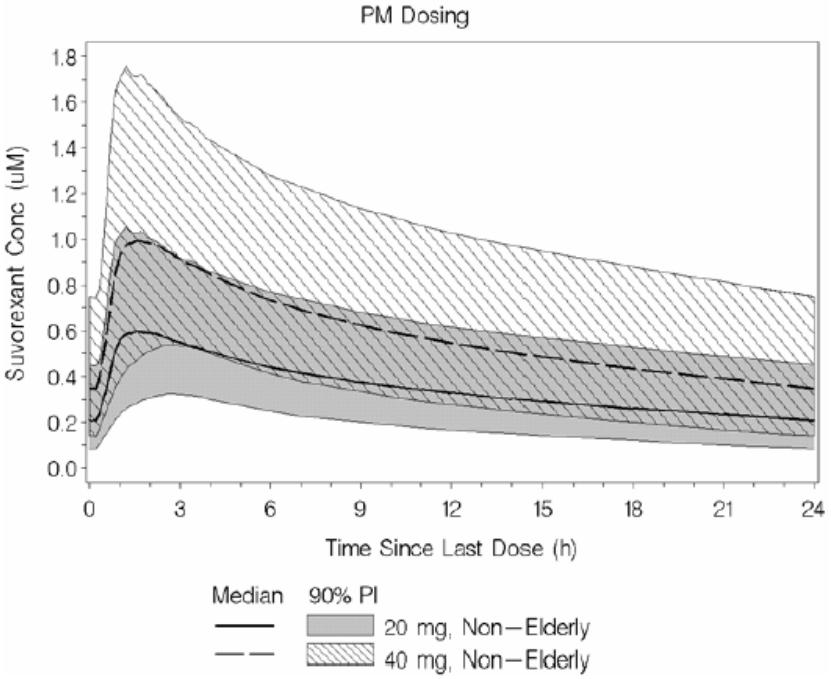
Multiple Dose Pharmacokinetics:

Suvorexant pharmacokinetics has been characterized in healthy subjects over a multiple-dose range of 10 to 100 mg/day. Additionally, the pharmacokinetics of suvorexant has been assessed in clinical trials of patients with insomnia following administration of doses up to 80 mg administered once daily at bedtime. A population approach was used by the sponsor to evaluate the pharmacokinetics of suvorexant in healthy subjects from 16 Phase 1 studies (12 single-dose and 4 multiple-dose) with dense pharmacokinetic sampling following doses ranging from 10 to 80 mg administered under fasted

conditions. The population PK model that best characterized the Phase 1 data was a 3-compartment model with dose-dependent F1, sigmoidal absorption (with lag time), linear distribution into the first peripheral compartment (Vp1/F) and and first-order elimination from the central compartment (Vc/F). The plasma clearance of suvorexant was estimated to 2.92 L/hour (95% CI: 2.34 to 3.63) following an IV dose of 20 mg. Following oral administration of suvorexant, the typical CL/F is in general agreement with that following IV dosing adjusting for absolute bioavailability.
Based upon the mean CL/F value and the blood/plasma concentration ratio of 0.59, the corresponding blood CL/F is estimated to be 2.89 L/h, which is <5% of hepatic blood flow, suggesting that suvorexant is a low hepatic clearance drug.

Population PK model predicted steady-state suvorexant AUC_{0-24}, C_{max} and C_{9hr} values following 40 mg dosing in non-elderly subjects represented in the Phase 2/3 population are 15.895 µM•h/L, 1.171 µM and 0.647 µM, respectively.
In the pooled data from Phase 2 and Phase 3, geometric mean (CV%) C_{9hr} was 0.555 (58.3) µM at steady-state in non-elderly patients receiving 40 mg and 0.563 (48.3) µM in elderly patients receiving 30 mg.

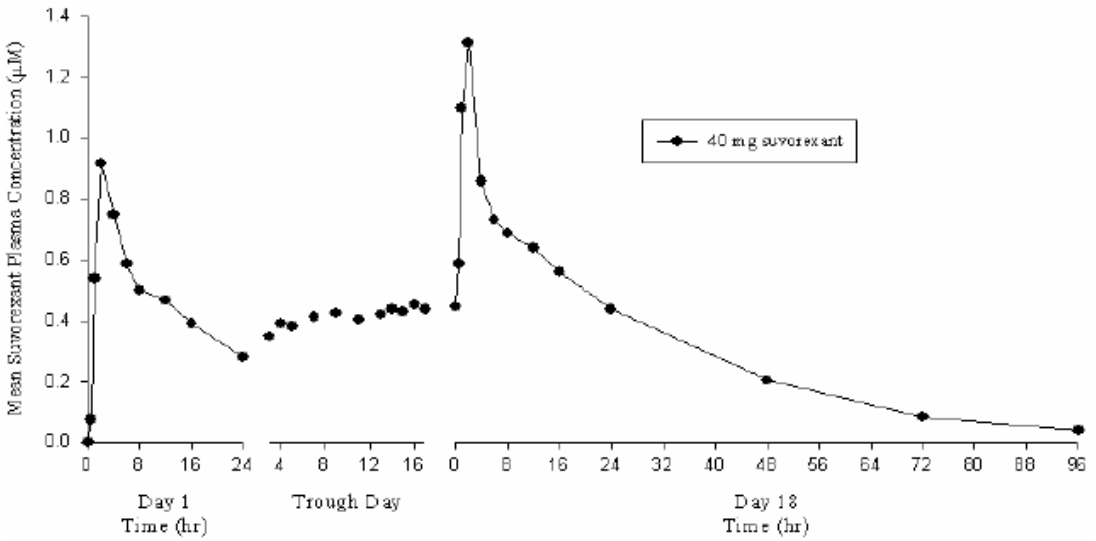
Simulated Steady-State Suvorexant Concentrations (Median, 90% Prediction Interval [90% PI]) Versus Time Since Last Dose in a Non-Elderly Population Representative of Phase 1 Subjects Following Daily PM Administration of 20-mg and 40-mg Suvorexant Doses



Summary of Pharmacokinetic Parameters of Suvorexant Following Multiple Dose PM Administration of 40 mg, Once Daily for 7 Days, in Healthy Elderly Male and Female Subjects (P027)

Dose	Gender	N	$AUC_{0\text{-}24\,hr}$ † (μM·hr)	C_{max} (μM) †	C_{24hr} (μM) †	C_{4hr} (μM) †	T_{max} (hr) ††	Apparent terminal $t_{1/2}$(hr) §
First Day (1st Day)								
Panel A 40 mg	C	16	13.36 (11.40, 15.66)	1.139 (0.965, 1.343)	0.356 (0.283, 0.446)	0.733 (0.645, 0.832)	2.0 (0.5, 6.0)	--
	M	8	11.83 (9.79, 14.29)	1.033 (0.831, 1.285)	0.283 (0.220, 0.363)	0.686 (0.582, 0.808)	2.0 (1.0, 6.0)	--
	F	8	15.09 (12.49, 18.23)	1.255 (1.009, 1.560)	0.447 (0.348, 0.575)	0.783 (0.665, 0.922)	2.0 (0.5, 4.0)	--
	F/M	8	1.28 (1.02, 1.59)	1.21 (0.94, 1.57)	1.58 (1.18, 2.12)	1.14 (0.94, 1.38)	--	--
Last Day (7th Day)								
Panel A 40 mg	C	16	17.88 (15.25, 20.96)	1.336 (1.132, 1.575)	0.567 (0.452, 0.711)	0.835 (0.735, 0.948)	2.0 (1.0, 10.1)	18.4 (4.4)
	M	8	14.48 (11.98, 17.49)	1.134 (0.912, 1.410)	0.416 (0.323, 0.534)	0.720 (0.611, 0.847)	1.5 (1.0, 6.0)	16.8 (3.7)
	F	8	22.07 (18.27, 26.66)	1.573 (1.266, 1.956)	0.772 (0.601, 0.993)	0.968 (0.822, 1.140)	2.0 (1.0, 10.1)	20.3 (4.6)
	F/M	8	1.52 (1.22, 1.90)	1.39 (1.08, 1.79)	1.86 (1.39, 2.49)	1.35 (1.11, 1.63)	--	--
Accumulation (7th Day / 1st Day)								
Panel A 40 mg	C	16	1.34 (1.26, 1.42)	1.17 (1.04, 1.32)	1.59 (1.51, 1.68)	1.14 (1.07, 1.21)	--	--
	M	8	1.22 (1.15, 1.30)	1.10 (0.93, 1.30)	1.47 (1.39, 1.55)	1.05 (0.98, 1.13)	--	--
	F	8	1.46 (1.37, 1.56)	1.25 (1.06, 1.49)	1.73 (1.64, 1.82)	1.24 (1.15, 1.33)	--	--

P013: Mean Plasma Concentration-Time Profile of Suvorexant Following Once Daily PM Dosing of 40 mg Suvorexant (MK-4305), with a Single Oral Dose of Ortho Cyclen™ Co-administered on Day 14 in Healthy Female Subjects (Linear Scale) (N=19/Day 1, N=17/Day 18)

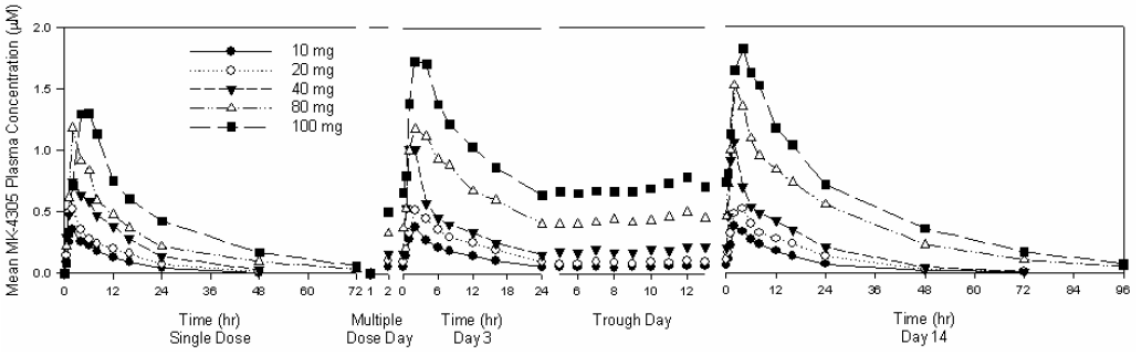


2.2.10 Do the pharmacokinetic parameters change with time following chronic dosing?

No. Pharmacokinetics of suvorexant following multiple-dose administration were consistent with those observed after single-dose administration, indicating time-independent pharmacokinetics of suvorexant. The results from Study P013 show that suvorexant trough concentrations remained stationary after steady state has been reached (see Figure above p. 32). In addition, the results of Study P003 showed that accumulation ratios for suvorexant $AUC_{0\text{-}24hr}$ ranged from 1.21 to 1.60 and were independent of dose. Assessments of linearity were not indicative of auto-induction or auto-inhibition as AUC ratios remained stationary across the dose range evaluated.

P003: Summary of Accumulation and Linearity Assessments of Suvorexant (MK-4305) Following a Single Dose and then Multiple Dose Administration (Daily for 14 Days) of 10 to 100 mg in Healthy Male Subjects

Pharmacokinetic Parameter	10 mg N=6	20 mg N=5	40 mg N=6	80 mg N=6	100 mg N=6
Accumulation Ratio: Multiple Dose Day 14 / Single Dose†					
$AUC_{0\text{-}24hr}$ (μM*hr)	1.27 (1.06, 1.52)	1.21 (1.00, 1.46)	1.25 (1.03, 1.51)	1.60 (1.33, 1.91)	1.53 (1.28, 1.83)
$AUC_{0\text{-}4hr}$ (μM*hr)	1.08 (0.83, 1.39)	1.00 (0.76, 1.31)	1.44 (1.10, 1.88)	1.46 (1.13, 1.89)	2.27 (1.76, 2.92)
C_{max} (μM)	1.16 (0.98, 1.39)	1.00 (0.83, 1.21)	1.35 (1.12, 1.62)	1.12 (0.94, 1.34)	1.46 (1.23, 1.75)
C_{4hr} (μM)	1.29 (1.10, 1.53)	1.34 (1.13, 1.60)	1.13 (0.95, 1.35)	1.45 (1.23, 1.71)	1.43 (1.21, 1.69)
C_{24hr} (μM)	1.65 (1.12, 2.43)	1.56 (1.03, 2.37)	1.59 (1.05, 2.41)	2.42 (1.64, 3.57)	1.60 (1.08, 2.36)
Linearity with time: Multiple Dose Day 14 $AUC_{0\text{-}24hr}$/ Single Dose $AUC_{0\text{-}\infty}$†					
$AUC_{0\text{-}24hr}$ / $AUC_{0\text{-}\infty}$	1.11 (0.87, 1.41)	1.02 (0.79, 1.32)	1.02 (0.79, 1.32)	1.18 (0.93, 1.50)	0.99 (0.78, 1.26)
† Back-transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log-transformed values.					



2.2.11 What is the variability in the PK data?

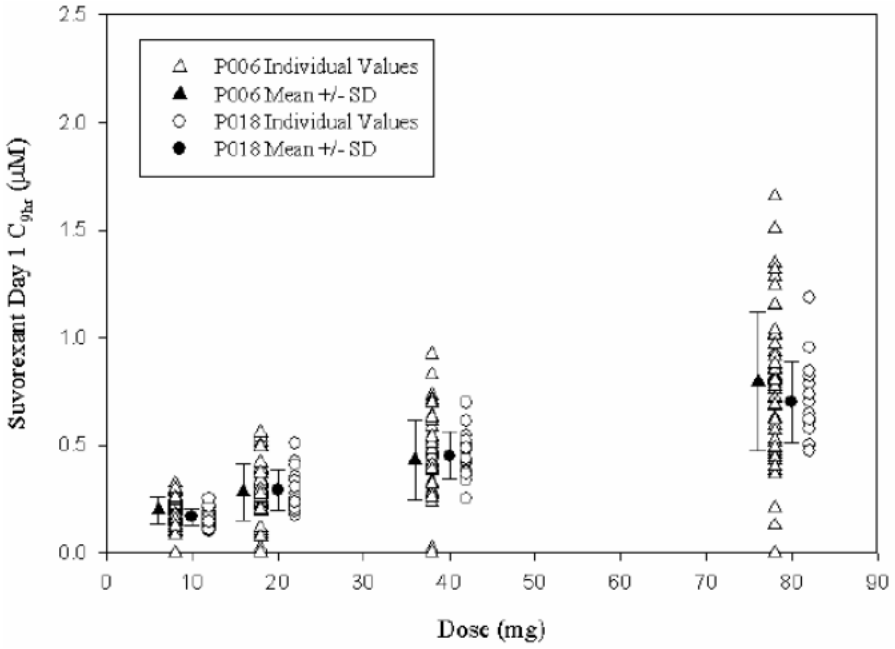
The variabilities of CL/F and C_{max} are summarized below:
Inter-subject Variability in CL/F: 21.77% (popPK)
Inter-subject Variability in C_{max}: 39% (for fasted or fed, study P020)

Parameter Estimates and Standard Errors from the Final Pharmacokinetic Model

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
k_a (h^{-1})	1.97	11.4	156.84	14.5
D1 (h)	0.556	9.0	NE	NA
ALAG1 (h)	0.186	6.0	NE	NA
F1[a] (20 mg)	1.03	3.5	22.72	12.3
F1[a] (30 mg)	0.984	5.9		
F1[a] (40 mg)	0.857(AM), 0.699(PM)	3.5		
F1[a] (60/80 mg)	0.638	4.0		
CL/F (L/h)	4.81	4.7	21.77	12.6
V_c/F (L)	58.3	4.3	14.25	41.3

2.2.12 How do the pharmacokinetics of the drug in healthy volunteers compare to that in patients?

The C_{9hr} values in patients from the Phase 2 study (P006) are comparable to those for healthy subjects from the definitive dose-proportionality study (P018) over a similar dose range as seen in the figure below. These results suggest that systemic exposure to suvorexant in patients is similar to that in healthy subjects receiving equivalent doses.



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

Results of a crossover study (P018) suggest that suvorexant pharmacokinetics are less than dose proportional over the 10 to 80-mg range. The slope (90% CI) from the power model was 0.78 (0.70, 0.86) for $AUC_{0-\infty}$ and 0.58 (0.51, 0.64) for C_{max}.

P018: Summary of PK Parameters of Suvorexant (MK-4305) Following Single Oral Dose Administration of 10 mg to 80 mg in Healthy Male and Female Subjects

PK Parameter	10 mg† N= 16	20 mg† N= 16	40 mg† N=16	80 mg† N= 16
$AUC_{0-\infty}$ (µM•hr)	5.32 (4.55,6.23)	9.51 (8.12,11.14)	16.21 (13.85,18.98)	27.26 (23.28,31.91)
C_{max} (µM)	0.456(0.403,0.516)	0.646 (0.572,0.731)	0.956 (0.845,1.082)	1.518 (1.342,1.717)
T_{max}‡ (hr)	1.5 (1.0,4.0)	1.0 (1.0,4.0)	2.0 (1.0,4.0)	2.0 (0.5,6.0)
Apparent terminal $t_{1/2}$§ (hr)	12.1 (1.8)	12.5 (2.6)	12.6 (2.5)	13.6 (2.9)

Assessment of Dose Proportionality of Suvorexant (MK-4305) Following Single Oral Dose Administration of 10 mg to 80 mg in Healthy Male and Female Subjects (N=16)

Parameter	Dose Range(mg)	Slope Estimate (90% CI)	Expected Fold-Change (90% CI)†	Expected Fold-Change with Perfect Dose-Proportionality
$AUC_{0-\infty}$	10-80	0.78 (0.70, 0.86)	5.10 (4.32, 6.03)	8
	10-40	0.80 (0.68, 0.93)	3.05 (2.57, 3.61)	4
	20-80	0.76 (0.63, 0.89)	2.87 (2.38, 3.45)	4
C_{max}	10-80	0.58 (0.51, 0.64)	3.32 (2.90, 3.80)	8
	10-40	0.53 (0.43, 0.64)	2.10 (1.82, 2.42)	4
	20-80	0.62 (0.51, 0.73)	2.35 (2.01, 2.73)	4

In comparison, following IV administration of suvorexant over the range of 5 to 20 mg, dose-proportional increase in AUC was observed with CL unchanged, suggesting absorption-rate limitations following oral administration rather than other nonlinear mechanisms.

P018: Summary of PK Parameters of Suvorexant (MK-4305) Following Administration of Single IV-Infusion Doses in Healthy Male and Female Subjects

PK Parameter	5 mg† N= 8	10 mg† N= 8	20 mg† N=8
$AUC_{0-\infty}$ (μM•hr)	3.46 (2.78,4.32)	6.92 (5.54,8.63)	15.10 (12.11,18.84)
C_{eoi} (μM)	0.543 (0.470,0.627)	1.044 (0.904,1.206)	1.751 (1.516,2.023)
CL (mL/min)	52.28 (42.00,65.08)	52.72 (42.35,65.63)	48.60 (39.04,60.50)
V_{dss} (L)	36.51 (31.20,42.72)	42.46 (36.29,49.69)	57.12 (48.81,66.84)
Apparent terminal $t_{1/2}$+ (hr)	9.2 (3.4)	9.9 (5.2)	13.5 (5.0)

Suvorexant bioavailability F1 decreases with increasing dose. For a typical subject, F1 is predicted to be 83.9%, 80.3%, 69.9%, and 52.0% for 20-, 30-, 40-, and 60/80-mg doses in relation to a reference 10-mg suvorexant oral dose, which was set as 100% BA.

In the pooled analysis of C_{9hr} in insomnia patients from Phase 2 (P006) and Phase 3 (P009, P028, P029) trials, the slope (95% CI) from the power model of combined Day 1 and steady-state data was 0.67 (0.63, 0.71). This result is similar to that obtained in the Phase 1 dose proportionality assessment and indicates that suvorexant in healthy subjects and insomnia patients has a similar, less than proportional behavior over the dose range 10 to 80 mg.

Day 1 and Steady State C_{9hr} in Insomnia Patients (10, 20, 40 and 80mg in Non-elderly and 15mg and 30mg in Elderly)

DAY	Dose (mg)	Elderly	n	Geometric Mean (%CV)	Median	Min	Max
Day 1	10	Nonelderly	60	0.194 (30.8%)	0.201	0.083	0.324
	15	Elderly	128	0.286 (35.1%)	0.282	0.087	0.911
	20	Nonelderly	223	0.292 (51.8%)	0.307	0.005	0.760
	30	Elderly#	230	0.456 (31.9%)	0.458	0.194	1.220
	40	Nonelderly*	361	0.482 (45.3%)	0.488	0.008	1.323
	80	Nonelderly	59	0.743 (47.5%)	0.812	0.131	1.661
Steady State	10	Nonelderly	58	0.213 (43.7%)	0.224	0.066	0.477
	15	Elderly	167	0.362 (40.9%)	0.374	0.093	0.858
	20	Nonelderly	282	0.321 (72.2%)	0.343	0.006	0.931
	30	Elderly#	489	0.563 (48.3%)	0.587	0.022	1.418
	40	Nonelderly*	537	0.555 (58.3%)	0.581	0.004	2.773
	80	Nonelderly	52	0.826 (66.1%)	0.958	0.051	1.856

includes one Nonelderly patient dosed at 30mg
* includes one Elderly patient dosed at 40mg

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

2.3.1.1 Gender

The comparisons of PK following single dose administration of suvorexant to healthy young male subjects (18 - 45 years) and elderly male and female subjects (65 - 77 years) in Study P004 suggested that suvorexant exposure was higher in elderly females compared to elderly males. The female/male ratio of geometric means GMR (90% CI) for AUC was 1.55 (1.17, 2.06) and 1.29 (1.08, 1.54) for C_{max}. In the same study, suvorexant exposure was comparable between elderly male and young male subjects with the GMR (90% CI) for AUC and C_{max} 0.89 (0.58, 1.35) and 0.89 (0.66, 1.20), respectively. The Body Mass Index (BMI) was < 31 kg/m^2 for the subjects in the study.

Suvorexant PK Parameters Following Single Oral Dose Administration of Suvorexant 16 mg in Healthy Elderly Male, Elderly Female, and Young Male Subjects

Population	N	$AUC_{0-\infty}$† (μM•hr) GM (95% CI)	C_{max}† (μM) GM (95% CI)	C_{4hr}† (μM) GM (95% CI)	T_{max}‡ (hr)	Apparent terminal $t_{1/2}$§ (hr)
Young Male#	26	6.30 (5.43, 7.31)	0.822 (0.724, 0.933)	0.389 (0.344, 0.439)	1.0 (0.5, 4.0)	8.6 (2.7)
Elderly Male	8	5.78 (4.53, 7.38)	0.590 (0.505, 0.690)	0.267 (0.212, 0.334)	1.0 (1.0, 2.0)	12.0 (2.3)
Elderly Female	8	8.99 (7.04, 11.47)	0.761 (0.652, 0.889)	0.293 (0.234, 0.367)	1.0 (0.5, 2.0)	15.0 (4.1)

Comparison	$AUC_{0-\infty}$ (μM•hr) GMR (90% CI)	C_{max} (μM) GMR (90% CI)
Gender‖		
Elderly Female Vs. Elderly Male	1.55 (1.17, 2.06)	1.29 (1.08, 1.54)
Age‖		
Elderly Male Vs. Young Male	0.92 (0.71, 1.19)	0.72 (0.58, 0.89)

Likewise, following once-daily multiple-dose administration of 40 mg suvorexant to healthy elderly male and female subjects (Study P027), steady-state AUC and C_{max} appeared higher in elderly female subjects with female/male GMR (90% CI) for AUC and C_{max} 1.52 (1.22, 1.90) and 1.39 (1.07, 1.80), respectively.

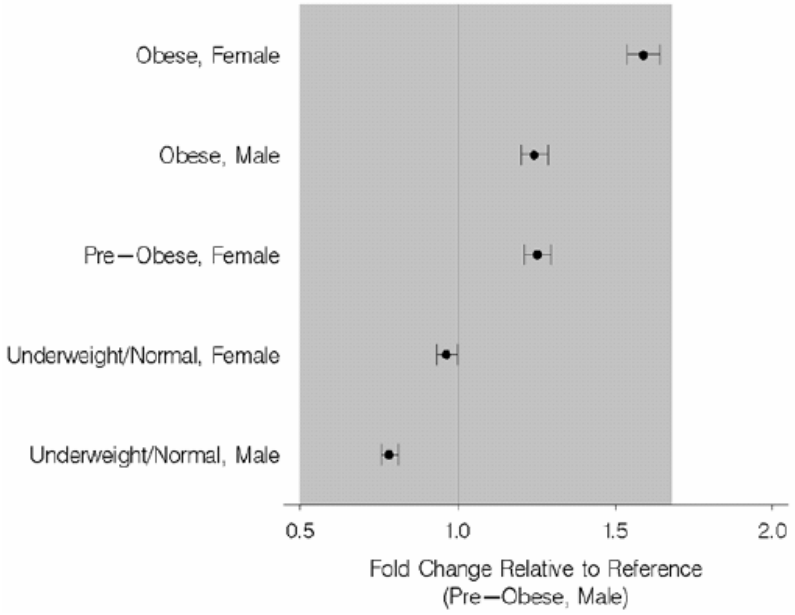
However, based on the composite analysis of pooled 40-mg pharmacokinetic data and the population PK model, the apparent oral clearance (CL/F) of suvorexant in females is predicted to be 20.5% lower compared to that in males. The higher exposure reported in Studies P004 and 027 in elderly subjects might be due to the confounding effect of BMI.

Recommendations: No dose adjustment for suvorexant is needed based on gender.

2.3.1.2 Weight and Body Mass Index (BMI)

A population-based nonlinear mixed-effects model identified BMI to be statistically significant predictor of suvorexant CL. Apparent oral clearance (CL/F) of suvorexant was inversely related to BMI, with population mean CL/F decreasing from 8.07 L/h to 3.32 L/h for a typical male and from 6.42 L/h to 2.64 L/h for a typical female with BMI values ranging from 17 kg/m^2 (underweight) to 35 kg/m^2 (overweight).

Forest Plot of Steady-State Suvorexant AUC_{0-24} Based Upon Gender and BMI Category in Non-Elderly Subjects Administered Daily 40 mg Suvorexant



In the Dose-C_{9hr} modeling of Phase 2 and 3 data, C_{9hr} is predicted to be ~19% higher in obese patients relative to normal BMI patients. This C_{9hr} effect is not expected to be clinically meaningful. In addition, in the phase 3 studies, somnolence rates were not higher in obese subjects compared to non-obese subjects.

Somnolence Events in Non-Obese, Over-Weight, and Obese Subjects in the Combined 0-3 Months Population (P028, P029, and P009)

	Placebo	**Suvorexant LD**	**Suvorexant HD**
Somnolence in Non-Obese Subjects (BMI <25)	2.2% (10/449)	7.4% (18/243)	11.0% (56/509)
Somnolence in Over-weight Subjects (BMI 25-30)	3.0% (12/405)	7.2% (14/194)	8.9% (49/548)
Somnolence in Obese Subjects (BMI >30)	5.3% (9/170)	1.8% (1/56)	13.4% (31/232)

However, the combined gender and BMI effect could be clinically meaningful.
The population PK model predicts 20.5% lower suvorexant CL/F in females compared to males. CL/F decreases with increasing BMI, according to a power function, resulting in the lowest CL/F in the heaviest female patients. An approximate 2- to 3-fold reduction in CL/F is expected when comparing men with relatively low BMI versus obese women. Per the Figure above, obese females have ~ 1.5-1.6 fold higher exposure compared to the majority population studied in the pivotal Phase 3 trials.

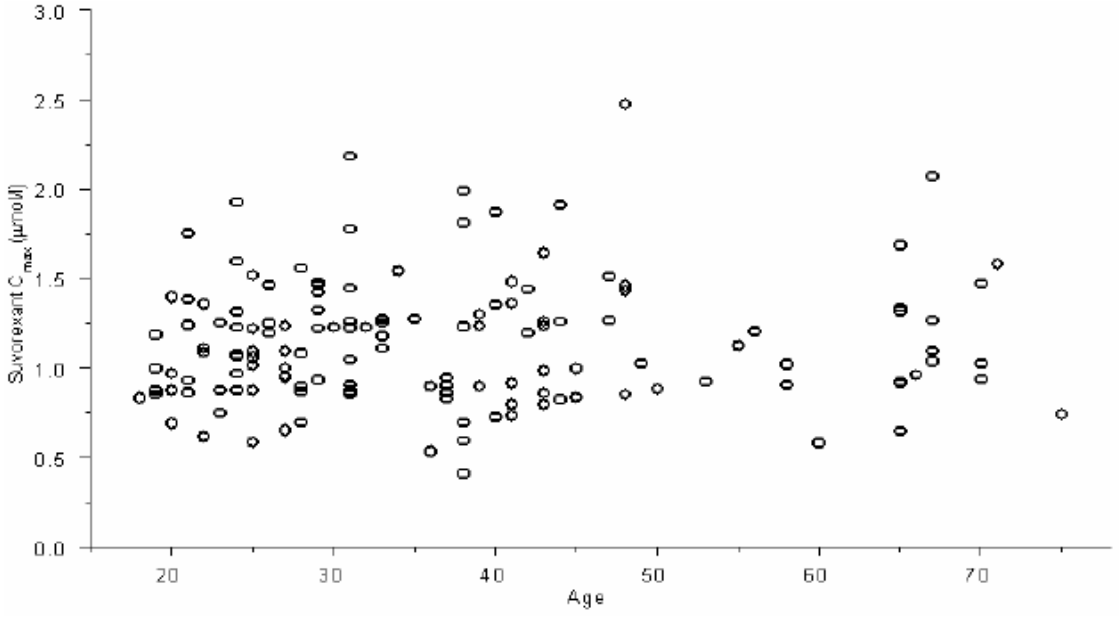
Therefore, the dose of suvorexant for obese women should be reduced to 10mg.

Recommendations: Suvorexant dose in obese females should be decreased. If the recommended suvorexant dose is 15 mg, the sponsor needs to develop a lower strength tablet, e.g 10 mg for this patient population. (PMC)

2.3.1.3 Age

Inter-study comparisons of PK following single dose administration to healthy young male subjects (18 - 45 years) and elderly male and female subjects (65 - 77 years) did not suggest higher suvorexant exposure in elderly compared to non-elderly: AUC and Cmax estimates appeared comparable between elderly male and young male subjects with the GMR (90% CI) for AUC and Cmax being 0.89 (0.58, 1.35) and 0.89 (0.66, 1.20), respectively, see Section 2.3.1.1.
In addition, the population-based nonlinear mixed-effects model did not indicate a significant effect of age on suvorexant CL/F and systemic exposure: elderly patients are predicted to have ~15% increased C_{9hr} relative to non-elderly patients based on a combination of covariate effects of age, BMI, and creatinine clearance.

Scatter Plot of Individual C_{max} vs. Age Following Administration of 40-mg Single Oral Dose of Suvorexant (N=140)



The lower doses for the elderly in the phase 3 trials were based on the belief that elderly subjects may be more sensitive to hypnitics than non-elderly subjects.
However, data from the phase 1 suvorexant driving studies and the sponsor's PK/PD Analysis of Adverse Effects (AEs) from the Phase 2 and 3 trials did not indicate that age has an effect on suvorexant PK and PD:

- Age was not shown to have an effect on suvorexant PK (elderly patients are predicted to have ~15% increased C_{9hr} relative to non-elderly)

• Contrast to the general belief, comparison of the results of the highway driving studies 035 (non-elderly subjects) and 039 (elderly subjects) revealed that elderly subjects may be slightly less sensitive than non-elderly subjects to the impairment on driving performance
• PK/PD Analysis of AEs from the Phase 2 and 3 trials (P006, P009, P028, and P029) did not identify patient age (elderly vs. non-elderly) as a statistically significant covariate, indicating that elderly patients are not more sensitive to somnolence than non-elderly. In the Phase 3 trials, somnolence incidence was 8.8% and 5.4% at 30 and 15 mg, respectively in elderly. Thus, the lower doses given to elderly in Phase 3 resulted in lower somnolence rates in elderly relative to 40 and 20 mg doses in non-elderly (12.5% and 7.6%).
Recommendations: No dose adjustment for suvorexant is recommended based on age.

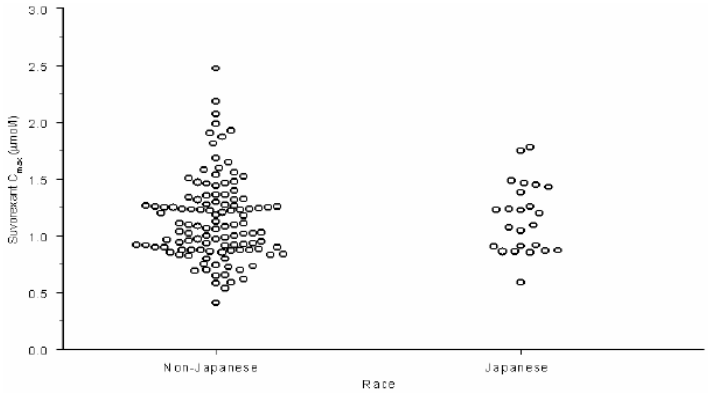
2.3.1.4 Pediatrics:

The PK of suvorexant have not been evaluated in pediatric subjects.
The safety and effectiveness of suvorexant in pediatric patients under 18 years of age have not been established.

2.3.1.5 Race:

The majority of subjects represented in the population pharmacokinetic analysis and composite PK analysis were White (>60%), with Black, Asian and Other (including Native American) subjects representing ≥10% of the subject population. No influence of race on suvorexant disposition was identified from the population pharmacokinetic analysis. Similarly, no statistical differences were observed in suvorexant C_{max} or T_{max} between races (Black/White and Asian/White) based upon the composite analysis of pooled 40 mg pharmacokinetic data.
In the Dose-C_{9hr} modeling of Phase 2 and 3 data, race [White (n=1249), Black (n=98), Asian (n=176), or Other (n=62)] was not a statistically significant predictor of C_{9hr}.
Based on the composite analysis of pooled pharmacokinetic data, no statistical differences were observed in C_{max} or T_{max} of suvorexant between Japanese (n=24) and non-Japanese (n=116) subjects.

Scatter Plot of Individual C_{max} vs. Japanese Race Following Administration of 40-mg Single Oral Dose of Suvorexant



Recommendations: No dose adjustment for suvorexant is recommended based on race.

2.3.1.6 Hepatic Impairment:

A single dose study (P017) was conducted to assess the effect of hepatic impairment on suvorexant PK. A single 20 mg suvorexant dose was administered to 8 healthy adults and 8 subjects with moderate hepatic impairment (Child-Pugh, 7 to 9 points). The results of the study indicated that suvorexant systemic exposure, expressed as unbound and bound, in subjects with moderate hepatic insufficiency is similar to that in matched healthy subjects. However, suvorexant half-life was increased from 14.7 h in healthy subjects to 19.1 h in subjects with moderate hepatic impairment.

Summary of Pharmacokinetic Parameters of Suvorexant Following a Single Dose of 20 mg MK-4305 Administered to Patients With Moderate Hepatic Impairment and to Healthy Matched Control Subjects

	MK-4305 in Patients With Moderate Hepatic Insufficiency			MK-4305 in Healthy Matched Control Subjects			MK-4305 in Patients With Moderate Hepatic Insufficiency / MK-4305 in Healthy Matched Control Subjects		
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE[†]
$AUC_{0-\infty}$[‡] (μM•hr)	8	14.09	(10.48, 18.93)	8	13.73	(10.09, 18.69)	1.03	(0.74, 1.43)	0.330
C_{max}[‡] (μM)	8	0.800	(0.603, 1.062)	8	0.854	(0.636, 1.147)	0.94	(0.68, 1.29)	0.316
$AUC_{0-\infty(unbound)}$[‡] (nM•hr)	8	118.19	(78.68, 177.52)	8	131.27	(85.91, 200.57)	0.90	(0.57, 1.42)	0.454
$C_{max(unbound)}$[‡] (nM)	8	6.710	(4.320, 10.422)	8	8.161	(5.157, 12.912)	0.82	(0.50, 1.35)	0.492
T_{max}[§] (hr)	8	1.0	(1.0, 2.1)	8	1.0	(1.0, 2.0)			
Apparent terminal $t_{½}$[‖] (hr)	8	19.1	10.6	8	14.7	3.9			

The exposure (AUC) and half-life of the metabolite M9 was increased in subjects with moderate hepatic impairment compared to healthy subjects.

Pharmacokinetic Parameter	M9 in Patients With Moderate Hepatic Insufficiency			M9 in Healthy Matched Control Subjects			M9 in Patients With Moderate Hepatic Insufficiency / M9 in Healthy Matched Control Subjects		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE[†]
$AUC_{0-\infty}$[‡] (μM•hr)	8	16.94	(12.80, 22.41)	8	12.80	(9.56, 17.13)	1.32	(0.97, 1.81)	0.312
C_{max}[‡] (μM)	8	0.531	(0.389, 0.726)	8	0.558	(0.403, 0.773)	0.95	(0.67, 1.35)	0.349
T_{max}[§] (hr)	8	4.0	(2.0, 4.0)	8	4.0	(2.0, 6.0)			
Apparent terminal $t_{½}$[‖] (hr)	8	20.8	9.9	8	15.8	4.0			

Suvorexant pharmacokinetics were not evaluated in subjects with severe hepatic impairment (Child-Pugh 10-15 points).
In the population pharmacokinetic analysis of subjects receiving suvorexant doses of 10 to 80 mg and the statistical evaluation of Phase 2/3 data from patients with insomnia, Child-Pugh data were not collected and could not be evaluated in the covariate analyses. In addition, patients with evidence of clinically significant hepatobiliary disease or an ALT/AST >3 times the upper limit of normal were excluded from participation in Phase 2/3 Studies and thus, no data are available from these patients.
Recommendations:
Suvorexant is not recommended in subjects with severe hepatic impairment.
No dose adjustment for suvorexant is needed in subjects with moderate hepatic impairment.

2.3.1.7 Renal Impairment:

A single dose study (P023) was conducted to assess the effect of renal impairment on suvorexant PK. A single 20 mg suvorexant dose was administered to 8 healthy subjects and 8 subjects with severe renal impairment (defined as 24 hr urinary creatinine clearance CrCL≤ 30 ml/min.). The results of the study indicated that suvorexant systemic exposure, expressed as unbound and bound, in subjects with severe renal impairment was similar to that in matched healthy subjects.

Plasma Pharmacokinetic Parameters of Suvorexant and M9 Following a Single Dose of 20-mg Suvorexant Administered to Patients with Severe Renal Impairment and to Healthy Matched Control Subjects

Pharmacokinetic Parameter	Severe Renal Impairment			Healthy Matched Control		
	N	GM	95% CI	N	GM	95% CI
$AUC_{0-\infty}$[†] (μM•hr)	8	11.98	(9.45, 15.20)	8	9.81	(7.72, 12.47)
C_{max}[†] (μM)	8	0.830	(0.723, 0.952)	8	0.724	(0.630, 0.832)
$AUC_{0-\infty(unbound)}$[†] (μM•hr)	8	0.13	(0.10, 0.18)	8	0.11	(0.08, 0.15)
$C_{max(unbound)}$[†] (μM)	8	0.009	(0.008, 0.011)	8	0.008	(0.007, 0.010)
T_{max}[§] (hr)	8	2.0	(1.0, 2.0)	8	1.0	(0.5, 2.0)
Apparent Terminal $t_{1/2}$[‖] (hr)	8	13.5	6.2	8	13.5	2.7

M9 Pharmacokinetic Parameter	Severe Renal Impairment			Healthy Matched Control		
	N	GM	95% CI	N	GM	95% CI
$AUC_{0-\infty}$ † (μM•hr)	8	11.80	(9.77, 14.23)	8	13.42	(11.10, 16.22)
C_{max} † (μM)	8	0.440	(0.387, 0.501)	8	0.572	(0.502, 0.651)
T_{max} § (hr)	8	2.0	(2.0, 16.0)	8	4.0	(2.0, 6.0)
Apparent Terminal $t_{1/2}$ ‖ (hr)	8	14.8	5.2	8	14.4	2.8

The ratio of geometric means (severe renal impairment patients/matched healthy control subjects) for plasma unbound $AUC_{0-\infty}$ and 90% CI were 1.18 and (0.83, 1.67). The GMR and 90% CI for plasma unbound C_{max} were 1.10 (0.91, 1.34). The GMR and 90% CI for $AUC_{0-\infty}$ were 1.22 and (0.93, 1.60) and C_{max} were 1.15 and (0.98, 1.34).
Suvorexant plasma protein binding was similar in severe renal impairment patients and matched healthy control subjects. The plasma fraction unbound of suvorexant based on *in vitro* assessments ranged from 0.9 to 1.3% in severe renal impairment patients and 0.9 to 1.5% in matched healthy control subjects.
Recommendations:
No dose adjustment for suvorexant is recommended in subjects with renal impairment.

2.4 EXTRINSIC FACTORS

2.4.1 Is suvorexant a substrate, inhibitor or inducer of CYP enzymes?

Yes. Metabolism of suvorexant was mediated primarily through oxidative processes. Three oxidative metabolites (M8, M9 and M10a) were formed in human liver microsomes with M9 being the predominant one. The formation of M9 was mainly mediated through CYP3A4/5 with CYP2C19 contributing to a lesser extent. CYP3A4/5 was also responsible for most of the formation of M8 and M10a.
Suvorexant was a weak reversible inhibitor of CYP1A2, 2B6, 2C8, 2C9 and 2D6 ($IC_{50} \geq 15$ μM), and had more potent effects on CYP2C19 and CYP3A4 with IC_{50} of 5.3 and 4.0 μM, respectively. Suvorexant was also shown to be a time-dependent inhibitor of CYP3A4 with K_{inact} and K_I values of 0.136 min^{-1} and 12 μM, respectively. The major metabolite, M9, was a weak reversible inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 with $IC_{50} \geq 35$ μM, and had more potent effect on CYP3A4 with IC_{50} of 11 μM or 26 μM. M9 was also a time-dependent inhibitor of CYP3A4.
Induction effects of suvorexant on CYP3A4, 1A2 and 2B6 were examined using cryopreserved human hepatocytes. The highest mRNA increase was 22-fold for CYP3A4 induced by 5 μM MK-4305 (43% of that achieved with rifamipicin), followed by 4.8-fold for CYP1A2 (20% of the effect of omeprazole) and 2.4-fold for CYP2B6 (19% of the fold induced by phenobarbital). The enzyme activities for CYP1A2 and 2B6 were increased by up to 2.7-fold and 2.3-fold, respectively (11% and 23% of the effects of omeprazole and phenobarbital, respectively). There was a decrease of CYP3A4 activity, probably due to the concomitant inhibitory effect of suvorexant on CYP3A4.

2.4.2 Is suvorexant a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system?

	P-gp substrate	Inhibitor (Transporter, IC_{50}, substrate)

Suvorexant	No The passive permeability across LLC-PK1 cells was high (apparent permeability P_{app} = 22.8 - 34.6 × 10^{-6} cm/s) at concentrations from 0.5 μM to 5 μM. The efflux ratio ($P_{app, B\text{-}to\text{-}A}/P_{app, A\text{-}to\text{-}B}$) across LLC-PK1-MDR1 cells transfected with human P-gp was 1.0-1.6. The efflux ratio for the positive control, verapamil, was 3.1 or 3.4.	P-gp: 19 μM (digoxin) BCRP: 10-15 μM (methotrexate) OATP1B1: 10 μM (pitavastatin) OCT2: 1.3 μM (metformin)
M9	Yes The efflux ratio was 3.2-4.3 at a concentration range from 0.1 μM to 1 μM.	P-gp: 73 μM (digoxin) BCRP: ~15 μM (methotrexate) OATP1B1: > 15 μM (pitavastatin) OCT2: > 15 μM (metformin)

2.4.3 Is there an *in vitro* basis to suspect drug-drug interaction?

Metabolism: Since suvorexant is mainly metabolized by CYP3A4, *in vivo* drug-drug interaction is expected when it is concomitantly used with CYP3A4 inhibitors and inducers. Studies have been conducted to evaluate the effects of strong CYP3A4 inhibitor (ketoconazole), moderate inhibitor (diltiazem), and strong CYP3A4 inducer (rifampicin) on PK of suvorexant.

Inhibition of CYPs: Suvorexant and M9 are not expected to significantly inhibit major CYP isoforms in humans except CYP3A4/5. The steady state C_{max} following 40 mg suvorexant dosing in non-elderly subjects is predicted to be 1.17 μM based on a population PK analysis. The ratio of C_{max}/IC_{50} of suvorexant for CYP1A2, 2B6, 2C8, 2C9 and 2D6 is less than 0.1, suggesting suvorexant is unlikely to inhibit these CYP isozymes *in vivo*. The maximum concentration of suvorexant at the inlet to the liver ($I_{in,max}$= fu,p×(Cmax+Fa×ka×Dose/Qh/(B/P)); fu,p is 0.01; absorption fraction (Fa) is set as the estimated absolute bioavailability – 0.47; absorption constant (ka) is estimated as 1.97 hr^{-1} from the popPK analysis; liver blood flow (Qh) is 1500 ml/min; Blood-to-plasma ratio (B/P) is 0.6) is estimated to be 2.71 μM. Since suvorexant is highly protein bound (≥99%), the free $I_{in,max}$ is 0.027 μM or less. Thus, the R-value (i.e., 1+ (fu,p × $I_{in,max}$ /IC_{50})) is less than a cut-off value of 1.25, indicating that suvorexant is not likely to be an inhibitor of CYP2C19 *in vivo*. The major metabolite, M9, is a weaker inhibitor of these CYP enzymes and has a C_{max} lower than that of suvorexant. Therefore, M9 is not expected to inhibit these CYPs *in vivo*, either. Suvorexant and M9 are time-dependent inhibitors of CYP3A4. Thus, there is possibility of CYP3A4 mediated drug-drug interaction after administration of suvorexant in humans. This has been evaluated in a study using a probe CYP3A4 substrate, midazolam.

Induction of CYPs: Suvorexant is not expected to significantly induce CYP1A2, 2B6 and 3A4 in humans. At a concentration of 1 μM, surorexant induced CYP1A2 and CYP2B6

mRNA levels by 2.2-fold and 1.2-fold, respectively, less than a cut-off of 4-fold suggested by literature (Fahmi OA, et al., Drug Metab Dispos. 2010 Sep;38(9):1605-11). In addition, the induction effects of suvorexant as measured by CYP1A2 and CYP2B6 activities were 2.2% and 9.7% of the corresponding positive controls, respectively. Thus, suvorexant is unlikely to induce CYP1A2 or 2B6 in humans. The induction effect of suvorexant on CYP3A mRNA expression has been futher characeterized by estimating its EC_{50} (14.5 or 13.4 μM) and E_{max} (12.7- or 9.3-fold) in two livers. Based on these values and the free $I_{in,max}$ concentration of suvorexant, a R3 value was calculated as 0.98 ($R_3=1/(1+d\times E_{max} \times [I]/(EC_{50} + [I])$, d is assumed as 1), which is above a cut-off value of 0.8. Thus, suvorexant is not expected to significantly induce CYP3A in humans. Effects of 40 mg suvorexant on CYP2C9 have been investigated in humans using warfarin as a substrate. The study did not show signicant change of S-warfarin exposure, indicating that suvorexant does not induce CYP2C9 *in vivo*, either.

Substrate of Transporters: Suvorexant is not a P-gp substrate. Studies have not been conducted to evaluate whether suvorexant is a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. Unchanged suvorexant excreted into urine after oral dose is negligible, indicating that OAT1, OAT3 and OCT2 play a minimal role in elimination of suvorexant. Since suvorexant has high permeability across LLC-PK1 monolayer, it is likely that passive permeability is predominant in entry of suvorexant into hepatocytes, and thus active uptake by OATPs may only play a limited role. For the same reason, absorption of suvorexant in gastrointestinal tract may be mainly due to its passive permeation across apical membrane of enterocytes. Thus, significant drug-drug interactions between suvorexant and inhibitors of these transporters are not expected.

Inhibtion of Transporters: Though the C_{max}/IC_{50} ratio of suvorexant on P-gp is less than 0.1, the $[I]_2/IC_{50}$ ratio is more than the cut-off value of 10 ($[I]_2$ = 40 mg / 250 mL, as an estimate of drug concentration in the gut for a dose of 40 mg suvorexant), indicating that suvorexant has the potential to inhibit P-gp at intestine level. Similarly, suvorexant had a C_{max}/IC_{50} ratio around or less than 0.1 for BCRP, but the $[I]_2/IC_{50}$ ratio is larger than 10, suggesting that suvorexant may also be able to inhibit BCRP present at the intestine. Effect of 40 mg suvorexant on the PK of a P-gp substrate, digoxin, has been examined in an *in vivo* study, which showed that digoxin AUC and C_{max} were increased by 27% and 21%, respectively, consistent with the prediction from *in vitro* results. Therefore, though *in vivo* study was not conducted with BCRP substrates, significant PK interactions of suvorexant with those substrates are possible, which could increase their exposure.

Suvorexant or M9 is unlikely to inhibit OATP1B1 *in vivo*, as the R-value (i.e., $1+ (fu,p \times I_{in,max} /IC_{50})$ is less than a cut-off value of 1.25. Though the IC_{50} of suvorexant or M9 on OATP1B3 is not measured, the potential of OATP1B3 inhibition by either moiety is low, considering that the estimated unbound $I_{in,max}$ for suvorexant or M9 is very low, 0.027 μM or less. Suvorexant or M9 is unlikely to inhibit OCT2 in humans, either, since the unbound C_{max}/IC_{50} ratio (0.009 for suvorexant) is more than 10-fold lower than the cut-off value 0.1. Though the IC_{50} of suvorexant or M9 on OAT1 or OAT3 has not been measured, they are not expected to have signicant inhibiton effects on OAT1 or OAT3 *in*

vivo, as both compounds are highly protein bound and thus the unbound C_{max} is very low (0.0117 μM or lower).

2.4.4 What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

Due to potential additive CNS effects, clinical studies have been conducted to evaluate the potential for PK and PD drug-drug interactions between suvorexant and CNS-active agents, including alcohol and paroxetine, a commonly prescribed selective serotonin reuptake inhibitor (SSRI).

Suvorexant and Alcohol Interaction Study (P010)

This was a randomized, double-blind, double-dummy, placebo-controlled, 4-period crossover study to evaluate the PK and PD interaction of suvorexant when coadministered with alcohol.

Subjects (28 healthy male and female subjects) received each of 4 treatments (suvorexant 40 mg, alcohol 0.7 g/kg, suvorexant + alcohol, placebo) which were administered in a randomly assigned order. This level of alcohol has reliably demonstrated impairment on cognitive testing battery and postural stability in other alcohol interaction studies with CNS depressants. At pre-determined time points postdose (1, 2, 5, and 9 hours), PK, PD and safety and tolerability assessments were performed. There was a 5 days of washout between each treatment period. The primary endpoint in this study was digit vigilance test (DVT) - reaction time. Other psychomotor/cognitive performance tests included Choice Reaction Time, Immediate and Delayed Word Recall, Numeric Working Memory and Digit Symbol Substitution Test (DSST). In addition, balance and the subjective alertness were evaluated.

When suvorexant 40 mg was coadministered with alcohol (0.7 mg/kg), an additive effect on psychomotor performance alcohol and suvorexant was demonstrated.

Coadministration of suvorexant and alcohol produced additive impairment as compared to suvorexant alone or alcohol alone on sustained attention/vigilance as assessed by DVT (speed) at 2 hours postdose. The co-administration of suvorexant with alcohol also produced additive impairment on balance and working memory as assessed by body sway and numeric working memory tests, respectively.

There was no PK interaction between alcohol and suvorexant.

PK Parameters of Suvorexant (MK-4305) Following Administration of a Single Dose of 40 mg Suvorexant With and Without Alcohol in Healthy Young Subjects

	MK-4305 with Alcohol			MK-4305 Alone			MK-4305 with Alcohol / MK-4305 Alone	
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (µM.hr)†	28	15.06	(13.31, 17.05)	28	13.76	(12.15, 15.57)	1.09	(1.04, 1.16)
C_{max} (µM)†	30	1.258	(1.158, 1.366)	30	1.200	(1.105, 1.304)	1.05	(0.98, 1.12)
T_{max} (hr)‡	30	3.0	[2.0, 5.1]	30	3.0	[1.0, 5.0]	-	-
Apparent terminal $t_{1/2}$ (hr)§	28	12.1	3.2	28	12.1	3.4	-	-

PK Parameters of Alcohol Following Administration of Alcohol With and Without Suvorexant (MK-4305) in Healthy Young Subjects

	MK-4305 with Alcohol			Alcohol Alone			MK-4305 with Alcohol / Alcohol Alone	
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0\text{-last}}$ (g/dL•hr)†	30	0.282	(0.265, 0.300)	30	0.285	(0.268, 0.304)	0.99	(0.95, 1.03)
C_{max} (g/dL)†	30	0.081	(0.077, 0.086)	30	0.082	(0.078, 0.087)	0.99	(0.95, 1.03)
T_{max} (hr)‡	30	2.0	[0.5, 3.0]	30	2.0	[0.5, 3.0]	-	-

Recommendations: Alcohol should not be co-administered with suvorexant due to the additive CNS effects.

Suvorexant and Paroxetine DDI Study (P026)

This was a randomized, double-blind, placebo-controlled, 3-period, fixed sequence, parallel group study in healthy male or female subjects (N=24) to determine the effect of steady-state paroxetine on suvorexant pharmacokinetics and pharmacodynamics as measured by the DVT, a psychomotor performance test. Four treatments (A, B, C, D) were administered in the study. Subjects received Treatments A (40 mg suvorexant) or B (suvorexant placebo) once-daily 30 minutes prior to bedtime (approximately 10 PM) for 4 nights in Period 1 (Days 1 - 4). All subjects received Treatment C (20 mg paroxetine and suvorexant placebo) once-daily at approximately 8 AM for 10 days in Period 2 (Days 6 to 15), followed by Treatments C or D (D: 20 mg paroxetine and 40 mg suvorexant).

	Prestudy		Period 1			Period 2		Period 3			
Study Day:	-14 to -2	-1	1-3	4	5	6-14	15	16	17-18	19	20
Treatment Sequence 1 (n=20)			MK	MK		P Pbo	P Pbo	P MK	P MK	P MK	P
Treatment Sequence 2 (n=2)			Pbo	Pbo		P Pbo	P Pbo	P Pbo	P Pbo	P Pbo	P
MK=Suvorexant (MK-4305), P=paroxetine, Pbo=suvorexant matching placebo. Suvorexant was dosed at approximately 10 PM, 30 minutes prior to lights out. Paroxetine was dosed at approximately 8 AM.											

There was no PK interaction between paroxetine and suvorexant. The absence of a PK drug interaction between paroxetine and suvorexant is consistent with the lack of potential for paroxetine for CYP3A mediated drug interactions (suvorexant is primarily metabolized by CYP3A) and the lack of potential for suvorexant for CYP2D6 mediated drug interactions (paroxetine is a CYP2D6 substrate).

Summary of PK Parameters of Suvorexant Following Multiple 40 mg Doses of Suvorexant Administered With and Without Multiple 20 mg Doses of Paroxetine to Healthy Subjects

Pharmacokinetic Parameter	Suvorexant Alone			Suvorexant + Paroxetine			(Suvorexant + Paroxetine / Suvorexant Alone)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0\text{-}24hr}$ (µM•hr) †	21	13.21	(11.15, 15.64)	18	12.84	(10.82, 15.22)	0.97	(0.92, 1.03)
C_{max} (µM)†	21	1.094	(0.954, 1.255)	18	1.148	(0.996, 1.323)	1.05	(0.96, 1.15)
T_{max} (hr) §	21	2.0	0.5, 4.0	18	2.0	1.0, 4.0	-	-

Summary of PK Parameters of Paroxetine Following Multiple 20 mg Doses of Paroxetine Administered With and Without Multiple 40 mg Doses of Suvorexant to Healthy Subjects

Pharmacokinetic Parameter	Paroxetine Alone			Suvorexant + Paroxetine			(Suvorexant + Paroxetine / Paroxetine Alone)	
	N*	GM	95% CI	N*	GM	95% CI	GMR	90% CI
$AUC_{0\text{-}24hr}$ (ng/mL•hr)†¶	18	671.0	(489.6, 919.5)	18	669.7	(488.7, 917.8)	1.00	(0.94, 1.06)
C_{max} (ng/mL)†	18	35.1	(26.0, 47.2)	18	38.2	(28.4, 51.4)	1.09	(1.03, 1.15)
T_{max} (hr)§	18	6.0	1.0, 12.0	18	6.0	6.0, 23.9	-	-

In addition, there was no clinically significant pharmacodynamic interaction between suvorexant and paroxetine.
Recommendations: A general precaution should be advised when suvorexant is co-administered with drugs that produce CNS depressant effects due to potential additive effects.

2.4.5 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.5.1 Influence of other drugs on suvorexant:

Suvorexant and Ketoconazole DDI Study (P008)
An open-label, 2-period, fixed-sequence study was conducted in healthy male subjects (n=10) to evaluate the impact of ketoconazole, a strong CYP3A and P-gp inhibitor, on suvorexant PK. In Period 1, subjects were administered a single dose of 4 mg suvorexant only. In Period 2, subjects were administered ketoconazole 400 mg once daily for 11 days (Days 1 to 11) and a single dose of 4 mg suvorexant on Day 2. There was at least a 5-day washout between the last dose in Period 1 and the first dose of ketoconazole in Period 2. Pharmacokinetic samples were obtained for suvorexant and M9 quantitation up to 72 hours (Period 1) and 240 hours (Period 2) following suvorexant administration.

Summary of PK Parameters of Suvorexant (MK-4305) Following a Single Oral 4 mg Dose of Suvorexant Administered With and Without Multiple 400 mg Ketoconazole Doses to Healthy Subjects

PK Parameter	MK-4305 alone			MK-4305 with Ketoconazole			MK-4305 with Ketoconazole / MK-4305 alone	
	N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI
$AUC_{0\text{-}\infty}$ (μM•hr) †	10	2.61	(1.84, 3.71)	10	7.28	(5.13, 10.32)	2.79	(2.35, 3.31)
C_{max} (μM) †	10	0.277	(0.222, 0.347)	10	0.342	(0.274, 0.428)	1.23	(1.05, 1.44)
T_{max} (hr) §	10	1.0	0.5, 2.0	10	2.0	1.0, 4.0		
Apparent $t_{1/2}$ (hr) ‖	10	11.2	4.2	10	19.4	6.9		

Summary of PK Parameters of M9 Following a Single Oral 4 mg Dose of Suvorexant Administered With and Without Multiple 400 mg Ketoconazole Doses

	MK-4305 alone			MK-4305 with Ketoconazole			MK-4305 with Ketoconazole / MK-4305 alone	
M9 PK Parameter	N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI
$AUC_{0-\infty}$ (μM•hr) †	10	2.30	(1.66, 3.20)	10	4.15	(2.99, 5.77)	1.80	(1.64, 1.98)
C_{max} (μM) †	10	0.123	(0.110, 0.137)	10	0.088	(0.078, 0.098)	0.71	(0.64, 0.80)
T_{max} (hr) §	10	4.0	1.0, 6.0	10	8.0	4.0, 24.0		
Apparent $t_{1/2}$ (hr) ‖	10	11.7	7.0	10	21.4	8.1		

Ketoconazole significantly increased suvorexant systemic exposure ($AUC_{0-\infty}$) and $t_{1/2}$. Only a 23% increase in suvorexant C_{max} was observed with prolongation in mean T_{max}. The increase in suvorexant AUC, with minimal increases in C_{max}, suggests that ketoconazole inhibits systemic clearance of suvorexant.
Following co-administration of suvorexant with ketoconazole, M9 exposure (AUC) increased 1.80 while C_{max} slightly decreased (0.71). Similar increases in $t_{1/2}$ and T_{max} of M9 to those reported for the parent were observed. However, the metabolite/parent ratio decreased from 0.88 to 0.57 with ketoconazole coadministration.
The decreased M9/MK-4305 ratio and the increased M9 $t_{1/2}$, indicates that both the formation and metabolism of M9 are inhibited by ketoconazole.
Recommendations: Suvorexant should not be co-administered with strong CYP3A inhibitors.

Suvorexant- Rifampin and Diltiazem Interaction Study (P038)
As the effect of strong CYP3A inhibitors on suvorexant PK was confirmed in study P008 (ketoconazole interaction study), this study was designed to further assess the effect of a moderate inhibitor (diltiazem) of CYP3A and a strong CYP3A inducer (rifampin) on suvorexant PK. This was a two-part, open-label, fixed-sequence, randomized study in healthy male or female subjects.
In Part I, subjects (n=10) were administered a single 40-mg dose of suvorexant only (Period 1) on Day 1; subjects received a dose of 40 mg suvorexant co-administered with rifampin (600 mg) on Day 14 of a 17-day (Days 1 to 17), once-daily rifampin dosing regimen (Period 2). There was at least a 5-day washout between the dose in Period 1 and the first dose of rifampin (Day 1) in Period 2. Pharmacokinetic samples, for suvorexant and M9 quantitation, were obtained predose to suvorexant administration and at selected time points up to 96 hours (Periods 1 and 2) following suvorexant administration.
In Part II, subjects (n=20) were administered a single 20-mg dose of suvorexant only (Period 1) on Day 1, subjects were administered diltiazem 240 mg once-daily for 6 days (Days 1 to 6) and a single dose of 20 mg suvorexant on Day 2 (Period 2). There was at least a 4-day washout between the dose in Period 1 and the first dose of diltiazem (Day 1) in Period 2. Pharmacokinetic samples, for suvorexant and M9 quantitation, were obtained predose to suvorexant administration and at selected time points up to 96 hours (Period 1) and 120 hours (Period 2) following suvorexant administration.
Following once-daily dosing of 600 mg rifampin, suvorexant exposure ($AUC_{0-\infty}$) was significantly reduced. The impact on C_{max} was slightly less than that on AUC.

M9 $AUC_{0-\infty}$ and C_{max} were also significantly decreased after coadministration with rifampin, consistent with CYP3A involvement in the biotransformation of M9. Although rifampin induces other CYP450s and P-gp, suvorexant is not a P-gp substrate, therefore the reported results are likely attributable to CYP3A mechanisms.

Summary of Pharmacokinetic Parameters of Suvorexant (MK-4305) and M9 Following a Single 40 mg Dose of Suvorexant Alone or Following Concomitant Administration with Multiple Doses of 600 mg Rifampin in Healthy Subjects

	MK-4305 Alone			MK-4305 + Rifampin			(MK-4305 + Rifampin / MK-4305 Alone)	
PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (µM•hr) †	10	13.63	(10.53, 17.64)	10	1.68	(1.30, 2.17)	0.12	(0.11, 0.14)
C_{max}(µM)†	10	0.852	(0.702, 1.033)	10	0.305	(0.252, 0.370)	0.36	(0.31, 0.42)
T_{max} (hr) §	10	2.0	(0.5, 4.0)	10	1.0	(0.5, 2.0)	.	
Apparent terminal $t_{1/2}$(hr) ‖	10	12.9	2.2	10	7.7	3.4	.	

	MK-4305 Alone			MK-4305 + Rifampin			(MK-4305 + Rifampin / MK-4305 Alone)	
M9 PK Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (µM•hr) †	10	16.21	(12.77, 20.58)	10	3.72	(2.93, 4.72)	0.23	(0.21, 0.25)
C_{max}(µM)†	10	0.859	(0.738, 1.000)	10	0.665	(0.571, 0.774)	0.77	(0.70, 0.86)
T_{max} (hr) §	10	4.0	(2.0, 4.0)	10	1.0	(1.0, 2.0)	.	
Apparent terminal $t_{1/2}$(hr) ‖	10	15.0	2.5	10	8.3	3.7	.	

Administration of diltiazem with a single 20 mg dose of suvorexant significantly (2-fold) increased suvorexant $AUC_{0-\infty}$ with a less pronounced effect on C_{max} (1.22). Suvorexant mean $t_{1/2}$ values were slightly prolonged while T_{max} remained generally unaffected. Co-administration of diltiazem also increased M9 $AUC_{0-\infty}$ (1.36), with a decrease in C_{max} observed. Similar trends in mean apparent $t_{1/2}$ and median T_{max} of M9 to those reported for the parent were observed.

Part II: Summary of Pharmacokinetic Parameters of Suvorexant (MK-4305) and M9 Following a Single 20 mg Dose of Suvorexant Alone or Following Concomitant Administration with Multiple Doses of 240 mg Diltiazem in Healthy Subjects

PK Parameter	MK-4305 Alone			MK-4305 + Diltiazem			(MK-4305 + Diltiazem / MK-4305 Alone)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (μM•hr) †	20	7.88	(6.57, 9.46)	18	16.13	(13.38, 19.44)	2.05	(1.82, 2.30)
C_{max}(μM)†	20	0.622	(0.543, 0.713)	18	0.756	(0.657, 0.871)	1.22	(1.09, 1.36)
T_{max} (hr) §	20	1.5	(1.0, 4.0)	18	2.0	(1.0, 4.0)	.	
Apparent terminal $t_{1/2}$(hr) ‖	20	12.4	3.3	18	16.1	5.3	.	

M9 PK Parameter	MK-4305 Alone			MK-4305 + Diltiazem			(MK-4305 + Diltiazem / MK-4305 Alone)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (μM•hr) †	20	7.67	(6.48, 9.08)	18	10.45	(8.81, 12.39)	1.36	(1.27, 1.47)
C_{max}(μM)†	20	0.420	(0.377, 0.467)	18	0.356	(0.319, 0.398)	0.85	(0.79, 0.92)
T_{max} (hr) §	20	4.0	(1.0, 6.1)	18	4.0	(2.0, 6.0)	.	
Apparent terminal $t_{1/2}$(hr) ‖	20	13.6	3.4	18	18.0	6.5	.	

Recommendations: The suvorexant dose in subjects receiving moderate CYP3A4 inhibitors should be reduced by half. If the recommended suvorexant dose is 15 mg, the sponsor needs to develop a lower strength tablet for dose adjustment in patients receiving moderate CYP3A4 inhibitors. (PMC)
The efficacy of suvorexant in subjects receiving CYP3A4 inducers may be decreased.

2.4.5.2 Influence of suvorexant on other drugs

Suvorexant and Midazolam Interaction Study (P015)
Based on *in vitro* data, suvorexant appeared to have the potential for inhibitory and inductive effects on CYP3A4. A clinical study was conducted to assess the CYP3A4 inhibitory potential of suvorexant on midazolam (a sensitive CYP3A4 substrate) pharmacokinetics. This was a 2-part, open-label, study in healthy male and female subjects (n=12) to evaluate the effect of steady-state suvorexant on single doses of oral midazolam (2 mg). In Part 1, subjects were administered a single dose of 2 mg midazolam (Day 1), followed by multiple once-daily doses of 80 mg suvorexant for 14 days (Days 3 to 16) and a single dose 2 mg midazolam on Days 3 and 16. On concomitant dosing days (Days 3, 6, and 16), midazolam was given 2 hours following the oral 80-mg dose of suvorexant. Blood samples were collected for midazolam PK up to 24 hours following midazolam administration on Days 1, 3, 6 and 16.
Pharmacokinetic samples for suvorexant quantitation were obtained predose to suvorexant administration and at specified time points up to 72 hours following suvorexant administration on Day 16. Additional suvorexant predose samples were collected during multiple-dose administration (Days 3, 4, 5, 6, 8, 10, 12, 14 and 15).
Part II (suvorexant 40 mg with or without co-administration of midazolam) was not conducted based on the minimal effect of suvorexant on midazolam in Part I.

Midazolam systemic exposure ($AUC_{0-\infty}$ and C_{max}) was similar after co-administration of midazolam with single dose suvorexant (Study Day 3) compared to midazolam administered alone. Midazolam T_{max} and $t_{1/2}$ estimates were similar under both conditions. Therefore, suvorexant has minimal potential for clinically meaningful reversible inhibition of CYP3A.

After co-administration of midazolam on Day 14 (Study Day 16) of multiple daily doses of suvorexant, midazolam $AUC_{0-\infty}$ increased by 47% compared to midazolam administered alone. The $AUC_{0-\infty}$ for midazolam following co-administration on Day 4 (Study Day 6) of multiple daily doses of 80 mg suvorexant increased approximately 25% compared to midazolam administered alone. Generally, the effects on midazolam C_{max} were less than those observed for $AUC_{0-\infty}$. Midazolam $t_{1/2}$ was also increased following coadministration with multiple daily doses of suvorexant. These results suggest that suvorexant is a weak, time-dependent CYP3A inhibitor.

Statistical Comparisons of Midazolam Plasma PK Parameters in Healthy Male and Female Subjects Following the Single-dose Administration of 2 mg Midazolam Alone, 2 mg Midazolam Co-administered with the First Dose of Multiple Daily Doses of 80 mg Suvorexant (MK-4305), and 2 mg Midazolam Co-administered on Days 4 and 14 of Multiple Daily Doses of 80 mg Suvorexant

Parameter	Treatment	N	GM	95% CI	Comparison vs Midazolam Alone: Geometric Mean Ratio	90% CI	rMSE†
$AUC_{0-\infty}$‡ (ng•hr/mL)	Midazolam Alone	12	26.20	(20.25, 33.91)	-	-	0.1807
	First Dose of Multiple Daily Doses of MK-4305 + Midazolam	12	25.08	(19.38, 32.46)	0.96	(0.84, 1.08)	-
	Multiple Daily Doses of MK-4305 (4 days) + Midazolam	12	32.85	(25.38, 42.52)	1.25	(1.11, 1.42)	-
	Multiple Daily Doses of MK-4305 (14 days) + Midazolam	12	38.55	(29.79, 49.90)	1.47	(1.30, 1.67)	-
C_{max}‡ (ng/mL)	Midazolam Alone	12	9.57	(7.77, 11.78)	-	-	0.2033
	First Dose of Multiple Daily Doses of MK-4305 + Midazolam	12	7.94	(6.45, 9.77)	0.83	(0.72, 0.95)	-
	Multiple Daily Doses of MK-4305 (4 days) + Midazolam	12	10.13	(8.23, 12.48)	1.06	(0.92, 1.22)	-
	Multiple Daily Doses of MK-4305 (14 days) + Midazolam	12	11.76	(9.55, 14.48)	1.23	(1.07, 1.41)	-
T_{max}‖ (hr)	Midazolam Alone	12	0.5	(0.5, 1.0)	-	-	-
	First Dose of Multiple Daily Doses of MK-4305 + Midazolam	12	1.0	(0.5, 1.5)	0.25¶	(0.01, 0.50)¶	-
	Multiple Daily Doses of MK-4305 (4 days) + Midazolam	12	1.0	(0.5, 1.1)	0.30¶	(0.25, 0.51)¶	-
	Multiple Daily Doses of MK-4305 (14 days) + Midazolam	12	1.0	(0.5, 1.0)	0.25¶	(0.24, 0.50)¶	-
Apparent Terminal $t_{1/2}$§ (hr)	Midazolam Alone	12	3.3§	2.6§	-	-	-
	First Dose of Multiple Daily Doses of MK-4305 + Midazolam	12	3.8§	3.1§	-	-	-
	Multiple Daily Doses of MK-4305 (4 days) + Midazolam	12	4.7§	2.6§	-	-	-
	Multiple Daily Doses of MK-4305 (14 days) + Midazolam	12	4.5§	2.2§	-	-	-

rMSE: Root mean square error on log-scale. When multiplied by 100, provides estimate of the pooled coefficient of variation.

Recommendations: No dose adjustment is needed for CYP3A substrates, however patients on sensitive CYP3A substrates with narrow therapeutic range (e.g., alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) should be closely monitored.

Suvorexant and Oral Contraceptives (OC) Interaction Study (P013)

This was an open-label, randomized, 2-period, crossover study in healthy female subjects (n=20) to evaluate the effect of multiple-dose (40 mg) suvorexant on oral contraceptive Ortho Cyclen™ (ethinyl estradiol 0.035 mg and norgestimate 0.250 mg). Additionally, the single- and multiple-dose PK of suvorexant when coadministered with oral contraceptives was assessed.

In Treatment A, subjects were administered a single dose of Ortho Cyclen™ alone on Day 1 in the evening. In Treatment B, subjects were administered suvorexant 40 mg once-daily for 18 days (Days 1-18) and a single dose of Ortho Cyclen™ was co-administered with suvorexant on Day 14. There was at least a 10-day washout between each treatment period. Plasma was collected for ethinyl estradiol (EE) and norelgestromin (NGMN; is an active metabolite of norgestimate) PK evaluation predose and up to 96 hours following Ortho Cyclen™ administration (Treatments A and B). Blood samples for suvorexant quantitation were obtained predose to suvorexant administration (Treatments A and B) and at specified time points up to 96 hours following suvorexant administration on Day 18 (Treatment B).

The mean EE and NGMN $AUC_{0-\infty}$ values were slightly increased by 7% and 16%, respectively, during coadministration with 40 mg suvorexant. The EE and NGMN C_{max} values were similar when Ortho Cyclen™ was given in combination with suvorexant, compared to oral contraceptive alone.

	Ortho Cyclen™ with MK-4305			Ortho Cyclen™ Alone			Ortho Cyclen™ with MK-4305 / Ortho Cyclen™ Alone		
	N	GM†	95 % CI	N	GM†	95 % CI	GMR	90 % CI	rMSE §
Ethinyl estradiol									
$AUC_{0-\infty}$ (nM•hr) †	17	3.14	(2.69, 3.67)	19	2.94	(2.52, 3.43)	1.07	(0.99, 1.16)	0.129
C_{max} (nM) †	17	0.169	(0.138, 0.206)	19	0.180	(0.148, 0.219)	0.94	(0.83, 1.06)	0.208
T_{max} (hr) ‡	17	2.0	(1.5, 6.0)	19	2.0	(1.5, 6.0)	.		.
Apparent terminal $t_{1/2}$ (hr) ‖	17	20.1	(4.9)	19	17.5	(3.9)	.		.
Norelgestromin									
$AUC_{0-\infty}$ (nM•hr) †	17	58.65	(53.08, 64.79)	19	50.74	(45.96, 56.02)	1.16	(1.11, 1.20)	0.066
C_{max} (nM) †	17	3.051	(2.540, 3.666)	19	2.829	(2.365, 3.383)	1.08	(0.95, 1.23)	0.220
T_{max} (hr) ‡	17	2.0	(1.0, 6.0)	19	2.0	(1.5, 8.0)	.		.
Apparent terminal $t_{1/2}$ (hr) ‖	17	31.3	(6.2)	19	29.4	(6.0)	.		.

These data are consistent with a low potential for suvorexant to alter the activities of CYP3A, uridinediphosphoglucuronosyltransferases (UGTs) and sulfotransferases (SULTs).
The pharmacokinetics of 40 mg of suvorexant administered once daily for 18 days, where Ortho Cyclen™ was co-administered on day 14, was also evaluated in this study. The summary for the suvorexant PK parameters is presented below. Healthy female subjects achieved 90% of steady state suvorexant levels generally by Day 3 of multiple once daily dosing, with a mean accumulation ratio of 1.53 for AUC_{0-24}, consistent with the mean terminal half life of 15.4 hours observed in this study.

Summary of PK Parameters of Suvorexant (MK-4305) On Day 1 and Day 18 Following Once Daily PM Dosing of 40 mg Suvorexant, with a Single Oral Dose of Ortho Cyclen™ Co-administered on Day 14 in Healthy Female Subjects

Pharmacokinetic Parameter	MK-4305 40-mg, Days 1-18 + Ortho Cyclen™, Day 14
Day 1 (Single Dose) (N= 19)	
AUC_{0-24hr} (μM•hr) †	10.61 (9.49, 11.87)
C_{max} (μM) †	1.037 (0.909, 1.182)
C_{24hr} (μM) †	0.257 (0.220, 0.299)
T_{max} (hr) ‡	2.0 (1.0, 4.0)
Day 18 (Last Dose) (N=17)	
AUC_{0-24hr} (μM•hr) †	16.28 (14.52, 18.25)
C_{max} (μM) †	1.409 (1.226, 1.620)
C_{24hr} (μM) †	0.421 (0.358, 0.494)
T_{max} (hr) ‡	2.0 (0.5, 2.0)
Apparent Terminal Half-life (hr) §	15.4 (3.8)
Accumulation Ratio: Day 18/ Day 1‖	
AUC_{0-24hr}	1.53 (1.43, 1.65)
C_{max}	1.36 (1.15, 1.60)
C_{24hr}	1.64 (1.41, 1.90)

The results of this study indicate that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of suvorexant.
Recommendations: No dose adjustment is needed for oral contraceptives when given in combination with suvorexant. No dose adjustment is needed for suvorexant when co-administered with oral contraceptives.

Suvorexant and Warfarin Interaction Study (P024)
Although the results from an *in vitro* human microsome study suggested that significant inhibition of CYP2C9 by suvorexant is unlikely (the IC_{50} for inhibition of CYP2C9 was 15 μM with steady-state suvorexant Cmax being approximately 14-fold lower than the IC_{50}), the sponsor conducted a DDI study with warfarin since warfarin has a narrow therapeutic index and there is potential for concomitant use in the target patient population.
This was an open-label, randomized, 2-period cross-over study in healthy male or female subjects (n=14), evaluating the effect of steady-state suvorexant on the R(+) and S(-)

enantiomers of warfarin following a single dose of warfarin. In Treatment A, subjects were administered a single dose of 30 mg warfarin only. In Treatment B, subjects were administered suvorexant 40 mg once-daily for 20 consecutive days (Days 1 to 20) with co-administration of a single dose of 30 mg warfarin on Day 14. There was at least a 14-day washout between the last dose in Period 1 and the first dose in Period 2. Blood PK samples were collected pre-dose and at selected timepoints up to 168 hours (Periods 1 and 2) following warfarin administration for R(+) and S(-) enantiomer quantitation. In addition, blood samples for determination of prothrombin time (PT) as measured by International Normalized Ratio (INR) values were collected at predose and up to 168 hours following warfarin administration in each treatment period.

Summary of PK Parameters of Warfarin Following Administration of a Single Oral Dose of 30 mg Warfarin and Daily Oral Doses of 40 mg Suvorexant (MK-4305) for 20 Days with Co-administration of a Single Oral Dose of 30 mg Warfarin on Day 14 (N=14 Warfarin with Suvorexant, N=13 Warfarin Alone)

	Warfarin with MK-4305		Warfarin Alone#		Warfarin with MK-4305 / Warfarin Alone
	N	GM† (95% CI)	N	GM†(95% CI)	GMR (90% CI)
R(+)Enantiomer					
$AUC_{0-\infty}$ (uM*hr)	14	322.57 (294.11, 353.79)	13	325.66 (296.56, 357.61)	0.99 (0.94,1.04)
AUC_{last} (uM*hr)	14	294.15 (271.72, 318.44)	13	295.82 (272.98, 320.58)	0.99 (0.95,1.04)
C_{max} (uM)	14	5.69 (5.21, 6.21)	13	6.02 (5.50, 6.59)	0.95 (0.87,1.03)
T_{max}‡ (hr)	14	1.00 (0.50, 4.00)	13	1.00 (0.50, 2.00)	.
Apparent $t_{1/2}$‡ (hr)	14	46.4 (7.6)	13	47.6 (7.7)	.
S(-)Enantiomer					
$AUC_{0-\infty}$ (uM*hr)	13	239.55 (187.64, 305.82)	12#	241.46 (189.06, 308.38)	0.99 (0.95,1.04)
AUC_{last} (uM*hr)	14	242.76 (189.78, 310.54)	13	244.13 (190.81, 312.35)	0.99 (0.96,1.03)
C_{max} (uM)	14	5.86 (5.33, 6.44)	13	6.18 (5.60, 6.82)	0.95 (0.86,1.05)
T_{max}‡ (hr)	14	1.00 (0.50, 2.00)	13	1.00 (0.50, 2.00)	.
Apparent $t_{1/2}$‡ (hr)	13	36.0 (9.5)	12#	37.3 (10.0)	.

The R(+) and S(-) enantiomers AUC and C_{max} values were similar when warfarin was administered in combination with suvorexant, compared to warfarin alone.

Summary of INR AUC_{0-168h} and INR_{max} Following Administration of a Single Oral Dose of 30 mg Warfarin and Daily Oral Doses of 40 mg Suvorexant (MK-4305) for 20 Days with Coadministration of a Single Oral Dose of 30 mg Warfarin on Day 14

	N	Warfarin + MK-4305 GM † (95% CI)	Warfarin Alone¶ GM † (95% CI)	Ratio Warfarin + MK-4305/warfarin alone GMR (90% CI)
$AUC_{0-168\ hr}$	14	237.50 (215.27, 262.02)	224.29 (203.25, 247.50)	1.06 (1.03, 1.09)
INRmax	14	1.96 (1.74, 2.21)	1.79 (1.59, 2.02)	1.09 (1.05, 1.14)

The slight increase in AUC_{0-168h} and INR_{max}, 6% and 9%, respectively, following co-administration of warfarin with suvorexant is not considered to be clinically meaningful. Note: This was confirmed with the Clinical Division (Dr. Illoh).

Recommendations: No dose adjustment is needed for warfarin when given in combination with suvorexant.

Suvorexant and Digoxin Interaction Study (P016)

As potential inhibition of P-gp transporters by suvorexant could not be ruled out based on the *in vitro* transporter evaluations, a clinical DDI study with digoxin (a P-gp substrate) was conducted.

This was open-label, randomized, 2-period cross-over study in healthy male or female subjects (N=20) to determine the effect of steady-state suvorexant on digoxin pharmacokinetics. In Treatment A, subjects were administered a single dose of 0.5 mg digoxin. In Treatment B, subjects were administered suvorexant 40 mg once daily for 11 consecutive days (Days 1 to 11) with co-administration of a single dose of 0.5 mg digoxin on Day 4. Blood samples for determination of digoxin concentrations were collected at pre-dose and at selected timepoints up to 120 hours (Treatment A) and up to 192 hours (Treatment B) following digoxin administration. Urine for digoxin quantitation was collected predose and up to 48 hours (Treatment A and B) following digoxin administration.

Summary of Plasma PK Parameters of Digoxin Following a Single Oral Dose of 0.5 mg Digoxin Administered With and Without Multiple Doses of 40 mg Suvorexant (MK-4305) to Healthy Subjects

Pharmacokinetic Parameter	Digoxin Alone			Digoxin with MK-4305			Digoxin with MK-4305 / Digoxin alone	
	N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI
$AUC_{0\text{-last}}$ (hr•ng/mL)†	19	19.98	(16.60, 24.05)	19	25.27	(21.00, 30.43)	1.27	(1.12, 1.43)
C_{max} (ng/ml)†	19	1.82	(1.56, 2.12)	19	2.20	(1.89, 2.56)	1.21	(1.05, 1.40)
T_{max} (hr)‡	19	1.5	(0.5, 2.0)	19	1.0	(0.5, 4.0)	.	

Summary of Urinary PK Parameters of Digoxin Following a Single Oral Dose of 0.5 mg Digoxin Administered With and Without Multiple Doses of 40 mg Suvorexant (MK-4305) to Healthy Subjects

Pharmacokinetic Parameter	N	Geometric Mean for Treatment † (95% CI)		Geometric Mean (90% CI) for Treatment Ratio
		Digoxin Alone	Digoxin with MK-4305	Digoxin with MK-4305 / Digoxin Alone
Renal Clearance (mL/min)†	19	106.81 (90.82, 125.63)	100.53 (85.48, 118.24)	0.94 (0.82, 1.08)
Fraction Excreted (%)§	19	23.04 (19.83, 26.77)	26.02 (22.39, 30.23)	--

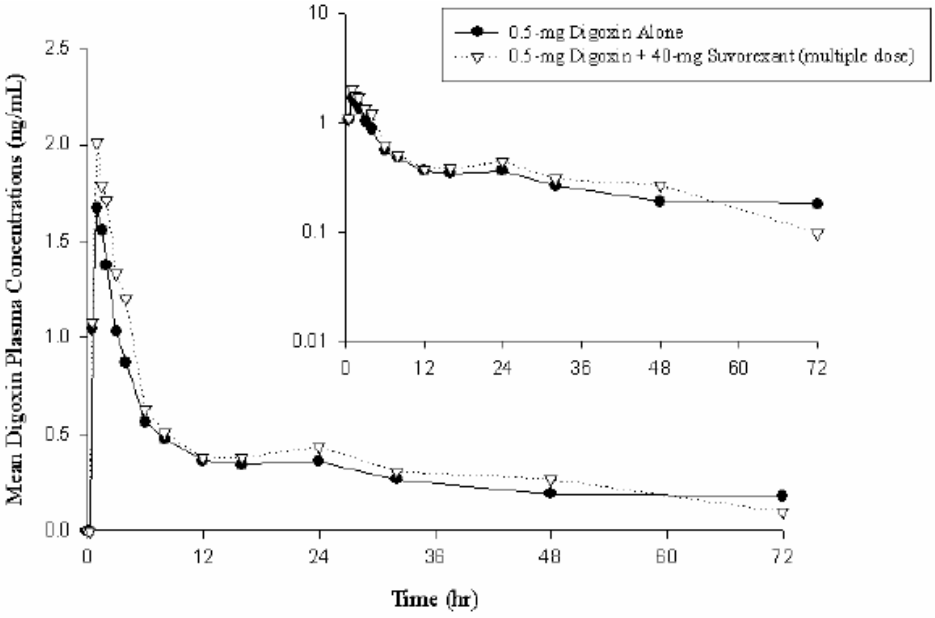
† Back-transformed least-squares mean and confidence interval from mixed effects model performed on natural log-transformed values.

§ Urine collected through 48 hours.

Concomitant administration of a single dose digoxin 0.5 mg with multiple daily doses of suvorexant 40 mg slightly increased $AUC_{0\text{-last}}$ by 27% and C_{max} by 21%. There was no

statistically significant change in digoxin renal clearance when administered with suvorexant. The geometric mean ratio (digoxin with suvorexant/ digoxin alone) for renal clearance with corresponding 90% confidence intervals were 0.94 and (0.82, 1.08). The increase in digoxin concentrations in the presence of suvorexant generally occurred within the first 6-hours, while plasma concentrations in the terminal phase were unchanged.

Mean Plasma Concentration-Time Profile of Digoxin Following a Single Oral Dose of 0.5 mg Digoxin Administered With and Without Multiple Doses of 40 mg Suvorexant (MK-4305) to Healthy Subjects (N=19)



Recommendations: No dose adjustment is needed for digoxin when co-administered with suvorexant, however serum digoxin concentrations should be monitored as clinically indicated.

2.5 GENERAL BIOPHARMACEUTICS

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

According to the Biopharmaceutics Classification System (BCS) definition, a drug substance is considered highly soluble when the highest dose strength is soluble in ≤250 mL of aqueous media over the pH range of 1 to 7.5. Based on this definition, suvorexant is classified as "low solubility", with aqueous solubility (b) (4) for (b) (4) drug substance found in the drug product formulation. Suvorexant shows very minor pH dependent solubility with slightly higher solubility at acidic pH values. However, overall

suvorexant has very low solubility that remains largely unchanged across the physiologically relevant pH range.
Equilibrium solubility data in various aqueous buffer solutions of (b) (4) suvorexant are listed in the table below.

Equilibrium Solubility of Suvorexant (MK-4305) in Aqueous Buffer Solution (72 hours)

(b) (4)

In addition, the ONDQA reviewer (Dr. Suarez) confirmed that suvorexant is considered a low solubility product based on the proposed specification for the dissolution of the FMI tablets release (b) (4) (Q= (b) (4)) of the dose in 30 minutes. For details, please refer to the ONDQA review.

Dissolution Profile of Suvorexant Tablets, 40 mg in USP II, 0.4% SLS at 75 rpm

(b) (4)

The passive permeability of suvorexant across LLC-PK1 cells was high at concentrations from 0.5 µM to 5 µM, with an apparent permeability (P_{app}) ranging from 22.8-34.6 × 10^{-6} cm/s), which is comparable to a high permeability compound, verapamil (P_{app}: 28.2 – 31.7 ×10^{-6} cm/s).

The compound is therefore classified as a BCS class 2 compound (high permeability and low solubility at physiological pH).

2.5.2 Is the proposed to-be-marketed formulation of suvorexant bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

Two key immediate release tablet formulations were used for the suvorexant development program: (1) a (b) (4) Fit for Purpose (**FFP**) formulation (**T1**) (b) (4) used for the initial Phase 1 studies; and (2) the Preliminary Marketing Formulation (**PMF**)/Final Market Image (**FMI**) (**P2**), (b) (4) used for the Phase 2b and Phase 3 studies as well as a majority of Phase I studies.
A comparison of biopharmaceutic performance between two primary candidate formulations (P1: Scale up of (b) (4) Phase 1 formulation; and P2: (b) (4)) relative to the Phase I fit-for-purpose formulation (T1) was performed in Protocol 007, resulting in the selection of P2 as the PMF used in further clinical development.

Summary of PK Results Following Single-Dose AM Administration in the Fasted State of Four Formulations of 60 mg Suvorexant to Healthy Subjects

		Formulation			
		T1 (N=17)	P1 (N=18)	P2 (N=18)	P3 (N=17)
$AUC_{0-\infty}$ (μM•hr)	GM†	16.76	17.26	17.30	17.70
	(95% CI)	(13.26,21.19)	(13.66,21.80)	(13.70,21.85)	(14.00,22.38)
	GMR† vs. T1		1.03	1.03	1.06
	90% CI		(0.95, 1.12)	(0.95,1.12)	(0.97,1.15)
C_{max} (μM)	GM	1.672	1.531	1.199	1.278
	(95% CI)	(1.439,1.943)	(1.321, 1.775)	(1.035,1.390)	(1.100,1.485)
	GMR vs. T1		0.92	0.72	0.76
	90% CI		(0.82,1.03)	(0.64,0.81)	(0.68,0.86)
AUC_{0-4hr} (μM•hr)	GM	4.34	4.07	3.57	3.84
	(95% CI)	(3.78,4.99)	(3.55,4.67)	(3.11,4.09)	(3.34,4.41)
	GMR vs. T1		0.94	0.82	0.88
	90% CI		(0.84,1.05)	(0.74,0.92)	(0.79,0.99)
AUC_{0-24hr} (μM•hr)	GM	11.98	12.42	11.62	12.22
	(95% CI)	(10.36,13.87)	(10.74,14.37)	(10.05,13.44)	(10.56,14.14)
	GMR vs. T1		1.04	0.97	1.02
	90% CI		(0.97,1.11)	(0.91,1.04)	(0.95,1.09)
C_{4hr} (μM)	GM	0.954	1.022	0.900	0.920
	(95% CI)	(0.839,1.084)	(0.902,1.158)	(0.794,1.019)	(0.810,1.045)
	GMR vs. T1		1.07	0.94	0.97
	90% CI		(0.95,1.21)	(0.84,1.07)	(0.85,1.09)
T_{max} (hr)	Median	2.0	2.0	2.0	1.0
	Min, Max	0.5, 4.0	1.0, 4.0	1.0, 4.0	1.0, 4.0
Half-life (hr)	Harmonic Mean	10.5	10.3	12.0	10.2
	(jack-knife SD)	(4.6)	(4.1)	(4.5)	(3.7)

The P2 (FMI) formulation, used in the Phase 3 trials (P028, P029), was slightly modified from the P2 (PMF) formulation used in the Phase IIb study (P006) and Phase 3 Long Term Safety Study (P009). The FMI formulation, which is the intended commercial formulation, is compositionally identical to the PMF, with no change in functional excipients [redacted] (b) (4) nd addition of [redacted] (b) (4) to the [redacted] (b) (4) film coat.
The modifications [redacted] (b) (4) are consistent with minor compositional changes described in the FDA Guidance for Industry – Immediate Release Solid Oral Dosage Forms Scale-Up and Post Approval Changes (SUPAC), and are not expected to have an impact on the in vivo performance of the FMI tablets relative to the PMF. Based on the similarities between PMF and FMI and use of both formulations in the Phase 3 studies of suvorexant, a bioequivalence study is not necessary.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of suvorexant in relation to meals or meal types?

The food effect on the pharmacokinetics of a single 40-mg dose of the FMI formulation, used in the pivotal Phase 3 studies, was evaluated with a high fat meal in Protocol 020 and with a standard Japanese breakfast, which has a lower fat and caloric content than the high fat meal, in Protocol 042.
Suvorexant $AUC_{0-\infty}$ and C_{max} were largely unchanged after administration with a high-fat meal compared to fasted conditions in the food effect study (P020) with the FMI. A small median increase of 1.5 hours in T_{max} was observed following suvorexant administration with a high-fat breakfast.

Summary of Pharmacokinetic Parameters of Suvorexant (MK-4305) Following Administration of a Single Oral Dose of 40 mg Suvorexant Following a High-Fat Breakfast or in the Fasted State

Pharmacokinetic Parameter	MK-4305 Fasted			MK-4305 Fed			(MK-4305 Fed/ MK-4305 Fasted)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (μM•hr) [†,††]	12	13.19	(10.60, 16.41)	12	12.99	(10.44, 16.16)	0.98	(0.91, 1.07)
C_{max} (μM) [†]	13	0.983	(0.790, 1.224)	13	1.074	(0.862, 1.337)	1.09	(0.90, 1.33)
T_{max} (hr) [§]	13	2.0	1.0, 4.0	13	3.0	1.0, 6.0	1.5 [#]	(1.0, 3.0) [#]
Apparent terminal $t_{1/2}$ (hr) [‖,††]	12	10.9	3.4	12	11.6	3.6	--	--

Similarly, there was no meaningful change in $AUC_{0-\infty}$ and C_{max} after administration of suvorexant FMI with a standard Japanese breakfast compared to fasted conditions; a median increase in T_{max} of 1.0 hours was observed.

Summary of Suvorexant (MK-4305) Plasma PK Parameters and Ratios (Fed/Fasted) Following Administration of a 40 mg Single Oral Dose of Suvorexant to Japanese Healthy Subjects in the Fasted State and Following a Standard Japanese Breakfast

PK Parameter	Gender	MK-4305 Fasted			MK-4305 Fed			Ratio (MK-4305 Fed /MK-4305 Fasted)	
		N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI
$AUC_{0-\infty}$ ($\mu M \cdot hr$)†	Male	6	12.10	(9.67, 15.13)	6	12.59	(9.83, 16.14)	1.04	(0.93, 1.17)
	Female	6	12.21	(11.06, 13.49)	6	14.20	(11.29, 17.86)	1.16	(1.03, 1.32)
C_{max} (μM)†	Male	6	1.06	(0.852, 1.324)	6	1.25	(0.926, 1.678)	1.17	(0.92, 1.50)
	Female	6	0.96	(0.703, 1.299)	6	1.24	(0.957, 1.610)	1.30	(0.92, 1.83)
T_{max} (hr)‡	Male	6	1.0	[1.0, 3.0]	6	2.5	[2.0, 6.0]	1.0#	(0.0, 3.0)#
	Female	6	2.0	[1.0, 3.0]	6	3.0	[1.0, 4.0]	1.0#	(0.0, 2.0)#

Estimate and 90% confidence interval for median difference (Fed - Fasted)

The proposed dosing recommendation that suvorexant be administered without regard to meals is consistent with the dosing instructions for Phase 2 and pivotal Phase 3 studies. For faster onset of sleep suvorexant should not be administered with or immediately after a meal.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

Plasma concentrations of suvorexant and the major human circulating metabolite M9 were determined using validated liquid chromatography-tandem mass spectrometric detection (LC-MS/MS) methods (method DM-909 for suvorexant and DM-928 for M9). HPLC-MS/MS method DM-909 was developed and validated by Merck Research Laboratories for the determination of suvorexant in human plasma. This method was later transferred and validated at two CROs (b) (4)
All plasma samples for the suvorexant or M9 assay were collected (b) (4)

The methods were linear in the range of 1.0 – 1000 ng/mL for both analytes. Bioanalytical stability studies were of sufficient scope and duration to assure the concentration values determined for pharmacokinetic samples collected during the development program are valid for all conditions experienced. A bioanalytical report was also generated for each clinical study.

The validation results from suvorexant and M9 bioanalytical assays are are considered acceptable and the results are presented in the table below.

Method DM-909: Suvorexant (MK-4305) Plasma Assay

	DM-909	
	n	Mean (%)
Intra-day Accuracy with Calibration Standards	6	95.6 – 105.0
Intra-day Precision (CV) with Calibration Standards	6	4.1 – 10.0
Intra-day Accuracy with Quality Control Samples	5	96.7 – 109.5
Intra-day Precision (CV) with Quality Control Samples	5	4.2 - 6.7
Inter-day Accuracy with Calibration Standards †	27	98.40 – 101.23
Inter-day Precision (CV) with Calibration Standards †	27	1.98 – 4.46
Inter-day Accuracy with Quality Control Samples †	54	97.61 – 103.82
Inter-day Precision (CV) with Quality Control Samples †	54	4.42 – 7.29
Extraction Recovery of Analyte	6	50.5 – 57.2
Extraction Recovery of ISTD	18	46.4
Absolute Matrix Effect	6	92.1 – 103.6
Absolute Matrix Effect of ISTD	18	100.6
Accuracy of Dilution Integrity (20X), 10,000 ng/mL	5	98.9
Precision (CV) of Dilution Integrity, 10,000 ng/mL	5	5.4
Difference of Reinjection Integrity Samples from Controls after 3 Days at Room Temperature	10	-2.0 – 1.4
Precision (CV) of Reinjection Integrity Samples after 3 Days at Room Temperature	10	3.1 – 11.2
Difference of Quality Control Samples from Control QCs after 3 Freeze/Thaw Cycles at -20°C	5	0.9 – 3.6
Precision (CV) of Quality Control Samples QCs after 3 Freeze/Thaw Cycles at -20°C	5	1.7 – 4.1
Difference of QCs from Controls after 6 hours at Room Temperature	3	0.4 – 3.6
Precision (CV) of QCs Assayed after 6 hours at Room Temperature	3	0.8 – 1.6
Accuracy of Long-Term Storage Stability (25 months) ‡: -20°C	5	97.6 – 106.7
Incurred Sample Re-analysis (% within specification) §	74	100%
Data from Assay Validation Report #DM-909 † Representative data from Study P003 (~1368 samples in 27 runs) ‡ Data from Merck Long Term Stability Memo § Data from Study P010		

Method DM-928: M9 Plasma Assay

	DM-928	
	n	Mean (%)
Intra-day Accuracy with Calibration Standards	6	96.0 – 103.8
Intra-day Precision (CV) with Calibration Standards	6	3.6 – 10.0
Intra-day Accuracy with Quality Control Samples	5	96.0 – 103.1
Intra-day Precision (CV) with Quality Control Samples	5	3.9 – 4.6
Inter-day Accuracy with Calibration Standards †	21-24	98.00– 103.31
Inter-day Precision (CV) with Calibration Standards †	21-24	3.00 – 5.47
Inter-day Accuracy with Quality Control Samples †	48	100.33 – 103.79
Inter-day Precision (CV) with Quality Control Samples †	48	7.15 – 9.3
Extraction Recovery of Analyte	6	76.2 – 80.4
Extraction Recovery of ISTD	18	65.9
Absolute Matrix Effect of Analyte	6	99.5 – 101.9
Absolute Matrix Effect of ISTD	18	98.7
Accuracy of Dilution Integrity (20X), 10,000 ng/mL	5	99.5
Precision (CV) of Dilution Integrity (20X), 10,000 ng/mL	5	3.8
Difference of Reinjection Integrity Samples from Controls after 2 Days at Room Temperature	10	1.1 – 11.1
Precision (CV) of Reinjection Integrity Samples after 2 Days at Room Temperature	10	3.7 – 8.4
Difference of Quality Control Samples from Control QCs after 3 Freeze/Thaw Cycles at -20°C	3	-9.2 – 8.8
Precision (CV) of Quality Control Samples QCs after 3 Freeze/Thaw Cycles at -20°C	3	4.1 – 5.8
Difference of QCs from Controls after 6 hours at Room Temperature	3	-4.8 – 6.5
Precision (CV) of QCs Assayed after 6 hours at Room Temperature	3	2.8 – 6.1
Accuracy of Long-Term Storage Stability (29 months)‡: -20°C	5	96.7 – 109.2
Incurred Sample Re-analysis (% within specification) §	10	100
Data from Assay Validation Report #DM-928 † Representative data from Study P003 (~1368 samples in 24 runs) ‡ Data from Merck Long Term Stability Memo § Data from Study P017		

Several drug-drug interaction studies were conducted with medications that were coadministered with suvorexant. Information regarding the analytical methods used to support the analysis of co-administered compounds can be found in the individual study reviews (P013, P015, P016, P024, P026).

3.0 DETAILED LABELING RECOMMENDATION

The clinical pharmacology labeling changes will be made after agreement for the dosing regimen is reached at the Advisory Commetee Meeting.

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA Number	204569
Brand Name	Suvorexant
Drug Components	Suvorexant (MK-4305)
Pharmacometrics Reviewer	Joo-Yeon Lee, Ph.D. (Exposure-Response Analyses) Satjit Brar, Pharm.D., Ph.D. (Population PK Analyses)
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
Sponsor	Merck & Co, Inc.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there any significant dose/exposure-response relationship? And does the relationship support the proposed dose?

No, there is no clear dose/exposure-response relationship for sleep onset (Latency to onset of persistent sleep: LPS) and sleep maintenance (Wakefulness after persistent sleep onset: WASO). However, the incidence of somnolence appears to be increasing with higher concentrations of suvorexant.

Sponsor conducted two Phase III studies (P028 and P029) and one Phase II dose-ranging study. The Phase III studies (P028/P029) were double-blind, placebo-controlled, parallel group trials in patients with primary insomnia. Patients aged 18 to <65 years (non-elderly) randomized to suvorexant, received 20 mg (low dose) and 40 mg (high dose) QD. Patients aged ≥65 years (elderly) randomized to suvorexant, received 15 mg (low dose) or 30 mg (high dose) QD. In the primary efficacy analyses on WASO and LPS, both dose groups showed statistically significant effectiveness compared to placebo in both elderly and non-elderly patients (p-vlaue < 0.00001) on days 1, 28 and 90.

The Phase II dose-ranging study (P006) was a double-blind, two-period crossover, polysomnograhic study in patients with primary insomnia. The design consisted of four 2-period crossover periods, wherein each patient received placebo or one of four suvorexant dose levels corresponding to 10, 20, 40, or 80 mg QD.

The sponsor conducted dose-response analyses on pooled data from the 1st period of the study 006 and data from the studies 028 and 029. The sponsor's dose-response analysis showed:

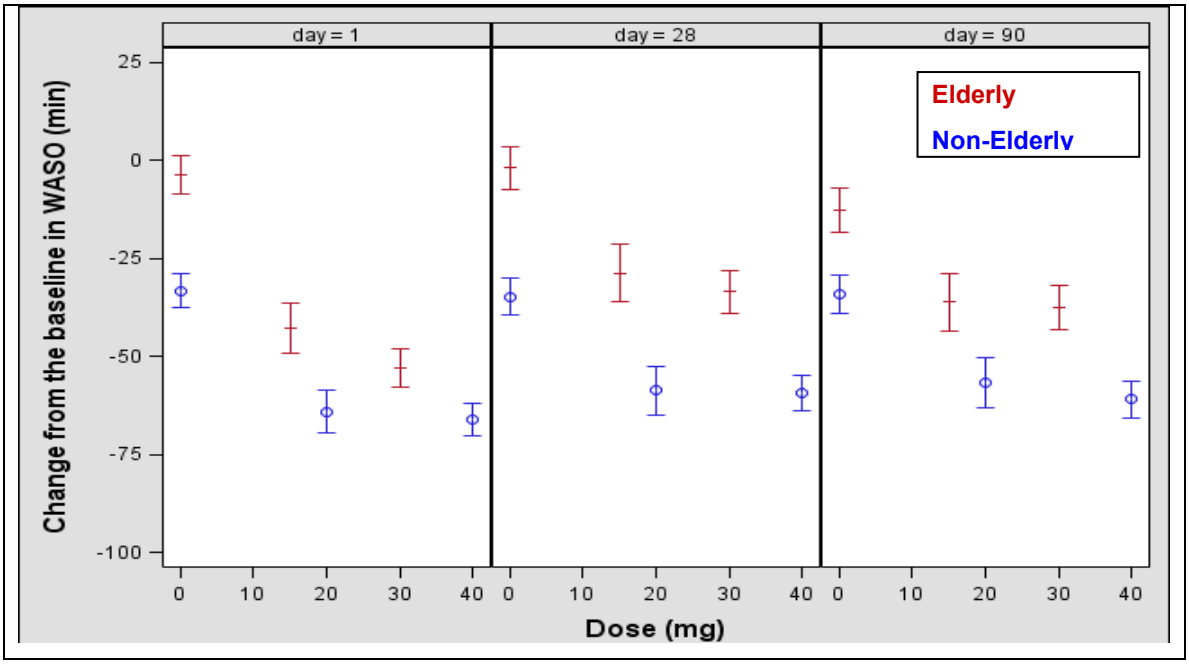
(A) Flat dose-response relationship for LPS over the dose range of 10 mg to 80 mg
(B) Dose dependent changes for WASO in both elderly and non-elderly patients.

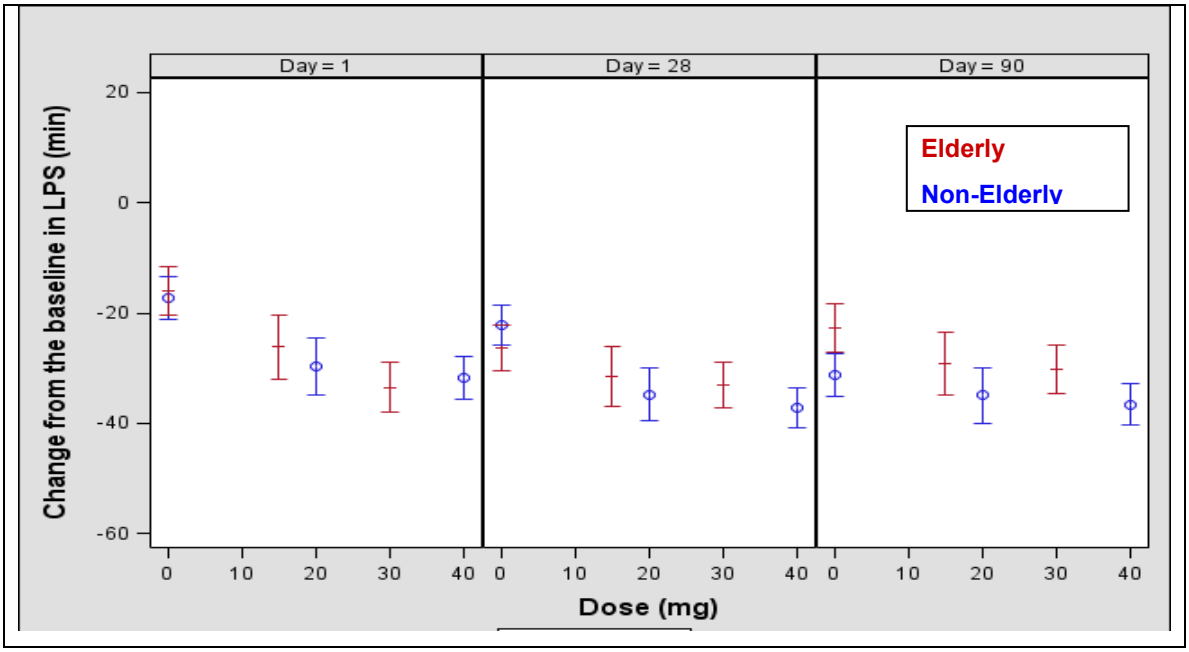
For reviewer comments on sponsor's dose-response analysis, please refer to reviewer's comments on Section 3.

The reviewer conducted independent analyses to assess whether the sponsor's proposed dosing regimen is reasonable or not. The data from only Phase III studies (P028 and P029) were pooled for the reviewer's assessment as there are differences between the Phase II study and Phase III studies in many aspects such as the study duration (1 month vs. 3 month) and population enrolled (non-elderly patients only vs. both elderly and non-elderly patients). The change from the baseline in two objective measures (ΔWASO, ΔLPS) were the endpoints used to assess the efficacy of suvorexant.

Figure 1 represents the dose-response relationship for sleep maintenance (ΔWASO) and onset (ΔLPS). It shows little difference in effectiveness between two dose groups for both elderly and non-elderly patients.

Figure 1: LS mean with 95% CI for Δ WASO (top) and Δ LPS (bottom) vs. Dose by day. LS means were adjusted by baseline value, age group, region and gender

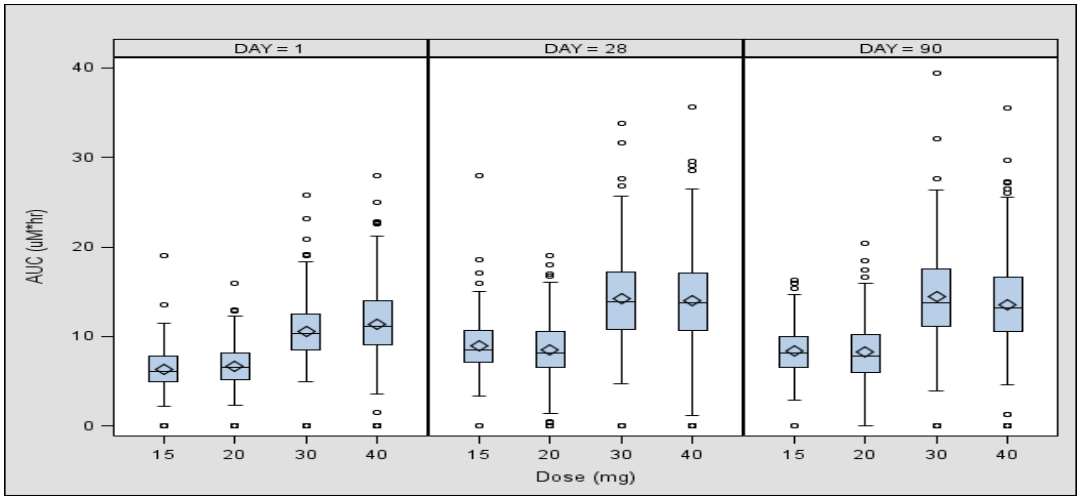




As a next step, the reviewer further looked into the same endpoints related to AUC_{0-24} which was predicted from the sponsor's model. AUC_{0-24} was categorized by 6 bins with same number of patients at each bin. All placebo patients were grouped in the first bin.

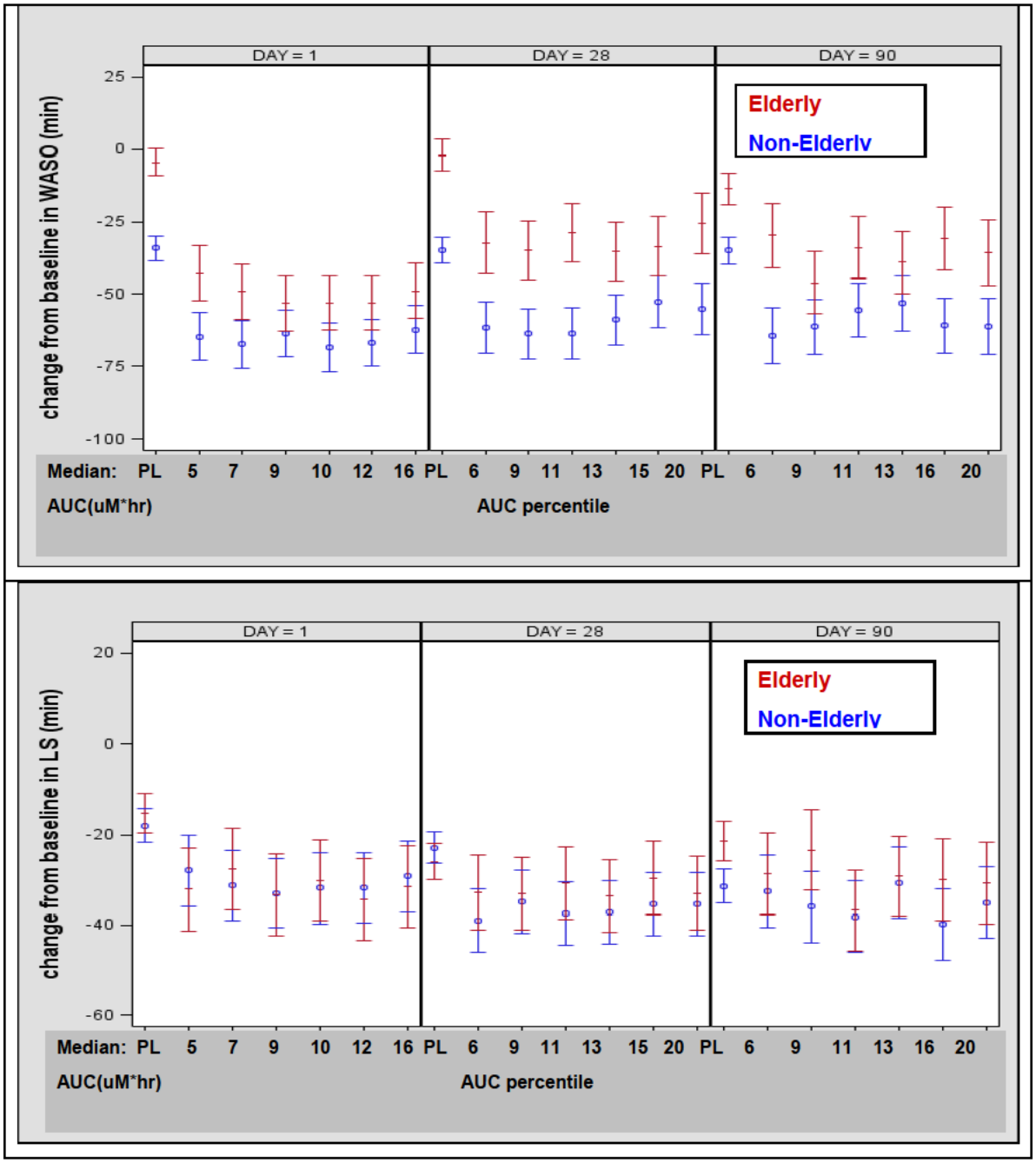
Figure 2 shows the distribution of the predicted AUC_{0-24}. The median AUC_{0-24} at Day 1 are 6 µM*hr, 7 µM*hr, 10 µM*hr, 11 µM*hr at 15mg, 20mg, 30mg and 40mg, respectively. As suvorexant PK reaches steady-state around day 3, AUC_{0-24} at Day 28 and Day 90 appears to be similar: 8 µM*hr, 8 µM*hr, 14 µM*hr, 14 µM*hr at 15mg, 20mg, 30mg and 40mg, respectively. Please note that the distributions of AUC_{0-24} for elderly and non-elderly patients are comparable.

Figure 2: Distribution of predicted AUC (µM*hr) at each dose by day



As shown in Figure 3, there appears to be no apparent exposure-dependent improvement in both sleep maintenance and onset measurements over the dose range of 15 mg to 40 mg.

Figure 3: LS mean with 95% CI for Δ WASO (top) and Δ LPS (bottom) vs. exposure (AUC_{0-24}) by day by elderly and non-elderly patients. LS means were adjusted by baseline value, age group, region and gender to be consistent with dose-response analysis.



For the safety analysis, the reviewer analyzed the relationship between C_{9hr} (Surovexant concentrations at 9h post-dose) and incidence of somnolence and digital symbol substitution test (DSST) score. As shown in Figure 4 the probability of somnolence increases with higher suvorexant concentrations go up. In addition, non-elderly patients showed higher risk of somnolence at the same concentration compared to elderly patients.

Figure 5 presents dose / concentration and Δ DSST relationship. In elderly patients dose dependent (30 mg vs. 15 mg relative to placebo) decrease in DSST was observed.

Table 1, shows the proportion of patients who got impaired after suvorexant administration (Δ DSST <0). However, the magnitude of difference does not seem to be noticeable, and DSST score does not show clear concentration-dependent relationship either.

Figure 4: Left: Overall model-predicted relationship for probability of somnolence and suvorexant concentration (C_{9hr}). Right: model-predicted relationship for probability of somnolence and suvorexant concentration (C_{9hr}) by elderly and non-elderly patients

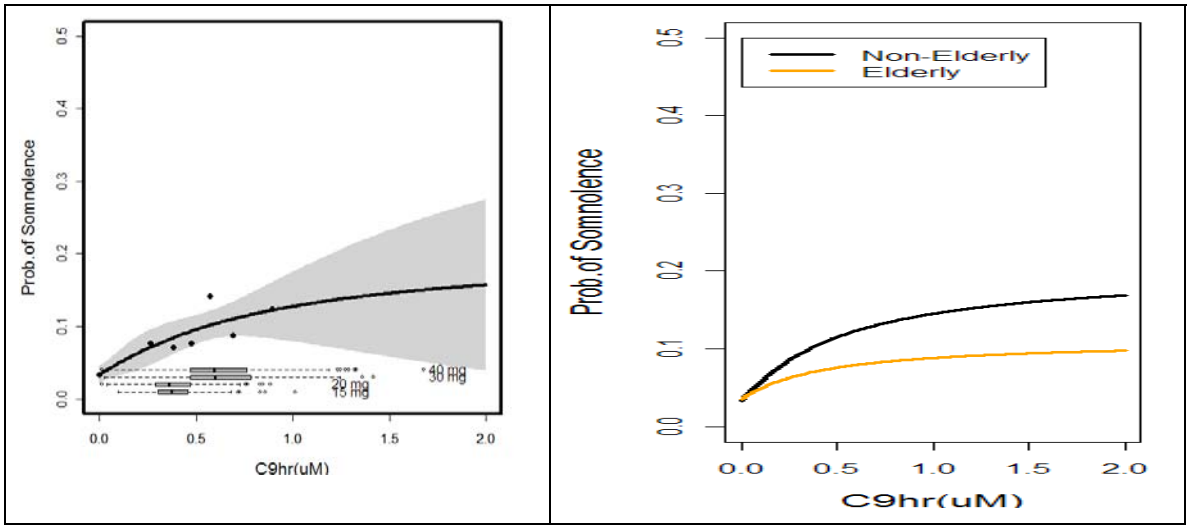


Figure 5: Dose vs. ΔDSST (top) and C_{9hr} vs. ΔDSST (bottom) relationship by elderly and non-elderly patients

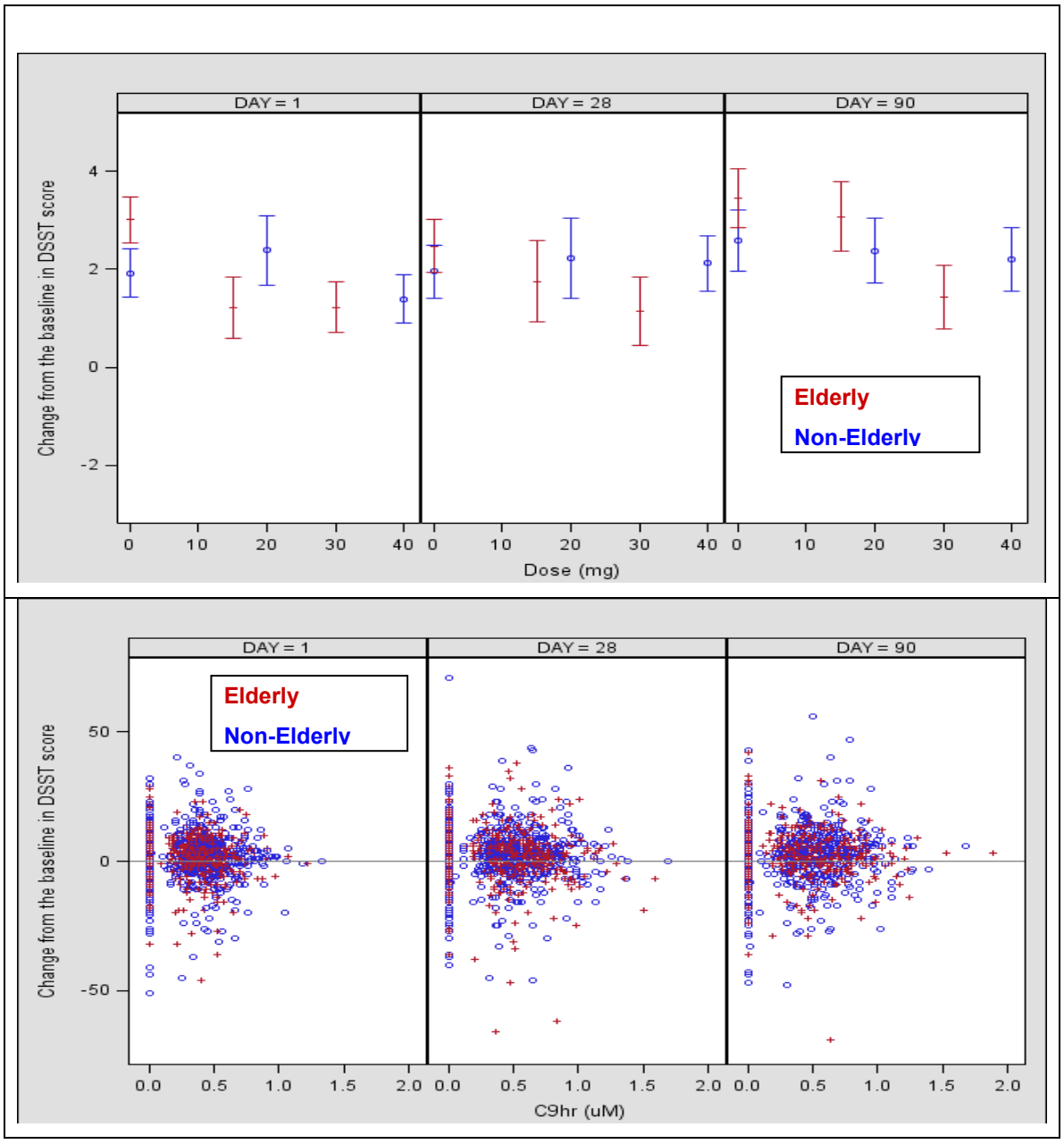


Table 1: Percent of patients who got impaired in DSST score compared to their score at baseline (ΔDSST < 0)

	Elderly			Non-Elderly		
	PL	15mg	30mg	PL	20mg	40mg
Day 1	24%	32%	32%	28%	33%	34%
Day 28	32%	32%	39%	33%	35%	36%
Day 90	28%	26%	35%	31%	30%	34%

In conclusion:

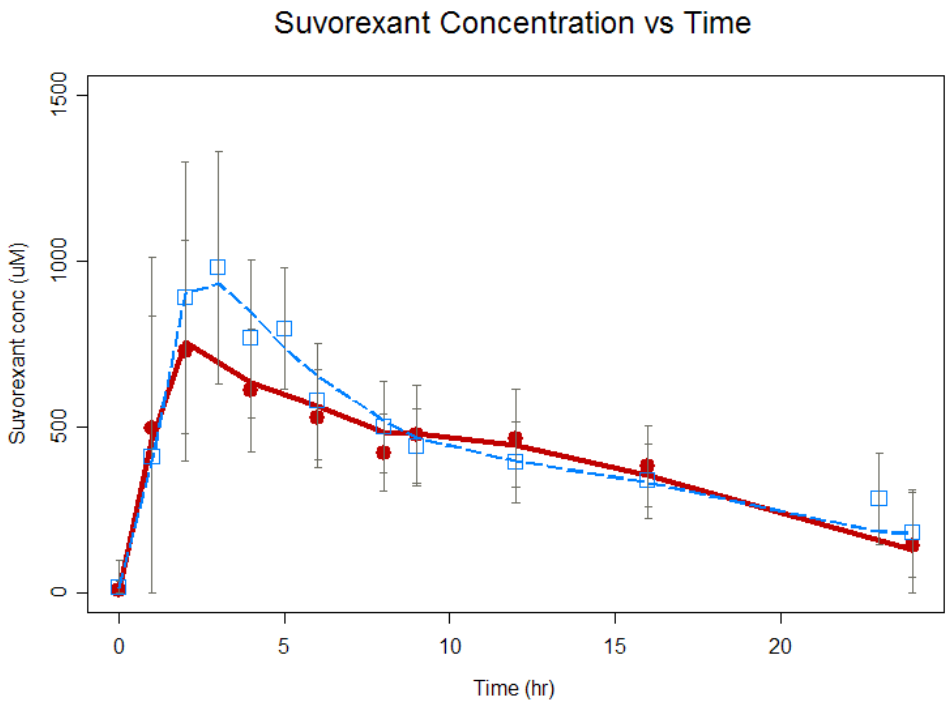
- The high dose relative to low dose, for both elderly and non-elderly patients, do not provide additional benefit based on the objective sleep maintenance (WASO) and onset (LPS) measures.
- The risk of somnolence increases with suvorexant concentrations.
- Non-elderly patients showed higher probability of somnolence than elderly patients.
- There is no significant difference in exposure between elderly and non-elderly patients.
- The dose of 10 mg also showed similar efficacy to 20 mg in sleep maintenance. There is no dose/exposure-dependent relationship for sleep onset in the study 06 but the data is too limited to make definitive conclusion (see section 4. Reviewer's analysis)
- Based on the reviewer's analyses, the dose of 15 mg would be reasonable starting dose for both elderly and non-elderly patients, although 15 mg was not studied in non-elderly patients (it is expected that 5 mg lower dose in non-elderly patients will not make much difference in suvorexant exposure based on population PK results and distribution of exposure at 10mg and 20mg from the study 006 (top panel of **Figure 23**).

1.1.2 Is there a need for surovexant dose adjustment based on intrinsic /extrinsic factors such as gender, age, body weight?

Age was the major factor that required the adjustment of dose. This was accounted for in the conduct of the Phase 3 studies where elderly individuals (≥65 years) were administered a 30 mg maximum dose while non-elderly were given 40 mg. The rationale

for this dosing adjustment is based on early phase 1 data, in which elderly subjects appeared to have modestly higher exposures compared to non-elderly subjects. Moreover, it is suspected that elderly individuals are more sensitive to the effects of suvorexant. Figure 6 depicts the concentration vs. time profile of suvorexant after the administration of 30 mg to elderly patients and 40 mg to non-elderly patients. A similar exposure to plasma suvorexant is obtained with non-elderly individuals having higher C_{max}.

Figure 6: Suvorexant plasma concentration vs. time for elderly (solid circles) and non-elderly (squares). The symbols represent the mean (+/- 95%CI) observations at the corresponding time.



Although there were other intrinsic and extrinsic factors that affected the PK of suvorexant, the magnitude of the difference does not warrant a dose adjustment. After dose adjustment for age, there was no significant influence race or renal function on suvorexant PK found.

1.2 Recommendations

The Division of Pharmacometrics has reviewed the submission (NDA 204569), and there is one recommendation on the dosing regimen as follows;

Given the efficacy and safety profiles of suvorexant, the dose of 15 mg would be reasonable starting dose for both elderly and non-elderly patients.

1.3 Label Statements

2 DOSAGE AND ADMINISTRATION

2.1 General

(b) (4)

(b) (4)

2.2

(b) (4)

(b) (4)

2.3

(b) (4)

(b) (4)

12.3 Pharmacokinetics [78]

Suvorexant exposure increases in a less than ~~strictly~~ dose-proportional manner over the range of 10-80 mg due to decreased absorption. Suvorexant pharmacokinetics are similar in healthy subjects and patients with insomnia.

Absorption

Suvorexant peak concentrations occur at a median tmax of 2.0 hours (range (b) (4) to 6.0) under fasted conditions. The mean absolute bioavailability of (b) (4)

Ingestion of suvorexant with a high-fat meal resulted in no meaningful change in AUC or Cmax (b) (4) a delay in tmax (b) (4) approximately 1.5 hours. Suvorexant may be taken with or without food.

Distribution

The mean volume of distribution of suvorexant is approximately 49 liters. Suvorexant is extensively bound (>99%) to human plasma proteins and does not preferentially distribute into red blood cells. Suvorexant binds to both human serum albumin and α 1-acid glycoprotein.

Metabolism

Suvorexant is mainly eliminated by metabolism, primarily by CYP3A with a minor contribution from CYP2C19. The major circulating entities are suvorexant and a

hydroxysuvorexant metabolite. This metabolite is not expected to be pharmacologically active.

Elimination

The primary route of elimination is through the feces, with approximately 66% of radiolabeled dose recovered in the feces compared to 23% in the urine. (b) (4)

The systemic pharmacokinetics of suvorexant are linear with accumulation (b) (4) Steady-state is achieved by 3 days (b) (4) mean t1/2 of approximately 12 hours (95% CI: 12.0 to 13.1).

Special Populations

The effects of renal and hepatic impairment on the pharmacokinetics of suvorexant were evaluated in specific pharmacokinetic studies (b) (4)

Gender, BMI, and race were included as factors assessed in the population pharmacokinetic model to evaluate suvorexant pharmacokinetics in healthy subjects and predict exposures in the patient population. (b) (4)

2 PERTINENT REGULATORY BACKGROUND

The sponsor is seeking the approval for suvorexant for the treatment of patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. Suvorexant is a highly selective antagonist for orexin receptors OX1R and OX2R. By blocking the binding of the wake-promoting neurotransmitters orexin A and orexin B to orexin receptors OX1R and OX2R, suvorexant inhibits activation of wakefulness promoting neurons of the arousal system, and thereby facilitates the physiological process by which the brain transitions from wake to sleep, enabling sleep to occur. The sponsor proposed dosing regimen as 40 mg QD for non-elderly adults and 30 mg QD for elderly adults before bedtime.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK analyses

The sponsor has submitted two (2) population pharmacokinetic analysis reports:

- "Population Pharmacokinetic Evaluation of Suvorexant Using Data From Phase 1 Studies" (Report 613) – This report summarizes the development of a population PK model of suvorexant.

- "Suvorexant (MK-4305) Absolute Bioavailability Estimate" (Report 611) – This report summarizes the use of a population PK model-based approach to estimate the absolute bioavailability of suvorexant 10, 20, 40, and 80 mg oral doses with the IV and PO dose proportionality data.

3.1.1 Population Pharmacokinetic Evaluation of Suvorexant Using Data From Phase 1 Studies (Report 613)

The objective of this analysis was to develop a population PK model of suvorexant using full-profile data from doses ranging from 10 mg to 80 mg in 16 Phase 1 studies. Moreover, a covariate analysis was performed to quantify the effect of select subject demographic factors, clinical laboratory tests, timing of dosing, and other relevant clinical factors on the variability in PK parameters. Data for population PK model development were obtained from 16 densely sampled Phase 1 studies sponsored by Merck & Co. Inc. In addition, data from 4 sparsely sampled Phase 1 studies were explored graphically.

A 3-compartment mammillary model with sigmoidal absorption (with lag time), linear distribution into the first peripheral compartment (Vp1/F) and saturable distribution into the Vp2/F, and first-order elimination was found to be the most appropriate model to fit these PK data. A schematic representation of the model structure is provided in Figure 7. An exponential model was used to describe the IIV in first-order absorption rate constant (ka), F1, CL/F, and Vc/F. A log error model (additive error model using logarithmically transformed concentrations) was used to describe the residual error. The parameter estimates for the final PK model, including associated precision estimates (%SEM), are provided in Table 2. The corresponding goodness-of-fit plots, stratified by dose amount (including single versus multiple dose), were presented by the sponsor. Representative diagnostic plots are shown in Figure 8 and Figure 9.

Figure 7. Schematic representation of the suvorexant popPK model structure

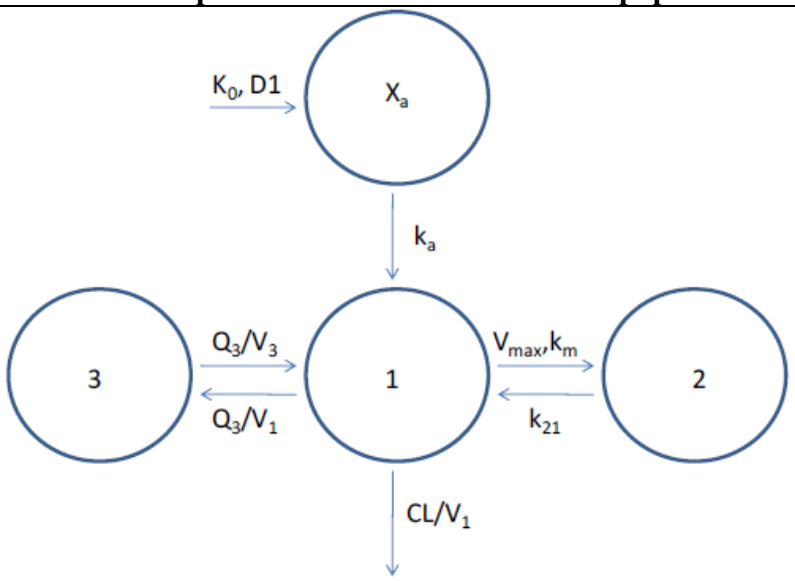


Table 2. Parameter estimates for the Full popPK model

Parameter Estimates and Standard Errors From the Final Pharmacokinetic Model

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
k_a (h^{-1})	1.97	11.4	156.84	14.5
D1 (h)	0.556	9.0	NE	NA
ALAG1 (h)	0.186	6.0	NE	NA
F1[a] (20 mg)	1.03	3.5	22.72	12.3
F1[a] (30 mg)	0.984	5.9		
F1[a] (40 mg)	0.857(AM), 0.699(PM)	3.5		
F1[a] (60/80 mg)	0.638	4.0		
CL/F (L/h)	4.81	4.7	21.77	12.6
V_c/F (L)	58.3	4.3	14.25	41.3
V_{p1}/F (L)	47.6	4.6	NE	NA
k_{21} (h^{-1})	0.0155	FIXED	NE	NA
V_{max} (μM/h)	0.197	FIXED	NE	NA
k_m (μM)	0.0732	FIXED	NE	NA
Q_{p1}/F (L/h)	9.77	6.3	NE	NA
Proportional Shift in k_a for AM Dosing	1.29	30.4	NA	NA
Proportional Shift in F1 for AM Dosing	0.226	20.7	NA	NA
Power Term for the Effect of BMI on CL/F	-1.23	7.7	NA	NA
Proportional Shift in CL/F for Females	-0.205	11.4	NA	NA
Ratio of Additive/Proportional RV Components[b] (σ_2/σ_1)	9.06	13.7	NA	NA
Proportional RV Component (σ_1)	0.064	5.2	NA	NA
Minimum value of the objective function = 52876.936				

Figure 8. Goodness-of-fit plots for final popPK model, by dose (40 mg multiple dose presented only)

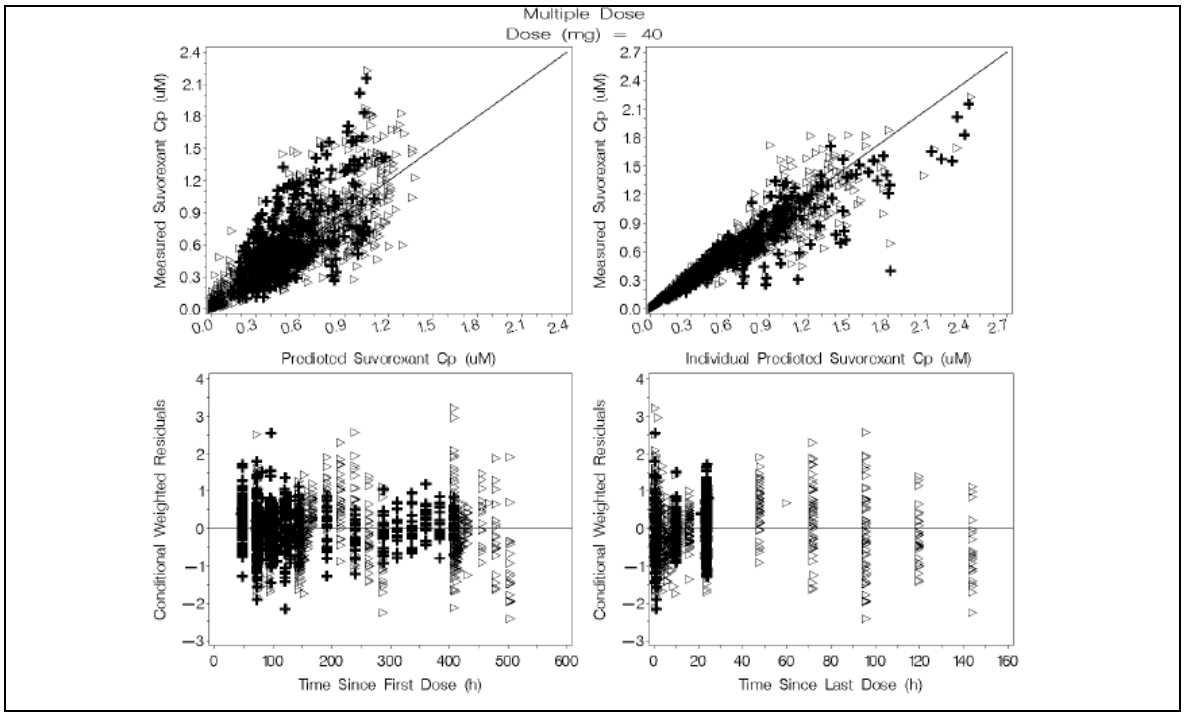
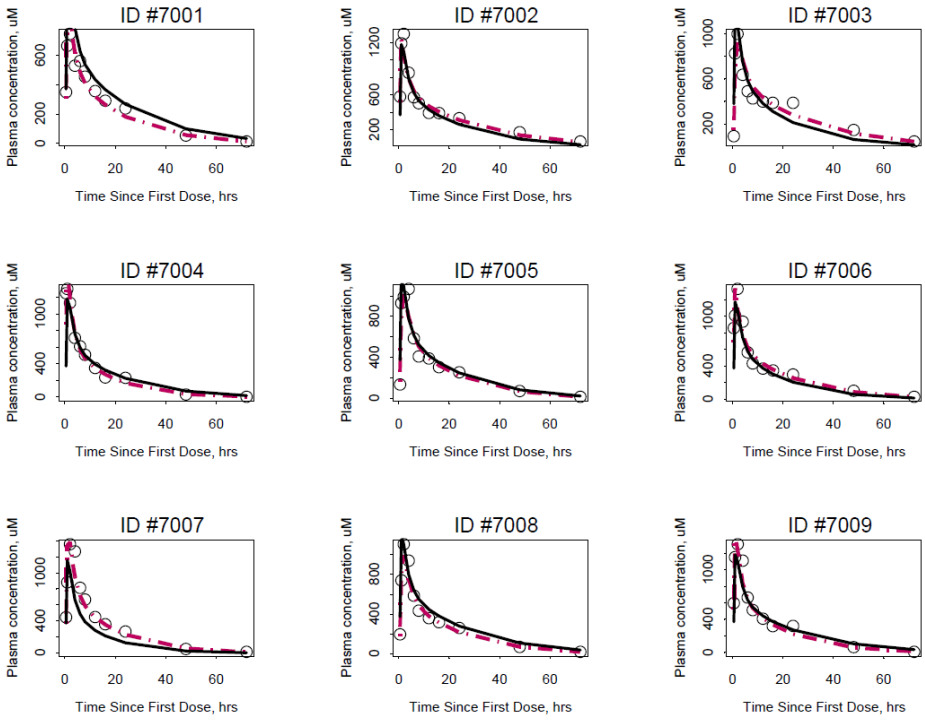


Figure 9. Goodness-of-fit plots – Representative Individual Suvorexant PK profiles. Circles represent observed data, dashed line represents individual prediction and solid line represents population prediction.



Four covariates were added to the model during the covariate analysis process. Gender and BMI were both found to be statistically significant predictors of CL/F. The effect of AM/PM dose time was found to be statistically significant on F1 and ka. The impact of time of dosing on F1 was confounded by dose because all dose levels, with the exception of 40 mg, were exclusively administered AM or PM. Relative bioavailability was predicted to be 22.6% higher following AM dosing compared to PM dosing. Therefore, the estimates of F1 values reflect a mix of dose-dependent differences in the extent of absorption combined with the influence of AM/PM dose time. The estimated F1 was 102.9% for 20 mg (AM), 98.4% for 30 mg (PM), 85.7% for 40 mg (AM), 69.9% for 40 mg (PM), and 63.8% for 60/80 mg (AM) doses, respectively (with F1 fixed to 100% for the 10-mg [AM] dose reference group). Age, race, and renal function were not found to be significant predictors of IIV in suvorexant pharmacokinetics. The equations to predict the typical values for F1, ka, and CL/F are provided in Equation 1, Equation 2, and Equation 3, respectively.

$$F1_i = F1_{Dose} \times (1 + flag_{AMi} \times 0.226) \quad (1)$$

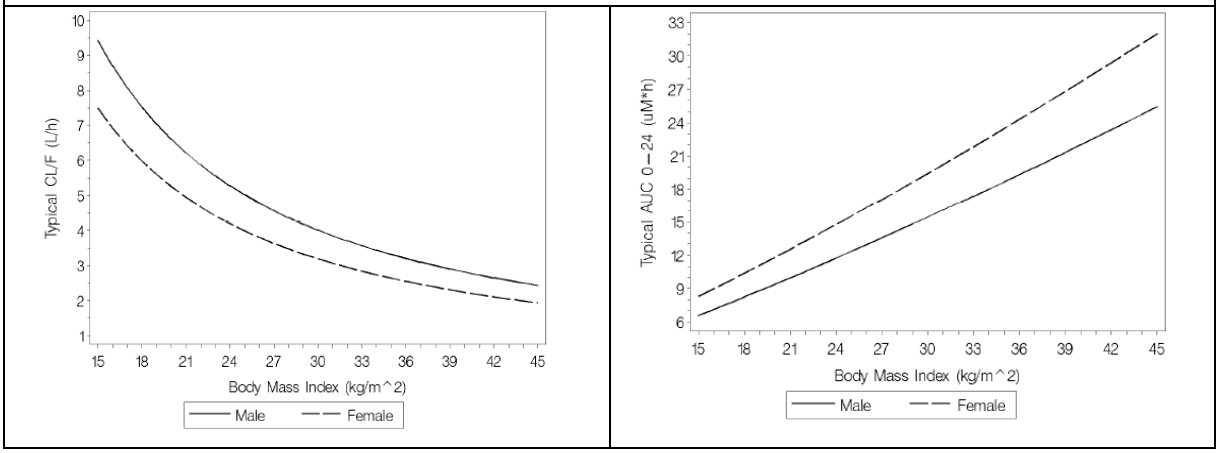
$$ka_i = 1.97 \times (1 + flag_{AMi} \times 1.29) \quad (2)$$

$$CL/Fi = 4.81 \times (BMI_i/25.9)^{-1.23} \times (1 - flag_{Femalei} \times 0.205) \quad (3)$$

Where:
$F1_i$ = relative bioavailability in the ith subject
$F1_{Dose}$ = typical relative bioavailability for a specific dose
$flag_{AMi}$ = flag variable for dose taken in the AM in the ith subject (0 for no; 1 for yes)
ka_i = first-order absorption rate constant in the ith subject
CL / F_i = apparent clearance (L/h) in the ith subject
BMI_i = body mass index (kg/m2) in the ith subject
$flag_{Femalei}$ = flag variable for gender of the ith subject (0 for male; 1 for female)

The suvorexant CL/F for a male subject with a median BMI of 25.9 kg/m^2 is estimated at 4.81 L/h. A 20.5% reduction in CL/F is predicted in female subjects, resulting in a suvorexant CL/F of 3.82 L/h for a typical female with the same median BMI of 25.9 kg/m^2. Suvorexant CL/F is negatively related to BMI, with the decrease in CL/F described by a power function as BMI increases. To illustrate the impact of these 2 significant covariates on the population mean CL/F and resultant drug exposure, the typical CL/F and steady-state AUC0-24 (for a 40-mg dose), graphically displayed as a function of BMI and gender, are provided in Figure 10. As these plots, along with Equation 3 indicate, the population mean CL/F will decrease from 8.07 L/h to 3.32 L/h for a typical male and will decrease from 6.42 L/h to 2.64 L/h for a typical female with BMI values ranging from 17 kg/m2 to 35 kg/m2.

Figure 10. Plots of Population Mean for CL/F (left plot) and AUC0-24 (right plot) for a 40 mg dose as a function of BMI and Gender



The statistically significant covariates included in the final PK model (BMI, gender, and AM dosing), as well as other plausible covariate predictors were assessed to determine if they exhibited a clinically relevant impact on suvorexant exposures (b) (4) a forest plot was constructed to communicate the relative differences in suvorexant exposure (geometric mean ratio of AUC0-24 and Cmax) as a consequence of intrinsic demographic features (age, BMI, and gender and race). The corresponding values for the geometric mean ratios (including 90% CI) for this series of covariates are provided in Figure 11.

The sponsor concludes the following:

- The PK of suvorexant are described by a 3-compartment mammillary model with sigmoidal absorption (with a lag time), dose dependent F1, saturable distribution into the deep-tissue compartment, and linear elimination.
- The F1 decreases with increasing dose, and is impacted by AM versus PM dosing. For a typical subject, F1 following PM dosing is predicted to be 83.9%, 80.3%, 69.9%, and 52.0% for 20-, 30-, 40-, and 60/80-mg doses in relation to a 100% bioavailability for a reference 10-mg suvorexant oral dose. The corresponding typical F1 following AM dosing is predicted to be 102.9%, 98.4%, 85.7%, and 63.8% for 20, 30-, 40-, and 60/80-mg doses.
- Apparent oral clearance for a typical subject is 4.81 L/h, with 21.77 %CV unexplained IIV. There was no detectable evidence of time-dependent changes in CL/F in these data, indicating a minimal likelihood of considerable auto-inhibition of clearance impacting suvorexant elimination.
- Suvorexant distributes in the body beyond the systemic circulation, as evidenced by an estimated Vc/F of 58.3 L (with 14.25 %CV IIV) and Vp1/F of 47.6 L.
- The absorption for suvorexant is relatively rapid and best described by a sigmoidal function, representing zero-order release of drug from the tablet formulation followed by first-order absorption. The estimated first-order absorption t1/2 was 0.35 h for a

typical subject; the estimated IIV in the first-order absorption process was 156.84 %CV.

- No statistically significant influence of age, race (including Japanese race), or renal function on suvorexant PK was found.
- Administration of suvorexant in the AM is predicted to increase F1 by 22.6% and increase ka by 129% compared to PM administration.
- Apparent oral clearance of suvorexant is lower by 20.5% in females compared to males and decreases with increasing BMI, according to a power function, resulting in the lowest CL/F in the heaviest female patients. An approximate 2- to 3-fold reduction in CL/F is expected when comparing men with relatively low BMI versus obese women.
- No statistically significant covariates were determined to exhibit a clinically relevant impact on suvorexant PK based on clinical bounds of 0.5 and 1.7 for geometric mean ratios of AUC0-24.

Reviewer's comments: A population PK analysis, utilizing rich PK data from 16 suvorexant Phase 1 studies, was performed. A sophisticated PK model was generated to characterize the sharp peaks observed during the absorption phase and the dose dependent bioavailability of suvorexant. Residual diagnostics based on the sponsor's analyses showed that the model fitted the data reasonably well. The reviewer reproduced a similar analysis. With regard to the covariates chosen, the analysis concluded similar results with similar parameter estimates. However, to determine the clinical relevance of the covariate effects on exposure, the sponsor has chosen a somewhat arbitrary clinical bound of 0.5 to 1.7 for the geometric mean ratios. The reviewer will defer to the comments from the exposure-response analysis to assess the importance of the clinical bounds.

The reviewer concludes the analysis, and the corresponding conclusions and interpretations, presented by the sponsor is reasonable. Plots depicting the covariate-PK parameter relationships are shown in the reviewer's analysis.

3.1.2 Suvorexant (MK-4305) Absolute Bioavailability Estimate

The objective of this analysis was to use a population PK model-based approach to estimate the absolute bioavailability of suvorexant 10, 20, 40, and 80 mg oral doses with the IV and PO dose proportionality data from P018. Due to the unusual exposures observed at the 30 mg IV dose, where exposures were similar to those observed at the 20 mg IV dose despite dose proportional increases in exposure over the 5 to 20 mg IV doses, the estimation of bioavailability values was done excluding and including the data from the 30 mg IV arm as a sensitivity analysis. This analysis was based on the PK data from the Oral and IV Dose Proportionality Study (P018). This study was an open-label, randomized, two-part study in healthy male and female subjects (n=48) to determine proportionality of MK-4305 following intravenous (IV) and oral (PO) administration.

Densely sampled PK data from the IV and PO doses of P018 were pooled to obtain estimates of absolute bioavailability for each of the oral doses (10, 20, 40, and 80 mg) using a population pharmacokinetic approach. Log transformed individual plasma concentration-time profiles were fit with a 3-compartment mamillary model based on the base structural model chosen in the "Population Pharmacokinetic Evaluation of Suvorexant Using Data From Phase 1 Studies" (Report 613).

The absolute bioavailability of the 40 mg dose was estimated, while the bioavailabilities of the 10, 20 and 80 mg doses were estimated as fractional changes relative to the bioavailability at 40 mg as follows:

$$F1_{40mg} = \theta 1$$

$$F1_{10mg} = F1_{40mg}*(1+ \theta 2*flag10)$$

$$F1_{20mg} = F1_{40mg}*(1+ \theta 3*flag20)$$

$$F1_{80mg} = F1_{40mg}*(1+ \theta 4*flag80)$$

where F1 is the bioavailability at each dose level, θ1 is the bioavailability at the 40 mg dose, θ2-4 are the fractional changes in bioavailability for the 10, 20, and 80 mg doses relative to 40 mg, and the flag terms are indicators for the dose (flag10=1 for the 10 mg dose and 0 for all other doses, etc.).

The estimated bioavailability for the 10, 20, 40, and 80 mg doses with and without the 30 mg IV arm are listed in Table 3 (reported as median and 90% percentiles based on the uncertainty in the parameter estimates). To obtain these values, 1000 sets of parameter estimates (F1 for 40 mg and fractional changes relative to 40 mg for all other doses) were sampled from the variance/covariance matrix for the final models assuming a multivariate normal distribution. The increases in the bioavailability estimates with inclusion of the 30 mg IV arm are at most ~6% and roughly within the standard error of the bioavailability estimates.

Table 3: Bioavailability Estimates for the 10, 20, 40, and 80 mg Oral Dose of Suvorexant

	Excluding 30 mg IV Arm		Including 30 mg IV Arm	
Dose (mg)	Bioavailability (5th and 95th Percentile)	Fractional Change Relative to 40 mg	Bioavailability (5th and 95th Percentile)	Fractional Change Relative to 40 mg
10	0.82 (0.74, 0.89)	0.74 Increase	0.88 (0.81, 0.94)	0.71 Increase
20	0.62 (0.55, 0.69)	0.33 Increase	0.68 (0.61, 0.74)	0.32 Increase
40	**0.47 (0.41, 0.53)**	**1**	**0.51 (0.46, 0.57)**	**1**
80	0.37 (0.31, 0.42)	0.21 Decrease	0.41 (0.36, 0.46)	0.21 Decrease

Inclusion or exclusion of the 30 mg IV arm, in a sensitivity assessment, had minimal impact on the absolute bioavailability estimates for the 10, 20, 40, and 80 mg doses. The absolute bioavailability at the 10, 20, 40, and 80 mg doses excluding the 30 mg IV arm were 0.82, 0.63, 0.47, and 0.37. Including the 30 mg IV arm, the absolute bioavailabilities at the 10, 20, 40, and 80 mg doses were 0.88, 0.68, 0.52, and 0.41. In both cases, the absolute bioavailability estimates indicate that suvorexant has a moderate bioavailability. The result excluding the 30 mg IV arm is used as the definitive bioavailability assessment, because it is unclear if the exposures observed in that arm accurately reflect the true exposure at that dose level. The range of absolute bioavailability estimates are consistent with those estimated based on IV and oral exposures at each dose level and are consistent with those observed for preclinical species. Lastly, the decreasing absolute bioavailability with increasing dose are consistent with the less than strictly dose proportional increases observed in clinical studies for suvorexant.

Reviewer's comments: Using the population PK model generated from the 16 pooled Phase 1 studies, the sponsor attempted to estimate the absolute bioavailability of suvorexant 10, 20, 40, and 80 mg oral doses with the IV and PO dose proportionality data. Based on the range of data, the reviewer concurs that the use of the prior model was appropriate to ascertain suvorexant bioavailability. With anomalous exposures seen with the 30 mg IV dose, the sensitivity analysis was performed with and without the 30 mg IV dose data. The reviewer concurs that exclusion of this data has a nominal effect on the bioavailability estimation. Thus, the reviewer concludes the analysis, and the corresponding conclusions and interpretations, presented by the sponsor is reasonable.

3.2 Exposure-Response Analyses

3.2.1 Efficacy

The sponsor's exposure-response analyses included data from a Phase 2B dose-ranging trial (P006, first period only) and the two pivotal Phase 3 trials (P028 and P029). Table 4 summarizes the design for each study included in the sponsor's exposure-response analyses.

Table 4: Summary of study design for studies P006, P028 and P029

Study Number	Design Features	Treatments	Measurements
P006	Two-period crossovers; non-elderly patients	Placebo, 10, 20, 40 or 80 mg QD for 4 weeks	PK: Day 1 (9 hr), Day 14 (floating[a]), Day 28 (9 hr) PSG: Day 0 (baseline), Day 1, Day 28 Subjective: Week 0, 1, 2, 3, and 4
P028	Parallel group; PQ-cohort (75%), Q-chort (25%, Japanese)	Non-elderly: Placebo, 20 or 40 mg QD Elderly: Placebo, 15 or 30 mg QD	PSG PK: Day 1 (9 hr), Day 14 (floating, Week 2), Day 28 (9 hr, Month 1), Day 90 (9 hr, Month 3) PSG: Day 0 (baseline), Day 1, Day 28, Day 90 Subjective PK: Day 14 (floating, Week 2), Day 28 (floating, Month 1), Day 90 (floating, Month 3) Subjective: Week 0, 1, 2, 3, 4, 6, 8, 10 and 12
P028	Parallel group; PQ-cohort (71%), Q-chort (29%)	Non-elderly: Placebo, 20 or 40 mg QD Elderly: Placebo, 15 or 30 mg QD	PSG PK: Day 1 (9 hr, Night 1), Day 14 (floating, Week 2), Day 28 (9 hr, Month 1), Day 90 (9 hr, Month 3) PSG: Day 0 (baseline), Day 1, Day 28, Day 90 Subjective PK: Day 14 (floating, Week 2), Day 28 (floating, Month 1), Day 90 (floating, Month 3) Subjective: Week 0, 1, 2, 3, 4, 6, 8, 10 and 12

[a] Floating time denotes sample drawn at an un-specified random time determined based on the time of the dose from the previous day and the time of the PK sample.

The sponsor evaluated subjective measures such as sTSTm (Weekly mean of subjective total sleep time), sTSOm (Weekly mean of subjective time to sleep onset) and sWASOm(Weekly mean of subjective wakefulness after sleep onset) as well as objective measures such as WASO (Wakefulness after persistent sleep onset), LPS (Latency to onset of persistent sleep) related to suvorexant dose or exposure. In addition to these, DSST (Number of correct responses in the digital symbol substitution test) was analyzed as an objective measure of next day residual effect.

For the objective measures, separate time-dependent placebo and drug effects were estimated for each of the 3 measurement visits since post-baseline time points were limited to Days 1, 28 and 90; whereas, for subjective measures, continuous functions of time (typically exponential relationships) were postulated for the weekly averages of the

subjective measures to describe the time-course of placebo response and the potential attenuation of the drug effect over time. Interindividual random effects were included on baseline, placebo and drug model parameters either as additive (normal) or exponential (log-normal) effects. The additive models assumed a normal (additive) residual error model while the multiplicative models assumed a log-normal residual error model. The key assumptions and limitations in the modeling approach were:

- Assumed potency (ED50 or EC50) is time-invariant
- Assumed covariate effects are time-invariant (i.e., no covariate by time interactions)
- Time course of subjective measures beyond 12 weeks not evaluated due to difficulties in pooling the long term safety study with the 3-month treatment phase from the double-blind efficacy studies
- Limited exposure-range in the elderly (only 15 and 30 mg doses evaluated – data limited to Phase 3)

The sponsor evaluated both dose and C_{9hr} concentrations (9 hours post dose) as potential predictors of the exposure-response model for each measure, and the sponsor found dose better predictor of response than C_{9hr}.
Dose was normalized by creatinine clearance (CrCL) to facilitate interpretation of the CrCL effect as pharmacokinetic effect as given by the expression:

$$D_{norm,i} = Dose_i \left(\frac{CrCL_i}{90} \right)^{\theta_1}.$$

For each endpoint model, age was included as a structural covariate on baseline and ED_{50} and E_{max} parameters. Covariate effects on baseline and drug parameters were also evaluated for baseline body weight, gender, race, ethnicity, creatininine clearance, and study cohort (Qcohort – patients recruited for the questionnaire only cohort, PQ-cohort – patients recruited to participate in the polysomnographic procedures as well as the sleep questionnaire) during the covariate model development step.
Table 5 and Table 6 present the summary statistics of each covariates which was evaluated in the sponsor's exposure-response analyses for objective and subjective measures.

Table 5: Summary of covariates included in the sponsor's exposure-response analyses for objective measures

Covariate	Statistic	Study			Total
		P006	P028	P029	
Age (years)	N	254	775	746	1775
	Mean±SD	44.4 ± 11.5	56.0 ± 15.3	56.9 ± 15.0	54.7 ± 15.3
	Median	45	59	60	56
	Min – Max	18 – 64	18 – 87	18 – 86	18 – 87
Weight (kg)[a]	N	253	773	746	1772
	Mean±SD	75.1 ± 16.5	73.4 ± 13.6	73.8 ± 14.3	73.8 ± 14.3
	Median	73.5	72.3	72.9	72.7
	Min – Max	42.3 – 123.4	40.4 – 119.3	40.2 – 125.2	40.2 – 125.2
BMI (kg/m^2)	N	253	773	746	1772
	Mean±SD	26.3 ± 4.5	26.0 ± 4.0	26.3 ± 4.1	26.2 ± 4.1
	Median	25.8	25.6	26.0	25.8
	Min – Max	16.7 – 39.0	16.0 – 39.8	16.3 – 41.7	16.0 – 41.7
CrCL (mL/min)[b]	N	253	772	746	1771
	Mean±SD	99.3 ± 24.1	84.1 ± 24.6	83.9 ± 26.6	86.2 ± 25.9
	Median	97.5	80.1	81.2	83.2
	Min – Max	42.5 – 163.6	30.2 – 200.8	26.5 – 193.2	26.5 – 200.8
Gender (N, %)	Males	106 (41.7)	291 (37.6)	240 (32.2)	637 (35.9)
	Females	148 (58.3)	484 (62.4)	506 (67.8)	1138 (64.1)
Race (N, %)	Whites	178 (70.1)	666 (85.9)	681 (91.3)	1525 (85.9)
	Blacks	30 (11.8)	58 (7.5)	43 (5.8)	131 (7.4)
	Asians	44 (17.3)	16 (2.1)	16 (2.1)	76 (4.3)
	Others	2 (0.8)	35 (4.5)	6 (0.8)	43 (2.4)
Japanese Race (N, %)	Non-Japanese	220 (86.6)	775 (100)	746 (100)	1741 (98.1)
	Japanese	34 (13.4)	0 (0)	0 (0)	34 (1.9)
Ethnicity (N, %)	Non-Hispanic	209 (82.3)	660 (85.2)	606 (81.2)	1475 (83.1)
	Hispanic	45 (17.7)	115 (14.8)	140 (18.8)	300 (16.9)

[a] Three subjects had missing baseline body weights imputed with the median value.
[b] One subject had missing serum creatinine concentration imputed with median value when calculating CrCL.

Table 6: Summary of covariates included in the sponsor's exposure-response analyses for subjective measures

Covariate	Statistic	Study			Total
		P006	P028	P029	
Age (years)	N	253	1021	1011	2285
	Mean±SD	44.4 ± 11.5	55.7 ± 15.3	56.4 ± 15.3	54.8 ± 15.4
	Median	45	58	59	56
	Min – Max	18 – 64	18 – 87	18 – 86	18 – 87
Weight (kg)[a]	N	252	1019	1009	2280
	Mean±SD	75.2 ± 16.4	69.6 ± 14.7	72.5 ± 14.4	71.5 – 14.9
	Median	73.7	68.2	71.2	70.3
	Min – Max	42.3 – 123.4	37.3 – 119.3	39.2 – 125.2	37.3 – 125.2
BMI (kg/m^2)	N	252	1019	1009	2280
	Mean±SD	26.2 ± 4.5	25.1 ± 4.1	26.1 ± 4.2	25.7 ± 4.2
	Median	25.8	24.8	25.8	25.4
	Min – Max	16.7 – 39.0	15.7 – 39.8	16.3 – 41.7	15.7 – 41.7
CrCL (mL/min)[b]	N	252	1018	1009	2279
	Mean±SD	99.4 ± 24.1	82.1 ± 24.7	84.0 ± 26.2	84.9 ± 25.8
	Median	97.7	78.1	81.0	81.5
	Min – Max	42.5 – 163.6	27.4 – 200.8	26.5 – 193.2	26.5 – 200.8
Gender (N, %)	Males	106 (41.9)	384 (37.6)	339 (33.5)	829 (36.3)
	Females	147 (58.1)	637 (62.4)	672 (66.5)	1456 (63.7)
Race (N, %)	Whites	178 (70.4)	665 (65.1)	810 (80.1)	1653 (72.3)
	Blacks	30 (11.9)	58 (5.7)	46 (4.6)	134 (5.9)
	Asians	43 (17.0)	263 (25.8)	78 (7.7)	384 (16.8)
	Others	2 (0.8)	35 (3.4)	77 (7.6)	114 (5.0)
Japanese Race (N, %)	Non-Japanese	219 (86.6)	774 (75.8)	1011 (100)	2004 (87.7)
	Japanese	34 (13.4)	247 (24.2)	0 (0)	281 (12.3)
Ethnicity (N, %)	Non-Hispanic	208 (82.2)	907 (88.8)	780 (77.2)	1895 (82.9)
	Hispanic	45 (17.8)	114 (11.2)	231 (22.9)	390 (17.1)
Cohort (N, %)	Q-Cohort	0 (0)	247 (24.2)	263 (26.0)	510 (22.3)
	PQ-Cohort	253 (100)	774 (75.8)	748 (74.0)	1775 (77.7)

[a] Five subjects had missing baseline body weights imputed with the median value.

The sponsor's exposure-response analyses showed that

- For WASO, the predicted ED_{50} for a 40 year old patient weighing 70 kg was 11.4 mg and the predicted ED_{50} for elderly and heavier (90 kg) patients was 16.8 and 18.0 mg, respectively.

- For LPS, the ED_{50} could not be estimated due to the flat response curve within the dose range suggesting the maximal drug effect is observed at the lowest dose studied (10 mg)

- For sWASOm, exposure-response relationship was adequately characterized by an additive model with instantaneous and time-dependent placebo effects and linear dose-response drug model for the non-elderly and a constant drug effect assuming the maximum drug effect is achieved at the lowest dose (15 mg) in the elderly.

- For sTSTm , exposure-response relationship was adequately characterized by an additive model with instantaneous and time-dependent placebo effects and an Emax dose-response drug model that attenuates with time. The predicted ED50 for both non-elderly and elderly patients was 14 mg.

- For sTSOm, exposure-response relationship was adequately characterized by a multiplicative model with instantaneous and time-dependent placebo effects and an Emax dose-response drug model that attenuates with time. The predicted ED50 for non-elderly and elderly patients was 18 and 52 mg, respectively.

- For DSST, the exposure-response was characterized by a linear model in C9hr concentration with a slope that was invariant with time.

- Many of the covariate effects including gender, race, ethnicity and cohort for certain response measures had an influence on baseline but not on the drug effect parameters. Table 7 shows listing of covariate effects for each response measures.

Table 7: Summary of covariates effects for each response variable in the sponsor's exposure response analyses. B, D, and P indicate the effect at baseline, drug and placebo; NS represent no effect for any of component; NE means that the covariate was not evaluated in the model.

Covariate	WASO	sTSTm	sWASOm	LPS	sTSOm	DSST
Age	B, D, P	B, D	B, D, P	B, D	B, D	B, D
Gender	B	NS	NS	NS	B	B
Weight	D	NS	NS	NS	NS	NS
Ethnicity	NS	NS	NS	B	NS	B
Race	B	B, D	B	D	B, D	NS
Cohort	NE	B	NS	NE	B	NE

The final models were used in simulations to provide dose predictions for non-elderly and elderly patients and the combined results are presented **Figure 12** and

Figure 13.

Figure 12: Mean Placebo-Corrected Change from Baseline (PC-CFB) Dose-Response of Onset, Maintenance, and Residual Effects in Non-Elderly Adults at Month 3 based on the sponsor's final models for each endpoint

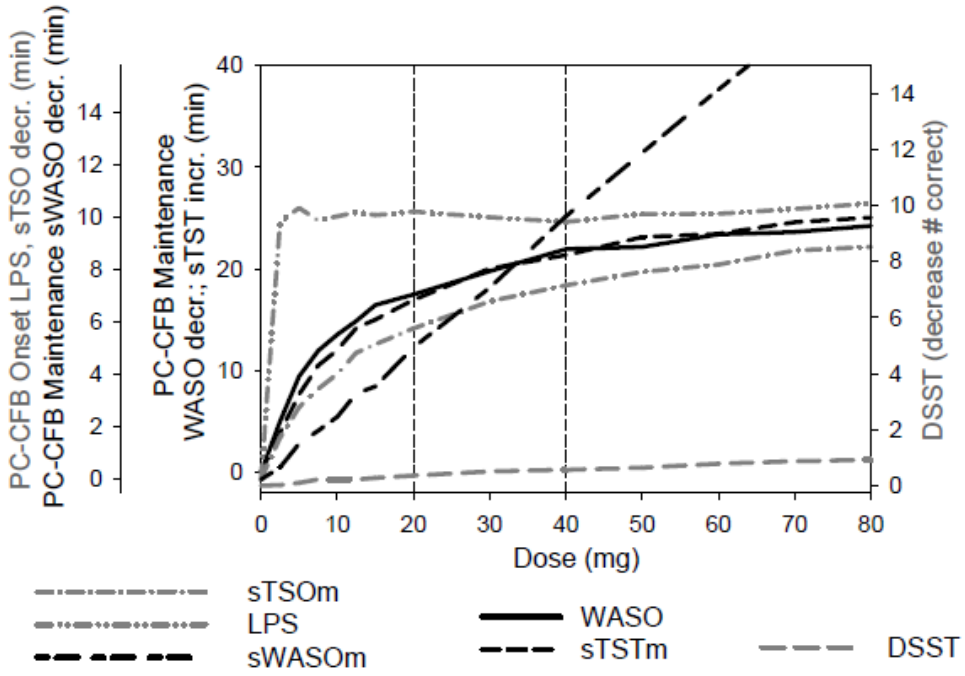
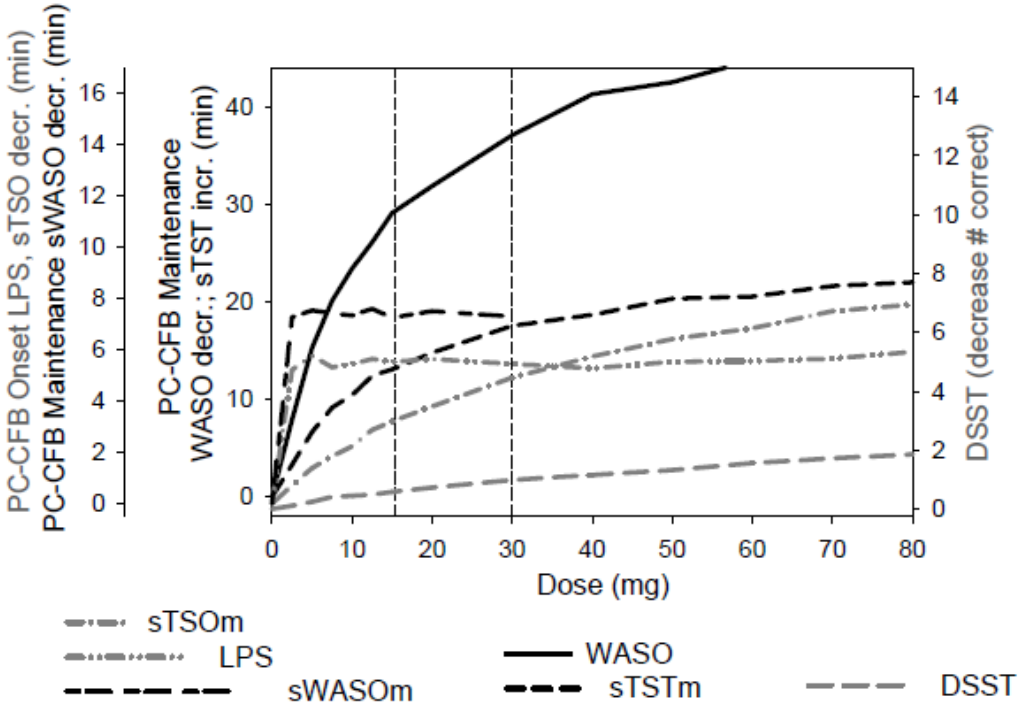


Figure 13: Mean Placebo-Corrected Change from Baseline (PC-CFB) Dose-Response of Onset, Maintenance, and Residual Effects in Elderly Adults at Month 3 based on the sponsor's final models for each endpoint



3.2.2 Safety

The sponsor investigated the occurrence of somnolence, sedation, fatigue, and excessive daytime sleepiness (EDS) using the data from one Phase IIb (P006) and three Phase III studies (P009, P028, and P029). .

Suvorexant plasma concentrations the morning after evening dosing (at ~9 hours post-dose –C_{9hr}) was used for the exposure in the sponsor's exposure-response analyses. The individual steady-state C_{9hr} values were determined as the geometric mean of all concentrations obtained in that individual that were obtained between 7 and 13 hours postdose on treatment day 3 or later. In some instances, if only one value is available, that value was used as the steady-state C_{9hr} values. If no values are available in a subject, C_{9hr} were treated as missing. Days 3+ were chosen because the pharmacokinetics were expected to be at steady-state in this period.

Table 8 summarizes the event rate for each adverse event along with summary statistics of C_{9hr}. Based on exploratory evaluations, formal PK/AE model development was developed for somnolence and fatigue, but evaluation of sedation and EDS were limited to the exploratory work, as the small number of patients with occurrence and the lack of apparent strong relationships with C_{9hr} precluded meaningful model development.

Table 8: Summary statistics for each adverse events and C_{9hr} from observed data

Adverse Events		N1[↑] (%)	N2[†] (%)	C9hr by Categories Mean (SD)	Max	Min
Somnolence	Yes	237 (7.18%)	193 (5.84%)	0.52 (0.34)	1.36	0
	No	3066 (92.82%)	2627 (79.54%)	0.28 (0.33)	2.77	0
	Missing	0 (0%)	483 (14.62%)	-	-	-
Fatigue	Yes	93 (2.82%)	71 (2.15%)	0.44 (0.32)	1.15	0
	No	3210 (97.18%)	2749 (53.23%)	0.30 (0.33)	2.77	0
	Missing	0 (0%)	483 (14.62%)	-	-	-
Sedation	Yes	17 (0.51%)	11 (0.33%)	0.37 (0.41)	0.97	0
	No	3286 (99.49%)	2809 (85.05%)	0.30 (0.33)	2.77	0
	Missing	0 (0%)	483 (14.62%)	-	-	-
EDS	Yes	26 (0.79%)	18 (0.54%)	0.41 (0.58)	1.32	0
	No	2786 (84.35%)	2341 (70.88%)	0.31 (0.33)	2.77	0
	Missing*	491 (14.86%)	944 (28.58%)	-	-	-

[↑] N1 is the number of total patient records by each AE category.

[†] N2 is the number of patient records with observed C9hr by each AE category.

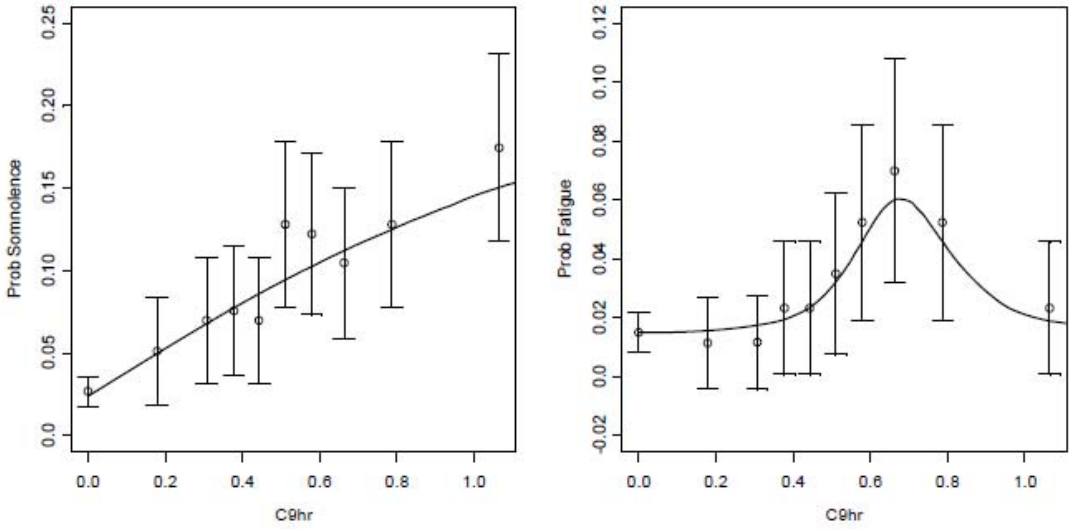
Each adverse event was counted as 1 if this was reported at any time during treatment regardless of severity or duration of the adverse event, otherwise 0.

The somnolence incidence rates with C_{9hr} were described by an E_{max} structural logistic regression model. The final parameter estimates corresponded to an incidence rate of ~2.7% in placebo patients rising to ~24.5% at maximal drug. The EC_{50} for this relationship was 0.60 μM, which is the mean C_{9hr} value obtained at ~38 mg suvorexant.

Fatigue incidence vs. C_{9hr} was described by bi-phasic structural logistic regression model, consistent with the incidence of fatigue initially increasing with increasing C_{9hr}, but then falling at higher C_{9hr} values. The biphasic structural form could be interpreted as describing the interplay of two drug effects (one positive and one negative) that create a rise and fall in probability, such as the interplay could arise if the risk for fatigue was increased by residual drug concentrations present in the morning and the risk for fatigue

was also decreased by beneficial treatment of the underlying insomnia condition. The final parameter estimates corresponded to a peak incidence rate of ~6% occurring at a C_{9hr} value of 0.67 μM (mean C_{9hr} at ~45 mg). The incidence of fatigue by dose was predicted to be fairly flat in the clinical range with fatigue incidence rates of 3.3%, 1.9%, and 1.5% at doses of 40 and 20 mg and placebo, respectively, in non-elderly adults.

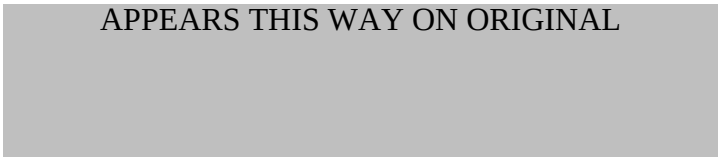
Figure 14: The predicted exposure-adverse event relationships for somnolence and fatigue from the sponsor's model. Each dot and bar represents the observed incidence rates with 95% CI at 10 bins of C_{9hr}

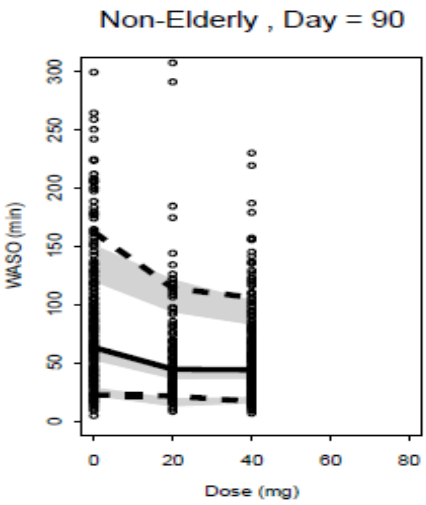


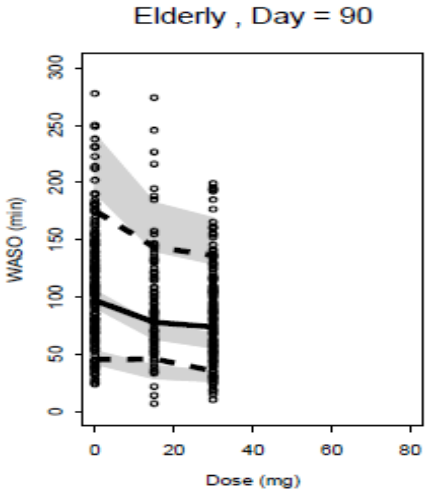
Reviewer's comments:

- *It would not be adequate to pool data from phase II study and phase III studies as there are many differences in the study design*
- *The sponsor's final models for two objective measures (LPS, WASO) are questionable in terms of predictability.*
    - *Shrinkage estimates for Emax parameters for LPS and WASO were reported as 100% and 81%, respectively, meaning that*
        - *Individual parameter estimates for Emax are not reliable or*
        - *The final model may not be correct as it is well-known that shrinkage can be falsely induced covariate relationship.*
    - *The sponsor's model's prediction is not consistent with the observed mean for both endpoints.*
        - *As shown figures below, the sponsor's model under- and over-predicts WASO in non-elderly and elderly patients, respectively, which is also reflected in prediction for WASO in* Figure 12 *and*

Figure 13.

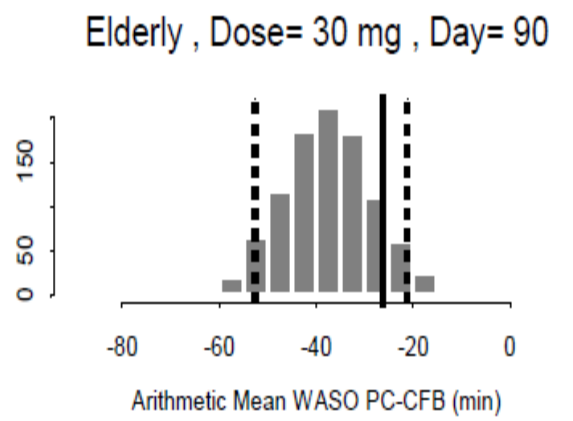


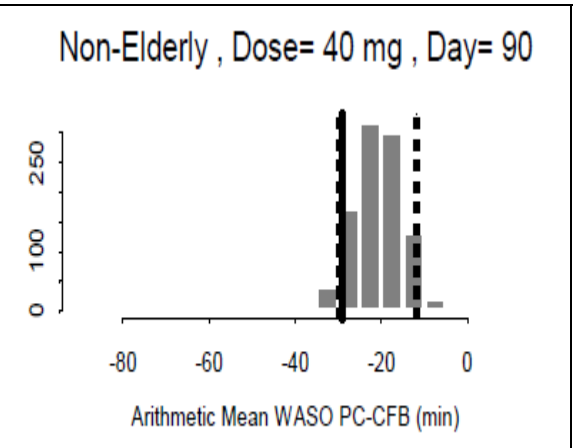




Observed data represented by symbols, observed geometric mean (solid line), observed 10th (lower dashed line) and 90th (upper dashed line) percentiles. The shaded grey areas correspond to the 90% prediction intervals for geometric mean (middle shaded area) and 10th (lower shaded area) and 90th (upper shaded area) percentiles.

Source: the sponsor's report, page 61.





The histograms summarize the distribution of the arithmetic mean ΔΔWASO predictions from 1000 simulated trials. The dashed lines correspond to the 5th and 95th percentiles of the predictions. The solid line corresponds to the observed arithmetic mean response.

Source: the sponsor's report, page 62.

4 REVIEWER'S ANALYSES

4.1 Objectives

To assess whether the sponsor's proposed dosing regimen is acceptable given benefit and risk profile of suvorexant by the reviewer's independent analyses
To determine if there is a need for surovexant dose adjustment based on extrinsic/intrinsic factors such as age, gender, body weight.

4.2 Methods

Population PK analysis

The reviewer produced a similar covariate analysis using the reviewed suvorexant popPK model. Univariate graphical analysis was performed to evaluate trends in the covariate-exposure relationships. The same covariates and similar criteria for covariate selection was chosen for the backward and forward stepwise covariate modeling (p-value <0.1 deemed to be a significant covariate).

Exposure-Response analyses

For the efficacy analyses, unlike the sponsor's analyses, the reviewer pooled data from two Phase III studies (P028 and P029) as the study of P006 is different from two Phase III studies in terms of study design and patients included in the study; the study of P006 is a two-way crossover study with only 1 month study duration and only non-elderly patients were included.

The reviewer analyzed the primary endpoint, the change from the baseline for all efficacy measures and the predicted AUC $_{0\text{-}24}$ was used for the exposure measure. AUC $_{0\text{-}24}$ was predicted the sponsor's model which was based on the data from 15 Phase I studies. The sponsor's final model is presented below;

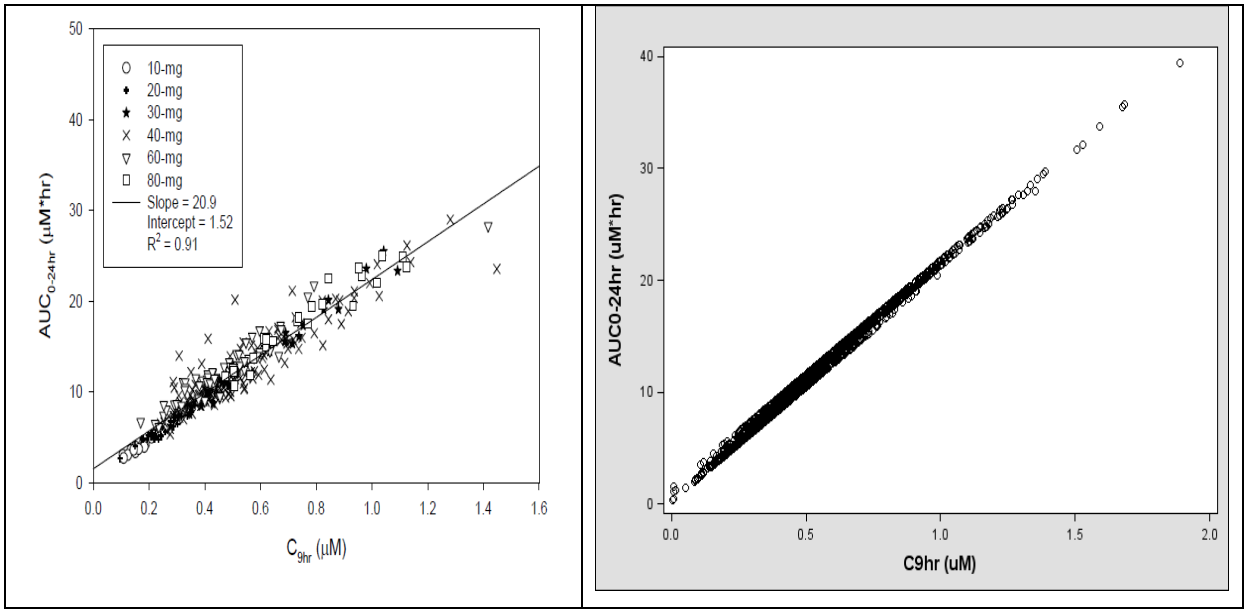
$$AUC_{0\text{-}24hr} = Slope * C_{9hr} + Y0 * (1 + Fr_{10\text{-}mg})*(1+ Fr_{20\text{-}mg}) *(1+ Fr_{PM}) *(1+ Fr_{Pre\text{-}obese})$$

Where Y0: intercept, Fr10mg: 10 mg dose effect on intercept, Fr20mg: 20mg dose effect on intercept, FrPM: PM dosing effect on intercept, Frpre-obese: Pre-obese BMI effect on intercept. The parameter estimates are presented in the appendix.

The sponsor's model shows good agreement between AUC $_{0\text{-}24}$ (μM*hr) and C9hr (μM) in Phase III studies as well as Phase I studies (Figure 15).

Figure 15: The correlation between predicted AUC_{0-24} (µM*hr) and C_{9hr} (µM).

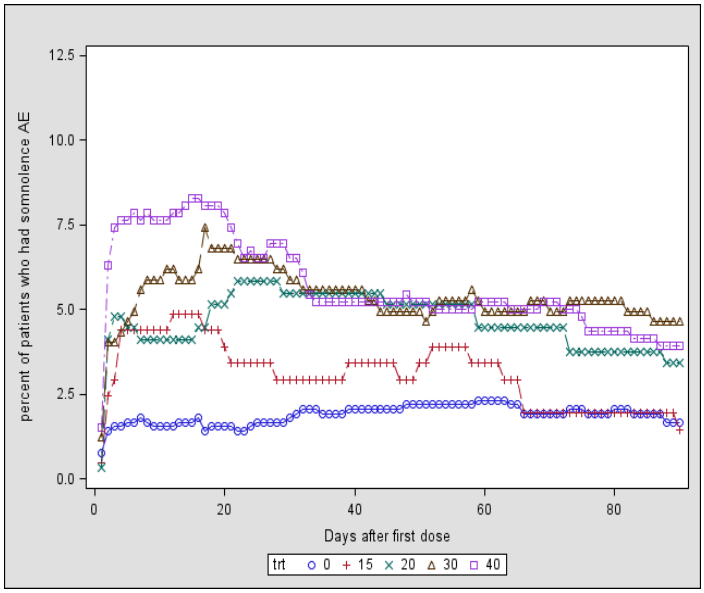
The left graph shows the relationship in Phase I studies which came from the sponsor's analysis, and the right graph is based on the data from two Phase III studies.



Through the series of internal team meetings there was an agreement that we should rely more on the objective efficacy measures (WASO, LPS) than the subjective measures (sTSOm, sTSTm and sWASOm) as the subjective measures could be influenced by a patient's personal mood. The reviewer's analyses for the subjective measures are consistent with the sponsor's analyses. The reviewer will present the results only for the objective measures in the exposure-efficacy analyses.

For the safety analysis, the reviewer focused on the incidence of somnolence, and C_{9hr} was used as an exposure. The reviewer observed that the majority of the incidence of somnolence occurred before day 3 (Figure 16). Hence, the concentrations measured at day 1 were linked to the incidence of somnolence if it occurred before day 3, and concentrations at steady state (geometric mean of two concentrations at day 28 and day 90) were related to the incidence otherwise. The logistic regression model was applied.

Figure 16: Time-profile of incidence of somnolence by dose



4.2.1 Data Sets

Data sets used are summarized in Table 9.

Table 9: Analysis Data Sets

Study Number	Name	Link to EDR
Pooled phase 1 studies Study 06 Study 028 Study 029	poolpk1.xpt WASO.xpt LPS.xpt Psg028.sas7bdat Psg029.sas7bdat Dsst.xpt Ae,xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PMReviews\Suvorexant_NDA204569_JYL\PPK Analyses\613\datasets \\Cdsnas\pharmacometrics\Reviews\Ongoing PMReviews\Suvorexant_NDA204569_JYL\ER Analyses

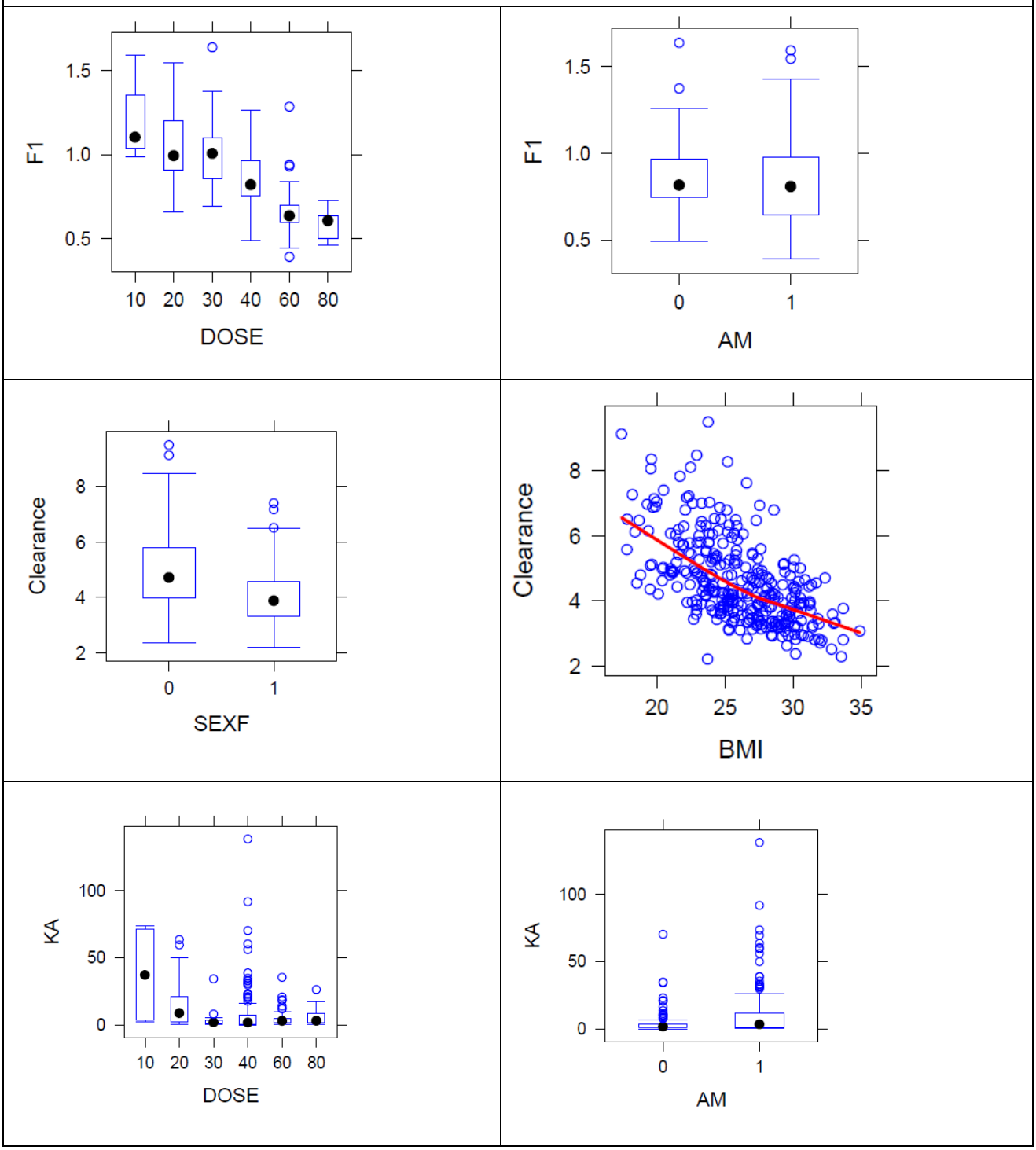
4.2.2 Software

SAS 9.2 and R 2.5 were used for the analysis.

4.2.3 Model Results

Population PK analyses

Figure 17. Influential covariates on Bioavailability (F1) *top*, Clearance (CL) *middle*, and Absorption Rate (Ka) *bottom.* Dose is in mg, AM refers to AM dosing (0 or 1 = yes or no), SEXF refers to sex female as reference (0 or 1 = yes or no), and **BMI (kg/m2)**



Note: For covariate-PK parameter relationships, blue circles represent individual parameter estimates and the solid black symbols on box-plots represent the median. For continuous covariates, the solid red line represents the moving average smoother.

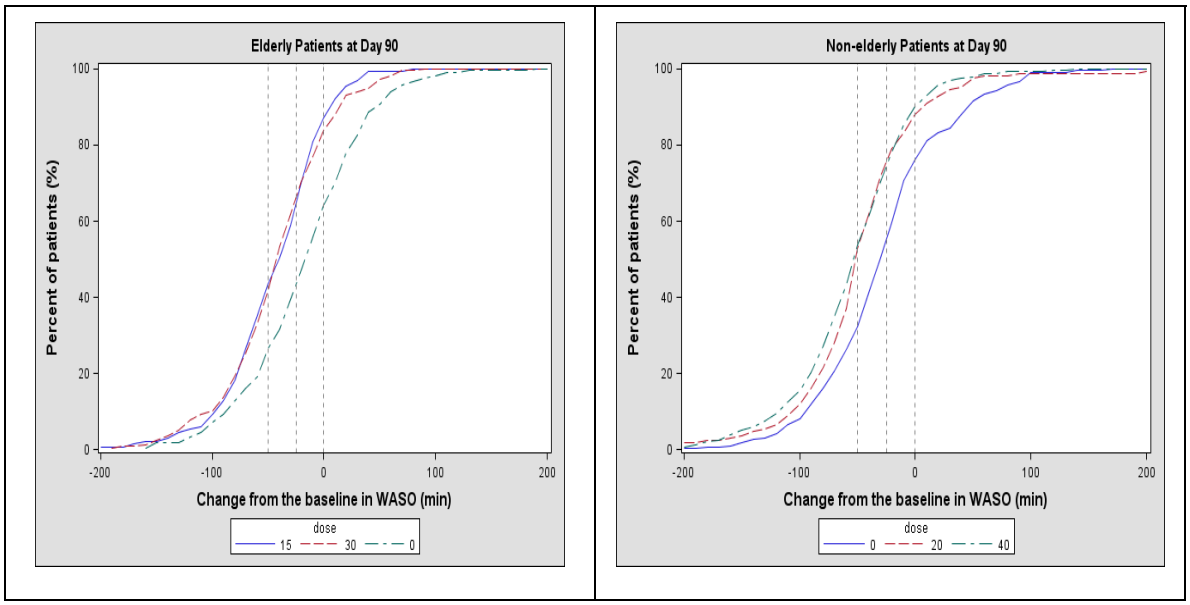
Exposure-Response Analyses

The top panel of Figure 1 presents the least square mean (LS mean) with 95 % CI of change from the baseline in WASO (hereafter Δ WASO) by dose group at each time point. Overall there is no apparent dose-dependent relationship shown for both elderly and non-elderly patients, which is consistent with the sponsor's efficacy analysis where high dose was compared to low dose with 95% CI including 0.

As a supplementary analysis, the reviewer made cumulative distribution which shows the percent of patients at each ΔWASO values ranged from -200 minutes to 200 minutes. For example, in elderly patients about 60 % and 80 % of patients in placebo and suvorexant groups had better sleep maintenance compared to baseline (ΔWASO < 0) whereas about 80 % and 90% of patients in placebo and suvorexant groups showed improvement in sleep maintenance in non-elderly patients. However, there is little difference between dose groups.

Figure 18: Cumulative distribution of ΔWASO

Xaxis is the value of ΔWASO, Yaxis is the percent of patients achieving corresponding ΔWASO on Xaxis by dose at day 90.



The bottom panel of Figure 1 shows dose-response profile in change from the baseline in LPS (hereafter Δ LPS) with no dose-response relationship for both elderly and non-elderly patients.

Based on the observations from dose-response relationship, the reviewer further examined whether the sleep onset or sleep maintenance would be improved in the exposure-dependent manner. Figure 19 presents the distribution of observed C9hr by dose at each day. Note that the distribution of concentration appears to be comparable between elderly and non-elderly patients at the same dose level. Also, the median C9hr is a bit higher in female patients than that in male patients but overall distribution seems to be comparable (Figure 20). As explained before, AUC_{0-24} was used for the exposure measure in the analyses. AUC_{0-24} was categorized by 6 bins with same number of patients at each bin. All placebo patients were grouped in the first bin. The median AUC_{0-24} at day 1 are 6 μM*hr, 7 μM*hr, 10 μM*hr, 11 μM*hr at 15mg, 20mg, 30mg and 40mg, respectively. As suvorexant PK reaches steady-state around day 15, AUC_{0-24} at day 28 and 90 appears to be similar: 8 μM*hr, 8 μM*hr, 14 μM*hr, 14 μM*hr at 15mg, 20mg, 30mg and 40mg, respectively. Please note that the distributions of AUC_{0-24} for elderly and non-elderly patients are comparable (Figure 2).

Figure 19: Suvorexant C_{9hr} (concentration post 9 hour dosing) distribution by dose at each measured day. The doses of 15 mg and 30 mg were assigned to elderly patients, and 20 mg and 40 mg were assigned to non-elderly patients.

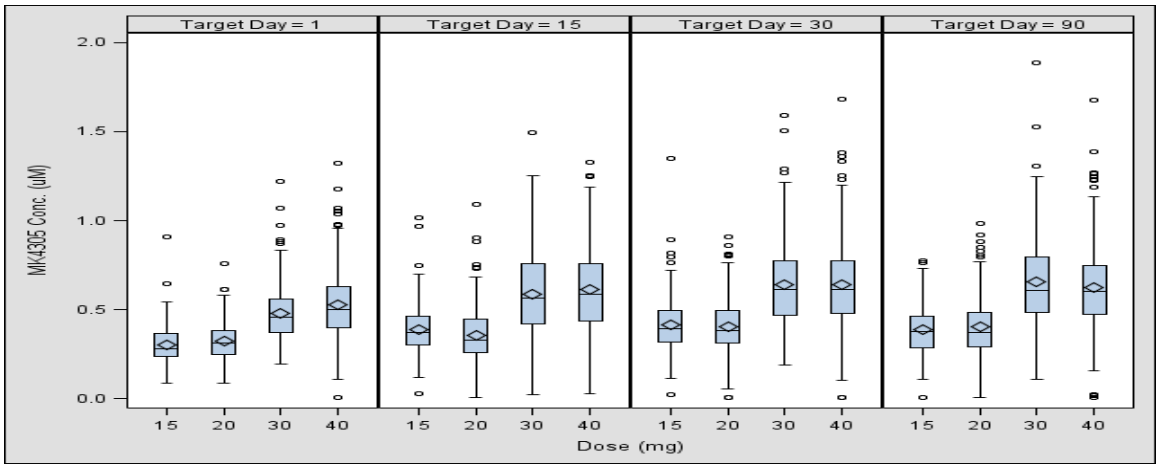


Figure 20: Suvorexant C_{9hr} (concentration post 9 hour dosing) distribution by dose and gender

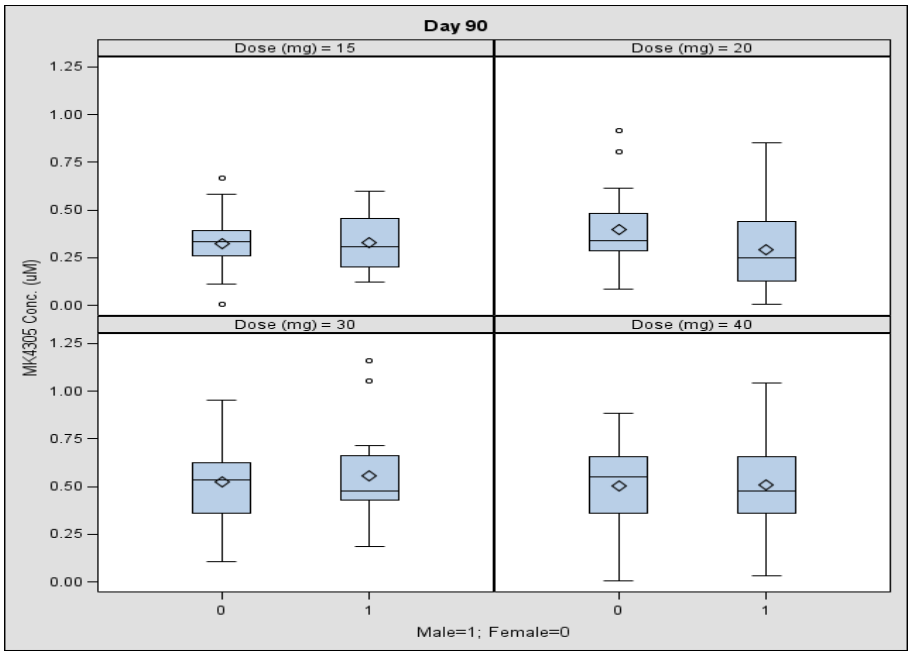


Figure 21 presents the exposure-response relationship for ΔWASO which shows no clear exposure-dependent improvement over the dose range of 10 mg to 40 mg.

The top panel of Figure 3 shows the results by elderly and non-elderly patients where non-elderly patients seems to get better benefit in ΔWASO compared to elderly patients but there appears to be still no clear exposure-dependent relationship in both populations. Note that the reviewer could not fit the model due to the flat exposure-response relationship.

Figure 21: The LS mean with 95% CI of Δ WASO (change from the baseline in WASO) vs. exposure (AUC $_{0\text{-}24}$) at each day. LS means were adjusted by baseline WASO value, age, region and gender to be consistent with dose-response analysis.

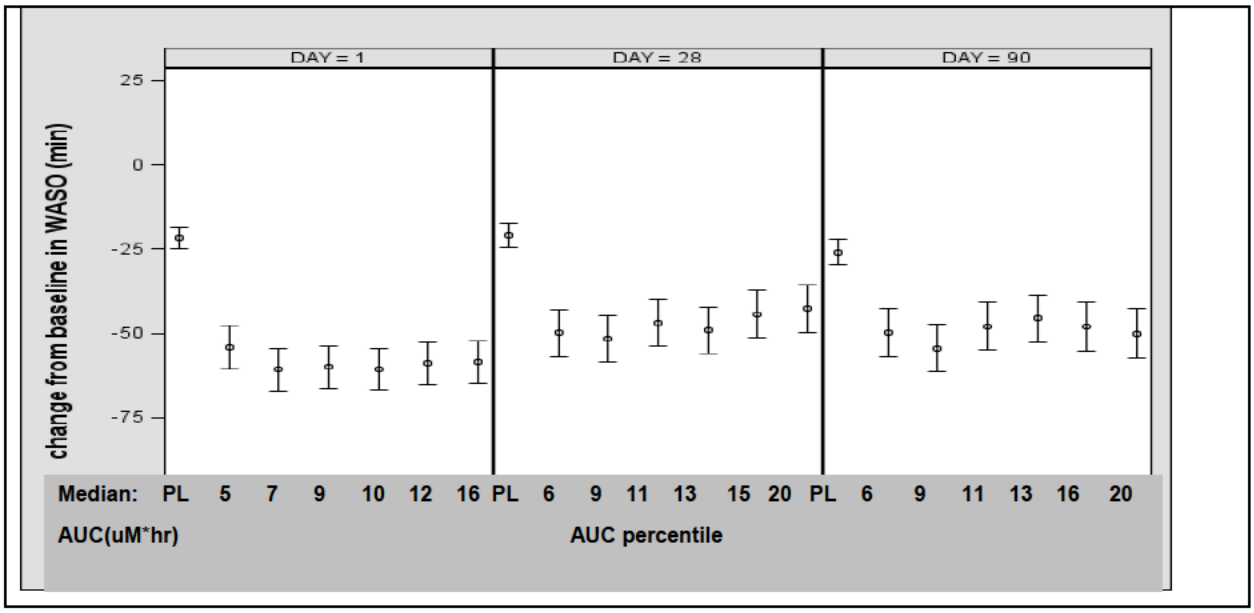
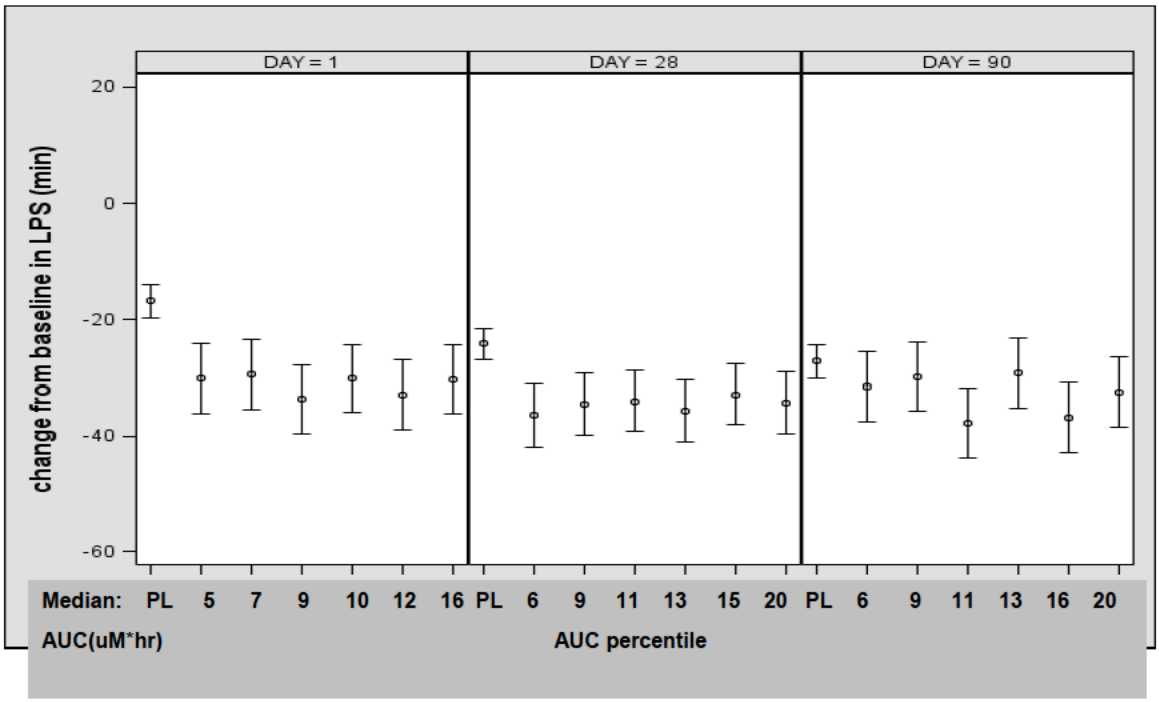


Figure 22 and Figure 3 (bottom panel) displays the exposure-response relationship for ΔLPS for all subjects and by elderly and non-elderly patients. No exposure dependent changes in sleep onset endpoint were observed.

Figure 22: The LS mean with 95%CI of ΔLPS (change from the baseline in LPS) vs. exposure (AUC $_{0\text{-}24}$) at each day. LS means were adjusted by baseline LPS value, age, region and gender to be consistent with dose-response analysis.

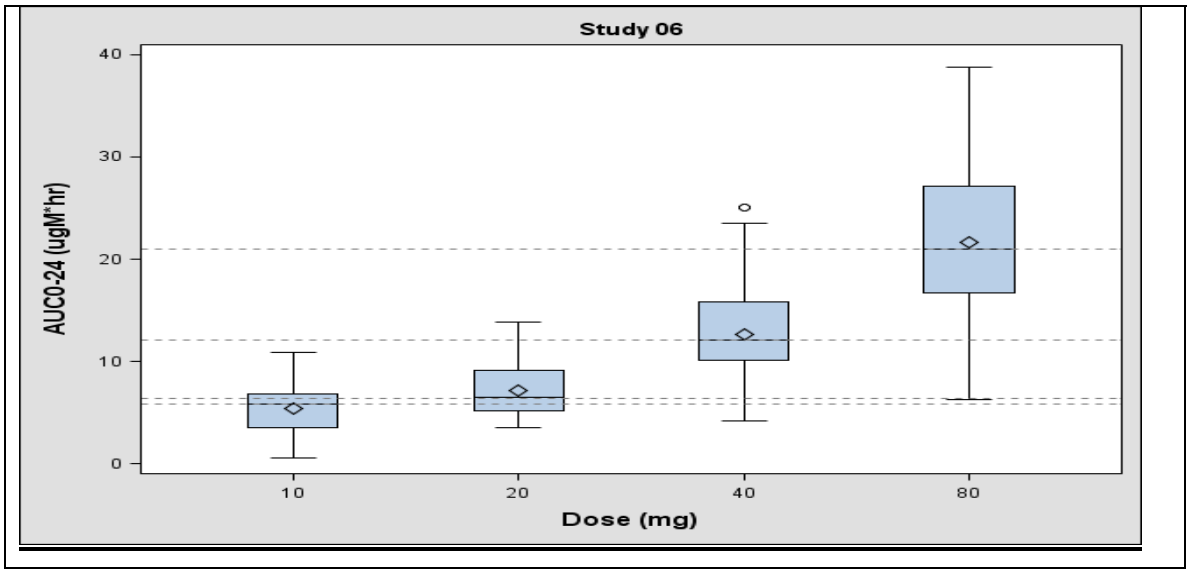


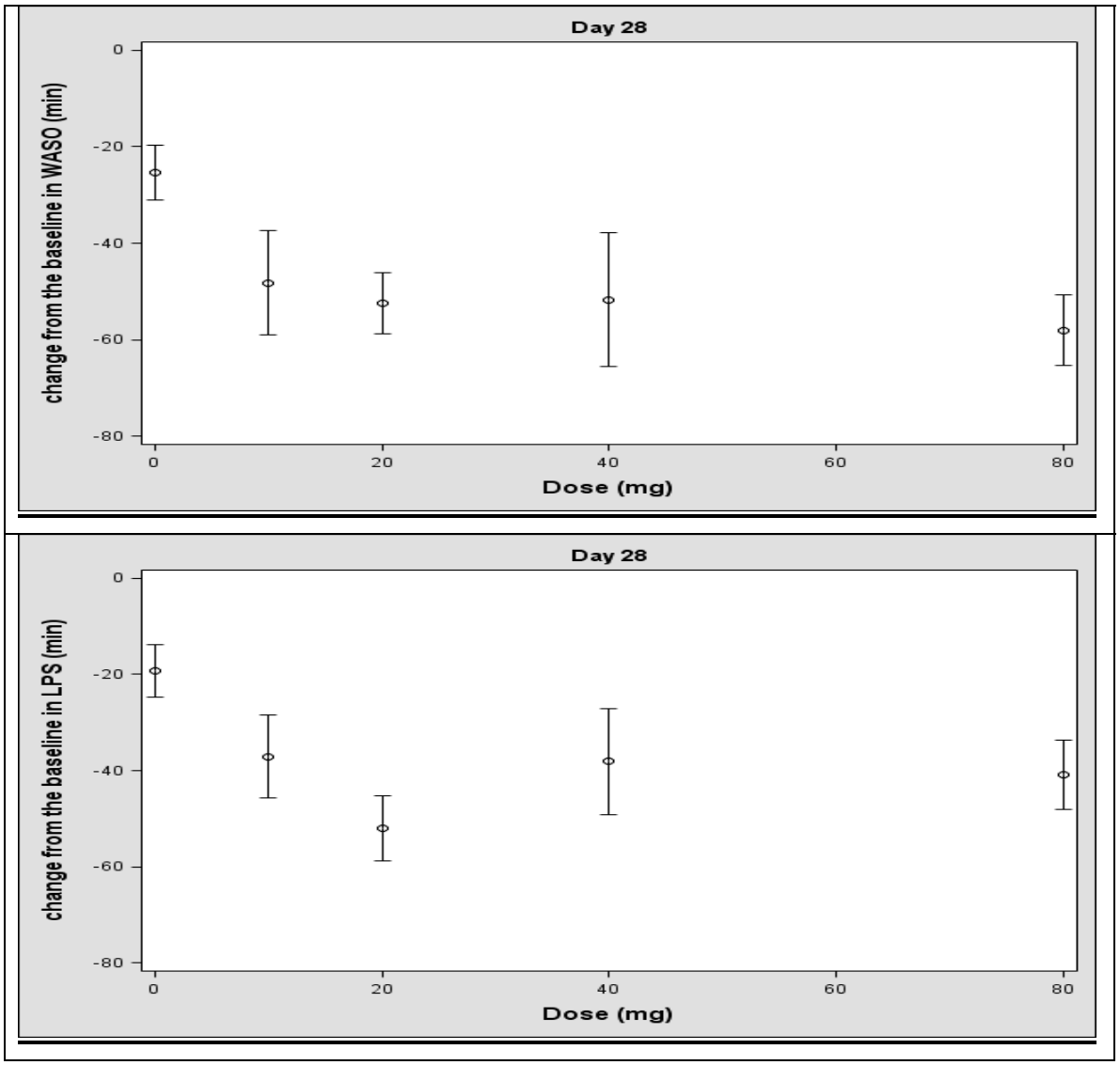
As there is little difference shown in both sleep maintenance and onset measures between two dose groups the reviewer further looked into the effectiveness of dose of 10 mg using data from the study 006 which is Phase II dose-ranging study. As the sponsor provided the data from the 1st period of study, the analysis was performed with only 1st period data. Also note that the patients enrolled in the study 06 were only non-elderly patients and the duration of study was 1 month. So the reviewer could evaluate the effectiveness only for non-elderly patients at day 28 (month 1).

The graph on the left panel of **Figure 23** shows the dose-proportionality of suvorexant over the dose range of 20 mg to 80 mg. The median AUC $_{0\text{-}24}$ for 10 mg dose was 5.3 µM*hr in comparison to 6.3 µM*hr for 20 mg.

Based on the exploratory look at the data from the study 06, the effectiveness at 10 mg seems to be little different from 20 mg in terms of both sleep maintenance and onset measures. However, this finding is not conclusive due to the limited data from the study 006.

Figure 23: The distribution of $AUC_{0\text{-}24}$ (µM*hr) at each dose (top), the mean ± SE of ΔWASO (middle) and the mean ± SE of ΔLPS (bottom). The data came from only 1st period of the study 006. The dotted horizontal lines on the top indicate the median $AUC_{0\text{-}24}$ at each dose: The median $AUC_{0\text{-}24}$ are 5 µM*hr, 6 µM*hr, 12 µM*hr and 21 µM*hr at 10mg, 20mg, 40mg and 80mg, respectively.





Somnolence

The results from the reviewer's safety analysis are presented in Figure 4. Being consistent with the sponsor's analysis result, the incidence of somnolence appears to increase as the residual concentration goes high. Given the same residual concentration non-elderly seems to have higher risk compared to elderly patients.

Number of correct responses in the Digital Symbol Substitution Test (DSST)

The reviewer also analyzed the data from digital symbol substitution test (DSST), which is one of objective psychometric measures.

Figure 5 presents the results from the analyses. In elderly patients dose dependent (30 mg vs 15 mg relative to placebo) decrease in DSST was observed.

Table 1, shows the proportion of patients who got impaired after suvorexant administration (Δ DSST <0). However, the magnitude of difference does not seem to be noticeable, and DSST score does not show clear concentration-dependent relationship either.

Table 1 displays the percent of patients who got worsened in DSST score compared to the baseline. Being consistent with the previous analysis, more elderly patients at high dose got impaired in DSST score than low dose at months 1 and 3 but there is little difference between two doses in non-elderly patients.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
WASO.primary.SAS	E-R analysis for WASO	
LPS.primary.SAS	E-R analysis for LPS	
AE.SAS	E-R analysis for somnolence	
DSST.SAS	E-R analysis for DSST	

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

/s/

HRISTINA DIMOVA
04/29/2013

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XINNING YANG
04/29/2013

VENKATESH A BHATTARAM
04/29/2013

YUXIN MEN
04/29/2013

MEHUL U MEHTA
04/30/2013