Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Suvorexant

Proprietary Product Name: Belsomra

Sponsor: Merck Sharpe and Dohme Australia Pty Ltd

First round evaluation report: 31 August 2013

Second round report: 2 January 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
AASM	American Academy of Sleep Medicine
AE	Adverse experience
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APAT	All Patients as Treated
APTS	All patients treated set
AUC	Area under the concentration-time curve
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to last observation
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
BZD	Benzodiazepine
CI	Confidence interval
CL	Clearance
C_{max}	Maximum concentration
COAD	Chronic obstructive airway disease
COPD	Chronic obstructive pulmonary disease
CRT	Choice Reaction Time
CSSRS	Columbia Suicide Severity Raring Scale
CV	Coefficient of variation
DBP	Diastolic Blood Pressure
DSCT	Digit Symbol Copy Test
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorder-Category IV-

Abbreviation	Meaning
	Text Revision
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
FAS	Full analysis set
FDR	False discovery rate
FSG	Fasting serum glucose
GCP	Good clinical practice
GI	Gastrointestinal
GMR	Geometric mean ratio
hCG	Human chorionic gonadotropin
HR	Heart rate
HRT	Hormone replacement therapy
IA	Interim analysis
IEC	Independent Ethics Committee
IM	Intramuscular
IN	Intranasal
IP	Intraperitoneal
IRB	Institutional Review Board
ISI	Insomnia Severity Index
IUD	Intrauterine device
IV	Intravenous
IVRS	Interactive Voice Response System
KSS	Karolinska Sleepiness Scale
LLOQ	Lower limit of quantitation
LOCF	Last observation carried forward

Abbreviation	Meaning
LPLV	Last patient last visit
LPS	Latency to persistent sleep
LREM	Latency to REM
LS means	Least-squares means
LSWS	Latency to slow wave sleep
MAR	Missing at random
MED	Minimal effective dose
MRM	Multiple reaction monitoring
MSE	Mean square error
msec	millisecond
MVAV	Motor Vehicle Accidents and Violations
NAW	Number of awakenings
NOA	Number of arousals
NREM	Non-REM
NSAID	Nonsteroidal anti-inflammatory drug
NSS_W_1	Number of stage shifts to wake or stage 1
NSSL	Number of shifts to lighter stages of sleep
OTC	Over the counter
PBO	Placebo
PSG	Polysomnography
PD	Pharmacodynamic
PDLOC	Predefined limits of change
PK	Pharmacokinetic
QIDS	Quick Inventory of Depressive Symptomatology
QTcB	Corrected QT interval, Bazets

Abbreviation	Meaning
QTcP	Population specific rate method of correcting QT interval
RBC	Red blood (cell) count
REM	Rapid eye movement
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard deviation
SDLP	Standard Deviation of Lateral Position
SDS	Sheehan Disability Scale
SE	Sleep efficiency
SEM	Standard error of the mean
siDMC	Standing internal data monitoring committee
sNAW	Subjective number of awakenings
SOL	Sleep Onset Latency
SRT	Simple Reaction Time
sTSO	Subjective time to sleep onset
sTST	Subjective total sleep time
SWA	Slow wave activity
sWASO	Subjective wake after sleep onset
SWS	Slow wave sleep
t½	Half-life
TIB	Time in bed
T_{max}	Time to maximum effect or concentration
TSO	Time to sleep onset
TST	Total Sleep Time
TTA	Total time awake

Abbreviation	Meaning
ULN	Upper limit of normal
VAS	Visual analog scale
Vss	Volume of distribution at steady state
WASO	Wake after sleep onset
WBC	White blood (cell) count

1. Clinical rationale

Insomnia is commonly reported as a symptom. The Sponsor argues that "Chronic insomnia affects about 10% to 30% of the total population (up to one-third of the adult population), with more than 50% of cases experiencing significant daytime consequences such as reduced energy, memory problems, and difficulty concentrating." The currently available treatments for insomnia are unsatisfactory because of the problems of tolerance, habituation and abuse. These agents induce sleep through global CNS depression by acting on the neurotransmitter GABA. Hence, there is a need for alternative treatments for insomnia.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 32 clinical pharmacology studies, including 25 that provided pharmacokinetic data and 15 that provided pharmacodynamic data.
- One population pharmacokinetic analysis.
- Two pivotal efficacy/safety studies.
- One dose-finding study.
- One long-term (12 month) /safety and efficacy study.
- Additional pooled analyses, *Integrated Summary of Efficacy*, *Integrated Summary of Safety*, and a tabulation of pooled safety data.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

The sponsor has stated that Good Clinical Practice (GCP) has been conformed to for each of the clinical studies included in the dossier.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Study P001
		Study P011
		Study P002
	Mass Balance	Study P012
		Study P018
	Multi-dose	Study P003
	Bioequivalence† - Single dose	Study P007
		Study P041
		Study P051
	Food effect	Study P020
		Study P042
PK in special populations	Target population § - Single dose[1]	
	Multi-dose[1]	
	Hepatic impairment	Study P017
	Renal impairment	Study P023
	Neonates/infants/children/adolescents	No data
	Elderly	Study P004
	Elderly	Study P027
	Japanese	Study P005
	Japanese	Study P022
Genetic/gender-related PK	Males versus females	Study P004
PK interactions	Ketoconazole	Study P008
	Combined Oral Contraceptive	Study P013

[1] Not conducted

PK topic	Subtopic	Study ID
	Midazolam	Study P015
	Digoxin	Study P016
	Warfarin	Study P024
	Paroxetine	Study P026
	Rifampin, diltiazem	Study P038
	Ethanol	Study P010
Population PK analyses	Healthy subjects	Study P018[2]

* Indicates the primary aim of the study.
† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Physicochemical characteristics of the active substance

The following information is derived from the Sponsor's summaries in Module 2.

Suvorexant (USAN adopted name, WHO rINN), also known as MK-4305, 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 chemical formula for suvorexant is $C_{23}H_{23}ClN_6O_2$ and the chemical name is 5-chloro-2-{(5R)-5-methyl-4-[5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl]-1,4-diazepan-1-yl}-1,3-benzoxazole. Suvorexant is a white to off-white powder that is insoluble in water, very slightly soluble in heptane, and soluble in methanol.

3.2.2. Pharmacokinetics in healthy subjects

3.2.2.1. Absorption

3.2.2.1.1. Sites and mechanisms of absorption

There were no studies addressing this issue.

3.2.2.2. Bioavailability

3.2.2.2.1. Absolute bioavailability

Absolute bioavailability decreased with increasing dose. Absolute bioavailability was estimated using a population pharmacokinetic model (Report 611). The mean (5th and 95th percentile) bioavailability for a 10 mg oral dose was 0.82 (0.74 to 0.89), for a 20 mg dose was 0.62 (0.55 to 0.69) for a 40 mg dose was 0.47 (0.41 to 0.53) and for an 80 mg dose was 0.37 (0.31 to 0.42).

[2] Erratum: Report 613

In a subsequent pooled analysis (Report 613), the Sponsor estimated bioavailability for an evening dose, using the 10 mg dose level as a reference, to be 83.9% for a 20 mg dose, 80.3% for a 30 mg, 69.9% for a 40 mg, and 52.0% for a 60/80-mg dose.

3.2.2.2.2. Bioavailability relative to an oral solution or micronised suspension

This was not addressed in the submission.

3.2.2.2.3. Bioequivalence of clinical trial and market formulations

Study P007 was conducted as part of formulation development. Three different potential Phase IIB formulations were tested against the early development formulation. The Sponsor elected to proceed with the P2 formulation into Phase IIB development because the PK profile was similar to the early development formulation, and it exhibited less variability than other potential formulations. In addition, the absorption was not influenced by food.

In Study P041 the Sponsor compared three formulations with the Phase 3 formulation. Formulation A was bioequivalent to formulation C (the reference, or Phase 3 formulation), and may also have been absorbed more rapidly as median T_{max} was 1.3 hours compared with 1.8 hours for the Phase 3 formulation.

3.2.2.2.4. Bioequivalence of different dosage forms and strengths

Study P051 compared the bioavailability of the 15 mg and 30 mg; and the 20 mg and 40 mg dose forms. The 15 mg and 30 mg dose forms were bioequivalent: GMR (95% CI) 2x15mg/30mg for $AUC_{0\text{-}inf}$ was 99.66 (96.52 to 102.91) % and for C_{max} was 108.74 (101.10 to 116.95) %. The 20 mg and 40 mg dose forms were bioequivalent: GMR (95% CI) 2x15mg/30mg for $AUC_{0\text{-}inf}$ was 102.33 (98.80 to 105.99) % and for C_{max} was 96.58 (90.96 to 102.55) %.

3.2.2.2.5. Bioequivalence to relevant registered products

This was not relevant to the present application.

3.2.2.2.6. Influence of food

In comparison with the fasted state, following a high fat breakfast, for the suvorexant 40 mg FMI tablet, the geometric mean ratio (90% CI) fed/fasted for $AUC_{0\text{-}inf}$ was 0.98 (0.91 to 1.07) and for C_{max} was 1.09 (0.90 to 1.33). However, T_{max} was increased in the fed state in comparison with the fasted: median (range) 3.0 (1.0 to 6.0) hours for fed compared with 2.0 (1.0 to 4.0) hours for fasted.

In Japanese subjects in comparison with the fasted state, following a standard Japanese breakfast, for the suvorexant 40 mg FMI tablet, the geometric mean ratio (90% CI) fed/fasted for $AUC_{0\text{-}inf}$ was 1.10 (1.02 to 1.19) and for C_{max} was 1.23 (1.02 to 1.49). T_{max} was increased in the fed state in comparison with the fasted: median (range) 3.0 (1.0 to 6.0) hours for fed compared with 1.5 (1.0 to 3.0) hours for fasted.

In Study P001, at the 10 mg dose level AUC was similar but C_{max} was decreased in the fed state: GMR (90% CI) fed/fasted for $AUC_{0\text{-}inf}$ 0.93 (0.79 to 1.09) and for C_{max} 0.55 (0.45 to 0.66).

In young healthy Japanese males there was an increase overall exposure in the fed state at the 10 mg dose level, but there was a decrease in C_{max} (Study P005). GMR (90% CI) fed/fasted for $AUC_{0\text{-}inf}$ 1.34 (1.15 to 1.56) and for C_{max} 0.88 (0.73 to 1.05).

3.2.2.2.7. Dose proportionality

In Study P018 there appeared to be dose proportionality for AUC and C_{max} in the intravenous dosing range of 5 mg to 30 mg, and in the oral dosing range of 10 mg to 80 mg.[3]

[3] Erratum: Dose proportionality was not fully demonstrated in P018.

In Study P001 dose proportionality was not demonstrated over the dose range 4 mg to 120 mg. The slope estimate (95% CI) was 0.78 (0.74 to 0.83) for $AUC_{0\text{-}inf}$ and 0.67 (0.61 to 0.74) for C_{max}, ie AUC and C_{max} decreased relative to increasing dose.

In Study P011 dose proportionality was not observed over the dose range 120 mg to 240 mg in females and 150 mg to 240 mg in males, with little incremental absorption in the higher dose levels.

In Study P005 in young healthy Japanese males, dose proportionality could not be concluded over the dose range 4 mg to 100 mg. There was decreasing exposure relative to dose.

In Study P002, in healthy male volunteers, single oral doses of suvorexant did not exhibit dose proportionality in the 10 mg to 100 mg range during evening administration. There was decreased exposure relative to dose as the dose increased.

In Study P022 in healthy volunteers the PK parameters for suvorexant were not dose proportional in the dose range 60 mg to 240 mg, with decreasing exposure relative to dose with increasing dose size.

3.2.2.2.8. Bioavailability during multiple-dosing

In Study P003 the single dose and multiple dose PK parameters were not dose proportional in the range of 10 mg to 100 mg once daily for 14 days. Steady state was reached in 3 days. The accumulation ratio for AUC over 14 days ranged from 1.27 for the 10 mg dose to 1.60 for the 80 mg dose. There was no apparent autoinduction of metabolism.

In Study 013, in healthy young females, a daily dose of 40 mg suvorexant resulted in an accumulation ratio (95% CI) over 18 days of 1.53 (1.43 to 1.65) for AUC0-24 and 1.36 (1.15 to 1.60) for C_{max}. Time to steady state was approximately 3 days.

3.2.2.2.9. Effect of administration timing

In Study P001, at the 76 mg dose level AUC was similar but C_{max} was decreased with evening compared to morning dosing: GMR (90% CI) PM/AM for $AUC_{0\text{-}inf}$ 1.00 (0.84 to 1.18) and for C_{max} 0.64 (0.52 to 0.78).

In young healthy Japanese males there was no difference in overall exposure between morning and evening dosing at the 76 mg dose level, but there was a decrease in C_{max} (Study P005). GMR (90% CI) PM/AM for $AUC_{0\text{-}inf}$ 1.05 (0.91 to 1.22) and for C_{max} 0.71 (0.59 to 0.86).

3.2.3. Distribution

3.2.3.1. Volume of distribution

In Study P018 in the intravenous dose range 5 mg to 30 mg the Vss ranged from 36.5 L to 57.33 L.

3.2.3.2. Plasma protein binding

The plasma protein binding of suvorexant is approximately 99%. In Study P017 the mean (SD) fraction unbound was 0.77 (0.18) % in subjects with hepatic failure and 1.01 (0.43) % in healthy volunteers.

3.2.4. Metabolism

3.2.4.1. Interconversion between enantiomers

There were no clinical data regarding interconversion between enantiomers.

3.2.4.2. Sites of metabolism and mechanisms / enzyme systems involved

Suvorexant undergoes extensive hepatic metabolism involving CYP3A4, CYP2C19 and glucuronidation.

3.2.4.3. Non-renal clearance

CL ranged from 48.60 to 80.62 mL/min, and apparent terminal half-life from 8.9 hours to 13.5 hours.

3.2.4.4. Metabolites identified in humans

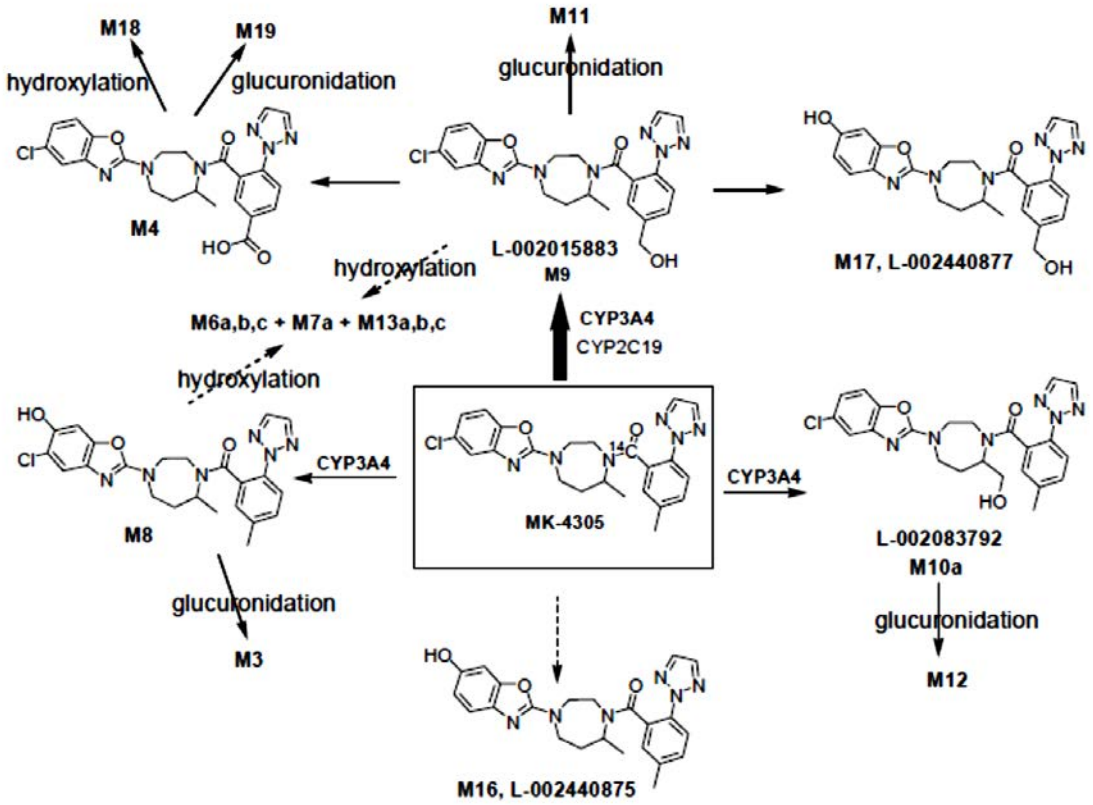
3.2.4.4.1. Active metabolites

Suvorexant does not appear to have active metabolites.

3.2.4.4.2. Other metabolites

The proposed metabolic pathways are displayed in Figure 1. In Study P012 the primary components in plasma were suvorexant (39.1%[4] of circulating suvorexant material) and the M9 metabolite (36.5%). The primary metabolites were the M4 (21.1% of dose), M18 (10.6%), M9 (9.5%) and M10a (9.2%).

Figure 1. Proposed Major Metabolic Pathways of MK-4305



*Bold arrow indicates major pathway and dotted arrows indicate tentative pathways

3.2.4.5. Pharmacokinetics of metabolites

In Study P003 the AUC and C_{max} for the M9 metabolite were not dose proportional in the dose range 10 mg to 100 mg, either as single dose or multiple daily dose over 14 days, with less than expected exposure with increasing dose. There was no accumulation of the M9 metabolite over 14 days.

[4] Erratum: 30.1%

3.2.4.6. Consequences of genetic polymorphism

There were no clinical data with regard to pharmacogenetics.

3.2.5. Excretion

3.2.5.1. Routes and mechanisms of excretion

Suvorexant undergoes extensive hepatic metabolism with biliary and renal excretion of its metabolites.

3.2.5.2. Mass balance studies

In the mass balance study (Study P012) the total recovery of radioactivity was 90% in urine and faeces, with 82% recovered in the first 144 hours post-dose. The major route of excretion was faecal (66% of dose recovered). Recovery in urine was 23% of dose. Unchanged (parent) suvorexant was not detected in urine and only a trace was detected in faeces.

3.2.5.3. Renal clearance

There is no significant renal clearance of parent suvorexant.

3.2.6. Pharmacokinetics in the target population

The target population in the clinical trials was otherwise healthy patients with primary insomnia. Hence, the healthy volunteer PK data is applicable to this population.

3.2.7. Pharmacokinetics in other special populations

3.2.7.1. Pharmacokinetics in subjects with impaired hepatic function

There was no effect of moderate hepatic impairment on the PK of suvorexant or the M9 metabolite. In Study P017 there was no difference in PK parameters between subjects with moderate hepatic impairment and healthy volunteers. The GMR (90% CI) hepatic insufficiency/healthy was 1.03 (0.74 to 1.43) for $AUC_{0\text{-}inf}$ and 0.94 (0.68 to 1.29) for C_{max}. Mean (SD) $AUC_{0\text{-}inf}$ for M9 in subjects with moderate hepatic failure was 17.24 (6.53) μM•hour and in healthy volunteers was 12.50 (2.32) μM•hour. Mean (SD) C_{max} for M9 in subjects with moderate hepatic failure was 0.517 (0.256) μM and in healthy volunteers was 0.594 (0.127) μM.

3.2.8. Pharmacokinetics in subjects with impaired renal function

In severe renal impairment (creatinine clearance ≤30 mL/min) there was a 22% increase in $AUC_{0\text{-}inf}$ compared with matched healthy controls: GMR (90% CI) severe renal failure/healthy 1.22 (0.93 to 1.60) (Study P023). There was a 15% increase in C_{max}: GMR (90% CI) severe renal failure/healthy 1.15 (0.98 to 1.34). For M9 there was a 12% decrease in $AUC_{0\text{-}inf}$ 0.88 (0.71 to 1.09).

3.2.9. Pharmacokinetics according to age

Overall exposure was similar for healthy elderly males compared with young males, but C_{max} was 28% lower. Healthy elderly males from Study P004 were compared with healthy young males from Study P001, and the dose normalized GMR (90% CI) for $AUC_{0\text{-}inf}$ was 0.92 (0.71 to 1.19) and for C_{max} was 0.72 (0.58 to 0.89).

In Study P027 in healthy elderly volunteers there was no indication of time dependent changes in the PK of suvorexant. For suvorexant 40 mg orally after 7 days the mean (95% CI) for $AUC_{0\text{-}inf}$ was 17.88 (15.25 to 20.96) and for C_{max} was 1.336 (1.132 to 1.575). For suvorexant 40 mg over 7 days the accumulation ratio (90% CI) for $AUC_{0\text{-}inf}$ was 1.34 (1.26 to 1.42) and for C_{max} was 1.17 (1.04 to 1.32). For suvorexant 30 mg orally after 21 days the mean (95% CI) for $AUC_{0\text{-}inf}$ was 14.93 (12.94 to 17.21) and for C_{max} was 1.133 (0.960 to 1.337). For suvorexant 40 mg over 21 days the accumulation ratio (90% CI) for $AUC_{0\text{-}inf}$ was 1.45 (1.35 to 1.56) and for C_{max} was 1.21 (1.08 to 1.35).

A pooled analysis (Study 616) estimated that at 9 hours post-dose the plasma concentration in an elderly subject following a 30 mg dose would be similar to that in a non-elderly subject following a 40 mg dose.

3.2.10. Pharmacokinetics related to genetic factors

No data were presented relating to pharmacogenetic factors.

3.2.11. Gender Effects on Pharmacokinetics

In Study P004, the mean $AUC_{0\text{-}inf}$ was 55% higher in healthy elderly females compared to healthy elderly males, and C_{max} was 29% higher: GMR (90% CI) 1.29 (1.08 to 1.54)[5] for $AUC_{0\text{-}inf}$ and 1.29 (1.08 to 1.54) for C_{max}. Exposure to the M9 metabolite was also 30% greater in the females: GMR (90% CI) 1.38 (1.05 to 1.81) for $AUC_{0\text{-}inf}$ and 1.05 (0.92 to 1.19) for C_{max}.

3.2.12. Pharmacokinetic interactions

3.2.12.1. Pharmacokinetic interactions demonstrated in human studies

In Study P008, co-administration of ketoconazole with suvorexant increased $AUC_{0\text{-}inf}$ by 179% and C_{max} by 23%. The GMR (90% CI) suvorexant + ketoconazole / suvorexant was 2.79 (2.35 to 3.31) for $AUC_{0\text{-}inf}$, and 1.23 (1.05 to 1.44). For the M9 metabolite, ketoconazole increased $AUC_{0\text{-}inf}$ by 80% and decreased C_{max} by 39%. The GMR (90% CI) suvorexant + ketoconazole / suvorexant for M9 was 1.80 (1.64 to 1.98) for $AUC_{0\text{-}inf}$, and 0.71 (0.64 to 0.80). This indicates significant metabolism of suvorexant by CYP enzymes.[6]

In healthy young females multiple daily dose suvorexant 40 mg did not significantly affect the PK of the combined oral contraceptive pill (Study P013). For ethinyl estradiol the GMR (90% CI) was 1.07 (0.99 to 1.16) for $AUC_{0\text{-}inf}$ and 0.94 (0.83 to 1.06) for C_{max}. For norelgestromin the GMR (90% CI) was 1.16 (1.11 to 1.20) for $AUC_{0\text{-}inf}$ and 1.08 (0.95 to 1.23) for C_{max}.

At steady state suvorexant exhibits weak inhibition of CYP3A4. In Study P015 a single dose of suvorexant did not alter the PK of midazolam but at steady state suvorexant increased AUC by 47%. For single dose suvorexant GMR (90% CI), midazolam + suvorexant / midazolam, for $AUC_{0\text{-}inf}$ was 0.96 (0.84 to 1.08) and for C_{max} was 0.83 (0.72 to 0.95). For steady state suvorexant GMR (90% CI), midazolam + suvorexant / midazolam, for $AUC_{0\text{-}inf}$ was 1.47 (1.30 to 1.67) and for C_{max} was 1.23 (1.07 to 1.41).

In Study P016, exposure to digoxin was increased with co-administration of suvorexant, but this was not due to altered renal clearance. The GMR (90% CI) digoxin + suvorexant / suvorexant was 1.27 (1.12 to 1.43) for $AUC_{0\text{-}last}$, and 1.21 (1.05 to 1.40) for C_{max}. However, the GMR (90% CI) digoxin + suvorexant / suvorexant for renal clearance of digoxin was 0.94 (0.82 to 1.08). The fraction of digoxin dose excreted unchanged in the urine was 23.04% when co-administered with suvorexant and 26.02% when administered alone.

Suvorexant had no effect on the PK parameters for either *R*-warfarin or *S*-warfarin (Study P024). The GMR (90% CI) warfarin + suvorexant / warfarin for *R*-warfarin for $AUC_{0\text{-}last}$ was 0.99 (0.95 to 1.04) and for C_{max} was 0.95 (0.87 to 1.03). The GMR (90% CI) warfarin + suvorexant / warfarin for *S*-warfarin for $AUC_{0\text{-}last}$ was 0.99 (0.95 to 1.04) and for C_{max} was 0.95 (0.86 to 1.05).

Paroxetine had no significant effect on the PK parameters for suvorexant (Study P026). The GMR (90% CI) suvorexant + paroxetine / suvorexant was 0.97 (0.92 to 1.03) for $AUC_{0\text{-}24}$ and 1.05 (0.96 to 1.15) for C_{max}.

Exposure to suvorexant was greatly decreased with rifampin co-administration (Study P038). The GMR (90% CI) suvorexant + rifampin / suvorexant was 0.12 (0.11 to 0.14) for $AUC_{0\text{-}inf}$, and

[5] Erratum: 1.55 (1.17 to 2.06)
[6] Erratum: This indicates significant CYP-mediated inhibition, leading to a higher plasma concentration of suvorexant.

0.36 (0.31 to 0.42) for C_{max}. Exposure to the M9 metabolite was also decreased: GMR (90% CI) suvorexant + rifampin / suvorexant was 0.23 (0.21 to 0.25) for $AUC_{0\text{-}inf}$, and 0.77 (0.70 to 0.86) for C_{max}.

Exposure to suvorexant was doubled with diltiazem co-administration (Study P038). The GMR (90% CI) suvorexant + diltiazem / suvorexant was 2.05 (1.82 to 2.30) for $AUC_{0\text{-}inf}$, and 1.22 (1.09 to 1.36) for C_{max}. Exposure to the M9 metabolite was also increased: GMR (90% CI) suvorexant + diltiazem / suvorexant was 1.36 (1.27 to 1.47) for $AUC_{0\text{-}inf}$, and 0.85 (0.79 to 0.92) for C_{max}.

In Study P010 ethanol had no significant effect upon the PK parameters for suvorexant. The GMR (90% CI) suvorexant + ethanol / suvorexant for suvorexant were 1.09 (1.04 to 1.16) for $AUC_{0\text{-}inf}$ and 1.05 (0.98 to 1.12) for C_{max}. The GMR (90% CI) suvorexant + ethanol/ethanol for ethanol were 0.99 (0.95 to 1.03) for $AUC_{0\text{-}last}$ and 0.99 (0.95 to 1.03) for C_{max}. Suvorexant had no significant effect on the PK of ethanol: median (range) ratio for $AUC_{0\text{-}last}$ 0.95 (0.84 to 1.36) and for C_{max} 0.96 (0.80 to 1.34).

3.3. Evaluator's overall conclusions on pharmacokinetics

Suvorexant was well absorbed orally but bioavailability decreased with increasing dose. The mean (5^{th} and 95^{th} percentile) bioavailability for a 10 mg oral dose was 0.82 (0.74 to 0.89), for a 20 mg dose was 0.62 (0.55 to 0.69) for a 40 mg dose was 0.47 (0.41 to 0.53) and for an 80 mg dose was 0.37 (0.31 to 0.42). The clinical trial formulations were bioequivalent to the FMI. The 15 mg and 30 mg dose forms were bioequivalent. The 20 mg and 40 mg dose forms were bioequivalent.

Food did not significantly affect exposure to suvorexant. AUC was similar fasted versus fed, but C_{max} was decreased by food.[7] Suvorexant PK were not dose-proportional[8], as exposure decreased with increasing dose. AUC was similar between morning and evening dosing but C_{max} was decreased in the evening.

Time to steady state was approximately 3 days. Suvorexant metabolism was not autoinduced. In the intravenous dose range 5 mg to 30 mg the Vss ranged from 36.5 L to 57.33 L. The plasma protein binding of suvorexant is 99%. The mean (SD) fraction unbound was 0.77 (0.18) % in subjects with hepatic failure and 1.01 (0.43) % in healthy volunteers. CL ranged from 48.60 to 80.62 mL/min, and apparent terminal half-life from 8.9 hours to 13.5 hours. Suvorexant undergoes extensive hepatic metabolism with biliary and renal excretion of its metabolites. The enzymes involved include CYP3A4, CYP2C19 and glucuronidation.

The PK of suvorexant was not significantly altered in either moderate hepatic impairment or severe renal impairment. At 9 hours post-dose the plasma concentration in an elderly subject following a 30 mg dose was similar to that in a non-elderly subject following a 40 mg dose.

Inhibition of CYP enzymes by ketoconazole increased exposure to suvorexant by more than double. Hence, in combination with drugs that inhibit CYP3A4 and CYP2C19 the dose of suvorexant will need to be reduced. Verapamil co-administration also increased exposure to suvorexant to a similar extent .[9]

[7] Erratum: Small increase in C_{max} with food.
[8] Erratum: Suvorexant PK increases in a less than dose proportional manner.
[9] Erratum: Diltiazem co-administration also increased exposure to suvorexant by more than double, albeit to a lesser extent than co-administrated ketoconazole (GMR 2.05 compared with GMR 2.79 (ketoconazole), respectively).

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 2. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on sleep	Study P003
		Study P011
		Study P005
		Study P002
Secondary Pharmacology	Effect on QTc	Study P022
	Abuse Potential	Study P025
	Effect on Driving Ability	Study P035
		Study P039
	Respiratory Safety: healthy	Study P040
	Respiratory Safety: COPD	Study P031
	Respiratory Safety: OSA	Study P036
Gender other genetic and Age-Related Differences in PD Response	Effect of age	Study P004
PD Interactions	Warfarin	Study P024
	Paroxetine	Study P026
	Ethanol	Study P010
Population PD and PK-AE analyses	Healthy subjects[10]	Report 615

* Indicates the primary aim of the study.
‡ And adolescents if applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

[10] Erratum: Phase II/III

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

4.2.1. Mechanism of action

From the in-vitro studies, suvorexant is a highly selective reversible high affinity orexin receptor antagonist at OX1R (Ki 0.55 nM) and OX2R (Ki 0.35 nM) receptors. The orexin neuropeptide signalling system is a central promoter of wakefulness. Orexin producing neuronal cell bodies are localised specifically in the hypothalamus and project to the wakefulness mediating neurons of the brain.

4.3. Pharmacodynamic effects

4.3.1. Primary pharmacodynamic effects

In Study P003, conducted at the dose range 10 mg to 100 mg, there was a dose dependent decrease in alertness that lasted from 2 to 12 hours post dose for the 40 mg dose level, but there was carry-over effect during the day for the 80 mg and 100 mg dose levels. There was no consistent change, or dose effect, in contentedness or calmness. There was also a dose dependent decrease in Karolinska Sleepiness Scale (KSS) that lasted from 2 to 12 hours post dose for the 40 mg dose level, but there was also carry-over effect during the day for the 80 mg and 100 mg dose levels. There was no significant effect on DSST, Immediate Word Recall or Delayed Word Recall.

In Study P011, the dose range 150 mg to 240 mg was investigated in males and 120 mg to 240 mg in females. Between 1.5 hours and 4 hours post-dose, Choice Reaction Time increased in a dose dependent manner; and Divided Attention Test score decreased in a dose dependent manner. Visual analogue score for drowsiness also increased in a dose dependent manner, with drowsiness persisting in the 240 mg group for up to 24 hours. There was a dose dependent increase in KSS that persisted for up to 24 hours in the 240 mg group in males, and at all the dose levels in females.

In Study P005 in young healthy Japanese males, there was a dose dependent decrease in alertness that persisted for up to 24 hours at the higher dose levels. There was no effect on calmness or contentedness. For KSS there was also a dose dependent increase but there was also an unexpected increase after 12 hours in the PM placebo group.

In Study P002 the effects on sleep of single doses of suvorexant were studied in the dose range 10 mg to 100 mg. There was little effect on SWA, even up to 100 mg. However, the duration of REM2 increased in a dose dependent manner. Sleep latency decreased significantly in a dose dependent manner up to 100 mg. WASO improved with suvorexant but not in a dose dependent manner. Sleep efficiency also increased in a dose dependent manner up to 100 mg. CRT, DSST and SRT all deteriorated in a dose dependent manner.

4.4. Secondary pharmacodynamic effects

4.4.1. Effects on QT prolongation

Study P022 was a thorough QT study performed to a maximum dose level of 240 mg suvorexant. The 90% CI for increase in QTcF and QTcP from baseline relative to placebo were less than 10 msec for suvorexant. The maximum dose of suvorexant used in the study was reduced from 240 mg to 150 mg because of issues with tolerability. The positive control was moxifloxacin 400 mg, which showed a maximum mean (90% CI) QTcF change from baseline relative to placebo of 11.06 (8.99 to 13.16) msec. The maximum increase in QTcF for the high dose suvorexant (240 mg/150 mg) was mean (90% CI) (change from baseline relative to placebo) 4.13 (2.03 to 6.23) msec at 8 hours post dose. The maximum increase in QTcP for the

high dose suvorexant (240 mg/150 mg) was mean (upper 90% CI) (change from baseline relative to placebo) 3.17 (5.33) msec at 8 hours post dose.

4.4.2. Abuse potential

In Study P025 a single dose of suvorexant in the dose range 40 mg to 150 mg had significantly greater abuse potential compared with placebo, using the Drug Liking VAS. However, at the highest dose of suvorexant (150 mg) there was lesser abuse potential compared with the higher dose of zolpidem (30 mg). For other pharmacodynamic measures of abuse potential, suvorexant had greater abuse potential than placebo. There was no significant difference for abuse potential compared with zolpidem except for less High in comparison with zolpidem 30 mg, less effects comparable to Morphine Benzedrine Group (MBG) and greater drowsiness for suvorexant compared with zolpidem.

4.4.3. Driving ability

Suvorexant 20 mg and 40 mg resulted in significant impairment in driving performance the day after evening dosing. In Study P035, for Standard Deviation of Lateral Position (SDLP) there was an increase in comparison to placebo for all the active treatments at both Day 1 and Day 9. The effect for suvorexant 40 mg was similar to that for zopiclone 7.5 mg. For Car Driving SDS there was significant impairment for all the active treatments at Day 1, but only for suvorexant 40 mg at Day 9. There was significant impairment of word recall time at Day 1 for suvorexant 40 mg and zopiclone 7.5 mg, but not at Day 9. Body sway, eyes open, was significantly impaired at Day 2 for all three active treatments relative to placebo at Day 2 but not at Day 9. The Driving Instructor VAS for driving quality indicated significant impairment for both doses of suvorexant at Day 2, but only the 40 mg dose at Day 9. The Driving Instructor VAS for sedation demonstrated impairment for suvorexant 20 mg and 40 mg at Day 2 and Day 9. There was no significant impairment in driving quality or sedation for zopiclone.

In elderly subjects suvorexant at the 15 mg and 30 mg dose levels did not significantly impair driving performance. In Study P039, in elderly subjects, neither the suvorexant 15 mg nor the 30 mg doses resulted in significant impairment in SDLP or Car Driving SDS at Day 2 or Day 9. Zopiclone 7.5 mg resulted in significant impairment in both parameters at both Day 2 and Day 9. There were no significant effects of suvorexant on word learning tests, body sway or Driving Instructor VAS.

4.4.4. Respiratory safety

Suvorexant did not impair respiratory safety during sleep at doses up to 150 mg in healthy volunteers. In Study P040 there was no impairment of mean SaO_2 during total sleep time, during wake time, NREM or REM. There was no impairment of the apnoea-hypopnea index.

In subjects with chronic pulmonary obstructive disease there was no significant impairment of sleep safety with suvorexant. In Study P032, on Day 1 there was no clinically or statistically significant difference between suvorexant and placebo for mean $Sa0_2$ during total sleep time, NREM, REM or wake time; percentage of total sleep time with $Sa0_2$ <90% or 85%, or in apneoa-hypopnea index. On Day 4, there was no clinically or statistically significant difference between suvorexant and placebo for mean $Sa0_2$ during total sleep time, NREM or REM; or percentage of total sleep time with $Sa0_2$ <90%. During wake time $Sa0_2$ was higher with suvorexant. However, the percentage of total sleep time with $Sa0_2$ <85% was higher with suvorexant: LS mean (95% CI) 0.32 (0.06 to 0.58) % compared with 0.01 (-0.26 to 0.28) %; LS mean difference (95% CI) suvorexant – placebo 0.32 (0.00 to 0.63) %. The apnoea-hypopnea index was higher with suvorexant than placebo: LS mean (95% CI) 8.27 (5.71 to 10.84) % compared with 6.22 (3.61 to 8.83) %; LS mean difference (95% CI) suvorexant – placebo 2.05 (0.33 to 3.77) %.

Respiratory safety was studied in subjects with mild to moderate obstructive sleep apnoea in Study P036. Apnoea-hypopnea index was higher in the suvorexant group at Day 4: LS mean (95% CI) 17.07 (13.30 to 20.84) compared with 14.41 (10.61 to 18.22); LS mean difference

(90% CI) 2.66 (0.22 to 5.09). There was no significant difference in mean SaO_2 during total sleep time, NREM, REM, or waking; or in the percentage of total sleep time that SaO_2 was <90% or <85%. There was no difference between the groups in any of the respiratory safety parameters at Day 1.

4.4.5. Time course of pharmacodynamic effects

The Sponsor performed a pooled analysis of the PKPD relationship between next day plasma concentrations of suvorexant and somnolence (Study 615). This study estimated a rate of next-day somnolence of 7.9% with 20 mg, 10.6% with 40 mg and 14.2% with the 80 mg dose level. The study estimated that elderly subjects would have similar rates of somnolence and fatigue to non-elderly subjects.

4.4.6. Relationship between drug concentration and pharmacodynamic effects

The plasma concentration at 9 hours post dose correlated with next day somnolence.

4.4.7. Genetic-, gender- and age-related differences in pharmacodynamic response

In Study P004, at a 16 mg single dose level, in the elderly female volunteers there was a decrease in alertness VAS at 2 hours post-dose, but no significant effect for the males. There were no significant changes in calmness or contentedness VAS. For KSS there was also an increase in sleepiness compared to placebo, but not for the male group. There was no change in Digit Symbol Substitution Test (DSST). There was an impairment in Power of Attention but not in Continuity of Attention, Quality of Working Memory, Quality of Episodic Memory or Speed of Memory.

In elderly subjects, suvorexant increased body sway, eyes open, at 1.5 hours post dose compared with placebo but to a lesser extent than zolpidem 5 mg (Study P021). At 1.5 hours post dose, there was a significant increase in body sway, eyes open, in comparison with placebo of approximately 50%: GMR (95% CI) suvorexant/placebo 1.49 (1.04 to 2.14). There was lesser increase compared with zolpidem: GMR (95% CI) suvorexant/zolpidem 0.76 (0.53 to 1.08). There was no significant difference compared to placebo for body sway, eyes closed. Total reaction time increased in the suvorexant group at 1.5 hours post dose by LS mean (95% CI) 67.91 (24.11 to 111.71) msec compared to placebo and 62.15 (17.13 to 107.18) msec compared to zolpidem. There were no differences between the treatments for immediate word recall, or delayed word recall. There were no significant differences in any of the parameters at 4 or 8 hours post dose.

4.4.8. Pharmacodynamic interactions

Suvorexant had no clinically significant effect on the PD parameters for warfarin (Study P024). The GMR (90% CI) warfarin + suvorexant / warfarin for INR $AUC_{0\text{-}168\ hours}$ was 1.06 (1.03 to 1.04) and for IMR_{max} was 1.09 (1.05 to 1.14). Hence, there may be a small, but not clinically significant, increase in INR with co-administration of suvorexant with warfarin.

In Study P026 there was an increase in digit reaction time with suvorexant that increased slightly with paroxetine co-medication: LS mean (90% CI) suvorexant + paroxetine – suvorexant alone 3.58 (-9.08 to 16.23). This additive effect would not be clinically significant, and was not statistically significant. There was no significant effect on word recall or digit substitution test.

In Study 010 suvorexant and alcohol exhibited a significant additive effect on impairment in cognitive function that lasted for up to 9 hours post-ingestion. For digit reaction time, targets detected correctly, words correctly recalled, numeric working memory sensitivity index and alertness there was significant additive impairment.

4.5. Evaluator's overall conclusions on pharmacodynamics

The time course of single dose suvorexant was examined in four PD studies at doses up to 240 mg. There did not appear to be persistence of effect beyond 8 hours for the 10 mg dose level, some persistence for the 20 mg and definite persistence for the 40 mg. The rate of next-day somnolence was estimated to be 7.9% with 20 mg, 10.6% with 40 mg and 14.2% with the 80 mg dose level. At high doses (>100 mg) the effects persisted for up to 24 hours. In a thorough QTc study at doses up to 240 mg (maximum tolerated) there was no QTc prolongation of regulatory concern. There was lesser abuse potential compared with zolpidem. There was significant next day driving impairment with suvorexant, similar to that for zopiclone, in non-elderly subjects but no significant impairment in elderly subjects. Suvorexant did not impair sleep safety in normal volunteers, subjects with chronic obstructive pulmonary disease or subjects with obstructive sleep apnoea. Suvorexant and alcohol exhibited a significant additive effect on impairment in cognitive function that lasted for up to 9 hours post-ingestion.

5. Dosage selection for the pivotal studies

5.1. Study P006

Study P006 was a multicentre, randomised, double blind, placebo controlled, two period adaptive, crossover polysomnography study to evaluate the safety and efficacy of suvorexant in subjects with primary insomnia. The study was conducted at 41 centres from November 2008 to December 2009.

The inclusion criteria included:

- Male or female between 18 and <65 years of age
- DSM-IV-TR diagnosis of Primary Insomnia based on the investigator's judgment and the patient's sleep history as assessed on the Sleep Diagnostic Interview/Sleep History
- Completed at least 6 years of formal education; obtains a score 6th grade level on Reading Subtest of Wide Range Achievement Test Version 4 (WRAT-4) at screening, or a comparable measure approved by Sponsor
- Good physical and mental health
- Total sleep time of ≤6.5 hours on at least 3 out of 7 nights each week within the 4 weeks prior to Visit 1, when not medicated on a hypnotic agent
- Sleep latency of≥30 minutes on at least 3 out of 7 nights each week within the 4 weeks prior to Visit 1, when not medicated on a hypnotic agent
- ≥1 hour of wakefulness after sleep onset
- 6.5 to 9 hours nightly in bed
- Regular bedtime between 9 PM (21:00) and 12 AM (00:00)
- Willing to refrain from napping
- Willing to limit alcohol to 2 drinks a day, at least 3 hours before going to bed on non-PSG visit days, and refrains from drinking alcohol on all PSG visits and at least 24 hours prior to a PSG visit. (A drink is defined as a 12-ounce bottle/can of beer (~14 grams alcohol) or a 4-ounce glass of wine (~12 grams alcohol) or 1 ounce of liquor (80 proof or 40 % alcohol, ~9 grams alcohol).)

- Willing to limit caffeine consumption to 5 standard 6-ounce cups of caffeinated beverages a day, or 600 mg caffeine, avoid caffeine after 4 PM (16:00) on non-PSG nights, and avoid caffeine after 1 PM (13:00) on PSG visits
- Female patients of reproductive potential are non-pregnant and agree to remain abstinent or to use appropriate double barrier contraception
- At screening the subject must also have LPS >20 minutes and WASO >45 minutes
- At Baseline the subject has LPS >20 minutes at both Screening and Baseline and a mean WASO 60 minutes on the combined Screening and Baseline nights, where neither night is 45 minutes.

The exclusion criteria included:

- History or current evidence of any condition, therapy, lab abnormality or other circumstances that might confound the results of the study
- History of a neurological disorder, including but not limited to seizure disorder, epilepsy, stroke, transient ischemic attack, multiple sclerosis, cognitive impairment, significant head trauma with sustained loss of consciousness, or classical migraine headaches in the last 10 years
- History within the past 6 months prior or current evidence of a clinically significant cardiovascular disorder, including, but not limited to: left ventricular hypertrophy, mitral valve prolapse, acute coronary syndrome, unstable angina, congestive heart failure (e.g., ejection fraction (EF) <40%), cardiogenic syncope, or symptomatic arrhythmia
- ECG clinically significant AV conduction disturbance (e.g., second or third degree AV block), sick sinus syndrome, bradycardia (resting pulse <40), accessory bypass tract (e.g., Wolff-Parkinson-White)
- ECG or physical exam a history or current evidence of long QT syndrome, Torsades de pointe, or a QTc interval of >450 msec
- SBP >160 mmHg, DBP >100 mmHg or pulse rate >100 beats/min
- Patient is taking, or plans to take, one or more of the following medications (non-inclusive), within the specified washout periods:
  - Clinically relevant CYP3A4 Inhibitors and Inducers: 4 weeks
  - Centrally acting anticholinergics or antihistamines: 2 weeks
  - Melatonin: 2 weeks
  - Antidepressants: 2 weeks
  - Fluoxetine: 4 weeks
  - Anxiolytics: 2 weeks
  - Benzodiazepines: 2 weeks or 5 t½ lives (which ever is longer)
  - Hypnotics: 2 weeks or 5 t½ lives (which ever is longer)
  - Any CNS depressants: 2 weeks
  - Over-the-counter medications that could affect sleep (e.g., kava-kava, valerian, Benadryl [diphenhydramine] St. John's wort): 2 weeks
  - Stimulants: 2 weeks
  - Diet pills: 2 weeks
  - Antihistamines (sedating): 2 weeks

- Positive prestudy urine drug screen
- Active Axis I or II disorder as defined in the DSM-IV-TR and as assessed by the Mini International Neuropsychiatric Interview, other than Primary Insomnia
- Evidence of ongoing depression as determined by a score 20 on the Quick Inventory of Depressive Symptomatology – Self Report Scale (QIDS-SR16), or scores 2 on the QIDS-SR16 suicide item #12, or in the judgment of the investigator the patient is impaired, suicidal or otherwise in such a way as to be unable to complete the study procedures in a safe and appropriate fashion
- History of substance abuse or dependence (including alcohol, marijuana, hypnotics, and drugs of abuse, but excludes nicotine dependence)
- History of transmeridian travel (across >3 time zones) or shift work (defined as permanent night shift or rotating day/night shift work) within the past 2 weeks or anticipates needing to travel (across >3 time zones) at any time during the study
- Subject consumes the equivalent of >15 cigarettes a day, and the Primary Investigator confirms that the patient's sleep disturbance is in part the result of this consumption and the patient is unable to refrain from smoking during the night
- History of any of following conditions: narcolepsy, cataplexy, circadian rhythm sleep disorder, parasomnia (including nightmare disorder, sleep terror disorder, sleepwalking disorder, and REM behaviour disorder), sleep-related breathing disorder, periodic limb movement disorder, or restless legs syndrome
- History of malignancy ≤5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Melanoma, leukaemia, lymphoma and myeloproliferative disorders of any duration are excluded
- History of uncontrolled diabetes as defined by HbA1c of greater than 8%
- Difficulty sleeping due to a medical condition
- BMI >40 kg/m^2
- Commenced a weight-loss diet in the past 30 days
- At screening, an underlying pathology of sleep identified during the screening PSG: Apnea Hypopnea Index >10, or >10 periodic leg movements associated with an arousal per hour of sleep
- Positive alcohol breath test as analyzed by a breathalyzer machine[11].

The treatment groups were:

1. Suvorexant 10 mg
2. Suvorexant 20 mg
3. Suvorexant 40 mg
4. Suvorexant 80 mg

Treatments were administered 30 minutes before bedtime on PSG nights and immediately prior to bedtime on non-PSG nights. Subjects were randomised by IVRS to 4 weeks active or with 4 weeks placebo, with crossover to the alternative treatment (active or placebo)[12].

[11] or urine drug screen

[12] following a 1 week single-blind placebo washout between treatment periods.

The primary efficacy outcome measure was SE, derived from TST from the PSG. The secondary efficacy outcome measures were:

- WASO
- LPS

The exploratory subjective assessments of sleep were:

- sWASO
- sTSO
- sNAW
- sTST
- Sheehan Disability Scale
- Insomnia Severity Index

Safety outcome measures were: AEs, laboratory safety tests, vital signs, ECG, Tyrer Withdrawal Symptom Questionnaire via the eDiary evening questionnaire, Digit Symbol Substitution Test, and Digit Symbol Copy Test.

A total of 254 subjects were allocated to treatment group: 62 in the suvorexant 10 mg group, 61 in the 20 mg, 59 in the 40 mg and 61 in the 80 mg. Of these 228 subjects completed. There were 148 (58.3%) females, 106 (41.7%) males, and the age range was 18 to 64 years. The treatment groups were similar in demographic characteristics. Morning eDiary compliance was 99.7% and evening diary compliance was 98.3%.

For SE on Night 1, the difference from placebo increased with dose up to the 80 mg dose level (Table 3). There was no significant difference between the active treatments. In Week 4, the difference was greatest for the 20 mg dose level, and similar for the 40 mg and 80 mg dose level. There was no significant difference between the treatments. While there was no formal pair-wise comparison for WASO, on Night 1 there was a progressive decrease with increasing dose in comparison with placebo, but in Week 4 the greatest decrease was with the 40 mg dose level. For LPS, on Night 1 there was a progressive decrease with increasing dose in comparison with placebo, but this was only significant for the 40 mg and 80 mg dose levels. In Week 4 the only significant decrease compared to placebo was with the 20 mg dose level. There was less effect on LPS in Week 4 than on Night 1 for the 40 mg and 80 mg dose levels.

Table 3. Analysis of Sleep Efficiency (SE) (%), Wakefulness after Persistent Sleep Onset (WASO) (minutes) and Latency to Onset of Persistent Sleep (LPS) (minutes) (Full Analysis Set / Data-as-Observed)

Endpoint	Timepoint	Treatment	Diff in LS Means vs. Placebo (SE)†	95% CI	p-Value
SE	Night 1	MK4305 10 mg	5.2 (1.71)	(1.9, 8.6)	**0.002**
		MK4305 20 mg	7.6 (1.72)	(4.2, 11.0)	**<.001**
		MK4305 40 mg	10.8 (1.72)	(7.4, 14.2)	**<.001**
		MK4305 80 mg	12.9 (1.73)	(9.5, 16.3)	**<.001**
	Week 4	MK4305 10 mg	4.7 (1.58)	(1.6, 7.8)	**0.003**
		MK4305 20 mg	10.4 (1.60)	(7.2, 13.6)	**<.001**
		MK4305 40 mg	7.8 (1.61)	(4.6, 10.9)	**<.001**
		MK4305 80 mg	7.6 (1.63)	(4.4, 10.9)	**<.001**
WASO	Night 1	MK4305 10 mg	-21.2 (6.27)	(-33.5, -8.8)	**<.001**
		MK4305 20 mg	-24.7 (6.31)	(-37.1, -12.3)	**<.001**
		MK4305 40 mg	-33.9 (6.33)	(-46.4, -21.5)	**<.001**
		MK4305 80 mg	-36.8 (6.36)	(-49.4, -24.3)	**<.001**
	Week 4	MK4305 10 mg	-21.4 (6.45)	(-34.2, -8.7)	**0.001**
		MK4305 20 mg	-28.1 (6.58)	(-41.0, -15.1)	**<.001**
		MK4305 40 mg	-33.2 (6.61)	(-46.3, -20.2)	**<.001**
		MK4305 80 mg	-28.9 (6.70)	(-42.1, -15.7)	**<.001**
LPS‡	Night 1	MK4305 10 mg	-3.4 (6.16)	(-15.6, 8.7)	0.577
		MK4305 20 mg	-9.4 (6.17)	(-21.5, 2.8)	0.130
		MK4305 40 mg	-23.1 (6.20)	(-35.3, -10.9)	<.001
		MK4305 80 mg	-25.4 (6.23)	(-37.7, -13.1)	<.001
	Week 4	MK4305 10 mg	-2.3 (5.00)	(-12.2, 7.5)	0.644
		MK4305 20 mg	-22.3 (5.08)	(-32.3, -12.3)	<.001
		MK4305 40 mg	-3.8 (5.09)	(-13.8, 6.3)	0.459
		MK4305 80 mg	-9.5 (5.17)	(-19.7, 0.7)	0.068

Results based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2x2 crossover study (i.e., multiplied by indicator variables for each 2x2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2x2 crossover studies.

‡Since there was a evidence of a carryover effect for LPS, an analysis of Period 1 LPS data revealed the following differences versus placebo and p-values for Night 1: 10 mg vs. placebo = -19.1 minutes (p-value = 0.020), 20 mg vs. placebo = -17.4 minutes (p-value = 0.030), 40 mg vs. placebo = -31.0 (p-value < 0.001), 80 mg vs. placebo = -22.3 minutes (p-value = **0.007**), and the following differences versus placebo and p-values for Week 4: 10 mg vs. placebo = -20.2 minutes (p-value = 0.019), 20 mg vs. placebo = -24.6 minutes (p-value = 0.003), 40 mg vs. placebo = -15.7 (p-value = 0.063), 80 mg vs. placebo = -19.6 minutes (p-value = **0.024**)

The results for the exploratory endpoints were:

- Total sleep time increased with dose on both Night 1 and Week 4. The estimated differences in TST between Night 1 and baseline were: 52.4, 85.3, 83.7, 113.8 and 104.5 minutes for placebo, suvorexant 10 mg, 20 mg, 40 mg and 80 mg, respectively; and in Week 4 were 59.2, 89.8, 91.8, 97.9 and 95.1 minutes respectively
- The estimated differences in TTA between Night 1 and baseline were: -52.4, -85.3, -83.7, -114 and -105 minutes for placebo, suvorexant 10 mg, 20 mg, 40 mg and 80 mg, respectively; and in Week 4 were: -59.2, -89.8, -91.8, -97.9 and -95.1 minutes respectively
- SOL was significantly decreased only on Night 1 for the 40 mg and 80 mg dose levels: -15.3 minutes and -12.7 minutes respectively
- There was no dose effect for number of non-REM epochs before REM
- There was no dose effect on latency to REM
- Number of awakenings after onset of persistent sleep was decreased only for the 80 mg dose on Night 1: -3.3 awakenings
- There was no apparent effect on the ratio of NAW to TST
- Number of arousals was increased for all doses of suvorexant on both Night 1 and Week 4 (in the range 3.1 to 6.3) relative to placebo, but there was no dose effect
- There was no consistent effect for the ratio of NOA to TST
- The number of shifts to Wake or Stage 1 from lights out to lights on increased relative to placebo for all the suvorexant doses (in the range 1.6 to 7.6), with no apparent dose effect

The results of the subjective endpoints were:

- Subjective total sleep time (sTST) at Week 4 was only increased relative to placebo for the 40 mg and 80 mg doses: mean (95% CI) 29.6 (17.1 to 42.1) minutes and 19.4 (7.1 to 31.7) minutes respectively
- Time to sleep onset (sTSO) at Week 4 was only decreased relative to placebo for the 40 mg and 80 mg doses: mean (95% CI) -17.4 (-24.1 to -10.7) minutes and -7.7 (-14.3 to -1.1) minutes respectively
- Wake after sleep onset at Week 4 was only decreased relative to placebo for the 40 mg and 80 mg doses: mean (95% CI) -20.5 (-29.2 to -11.7) minutes and -12.4 (-21.2 to -3.5) minutes respectively
- Number of sleep awakenings at Week 4 was only decreased relative to placebo for the 40 mg and 80 mg doses: mean (95% CI) -0.3 (-0.5 to -0.1) and -0.2 (-0.4 to -0.0) respectively
- Quality of sleep at Week 4 decreased relative to placebo for the 40 mg and 80 mg doses: mean (95% CI) -5.5 (-9.7 to -1.4) and -5.7 (-9.8 to -1.6) respectively
- Suvorexant 80 mg, 40 mg and 20 mg had greater improvement of insomnia compared to placebo as assessed by the total score for the Insomnia Severity Index. The mean change (95% CI) from Baseline to Day 28, relative to placebo was -0.4 (-1.7 to 1.0) for 10 mg, -2.0 (-3.4 to -0.6) for 20 mg, -1.8 (-3.2 to -0.4) for 40 mg and -1.6 (-3.0 to -0.2) for 80 mg
- The Shehan Disability Scale was only decreased relative to baseline and placebo for the 20 mg dose level.

5.2. Evaluator's overall conclusions on dose selection

Although the data, with the exception of LPS, were supportive of efficacy for the 10 mg dose level, the strongest support was for the 20 mg dose level. For the objective endpoints (PSG): SE supported the 20 mg dose level, WASO supported the 40 mg, and LPS supported the 20 mg dose level. The subjective endpoints were most supportive of the 40 mg dose level, except for the ISI which supported the 20 mg dose level.

6. Clinical efficacy

6.1. Primary insomnia

6.1.1. Pivotal efficacy studies

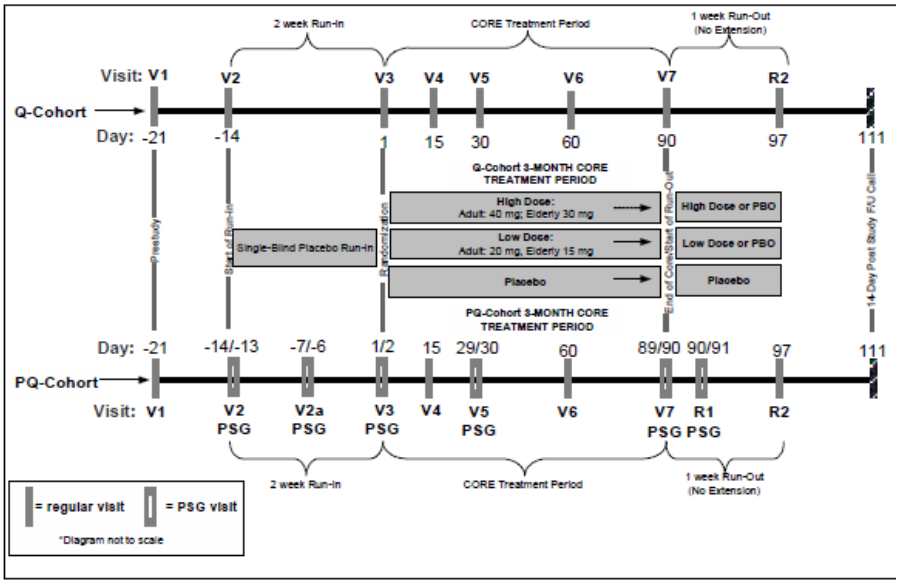
6.1.1.1. Study P028

6.1.1.1.1. Study design, objectives, locations and dates

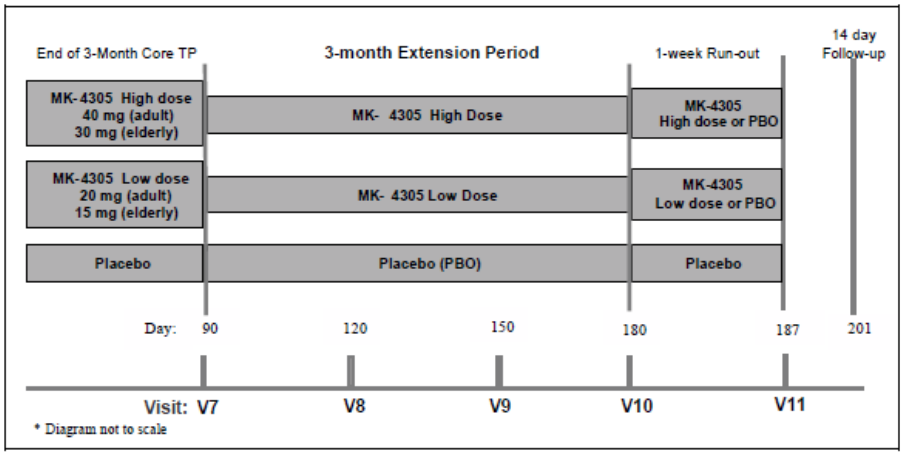
Study P028 was a multicentre, randomised, parallel group, Phase III study to evaluate safety and efficacy of suvorexant in subjects with primary insomnia. The subjects were randomized in two cohorts: Questionnaire only and PSG + Questionnaire. The study was conducted at 91 centres in 16 countries from May 2010 to November 2011. There was an optional 3 month extension phase, and a run-out phase. The study design is summarised in Figure 2.

Figure 2. Study Flow Diagram Study P028

Study design flow diagram: 3-Month Core Treatment Period, no Extension



Study Flow Diagram: 3-Month Extension (Q and PQ-Cohorts)



6.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female and ≥ 18 years of age
- DSM-IV-TR diagnosis of Primary Insomnia based on the Investigator's judgment and the patient's sleep history as assessed on the Sleep Diagnostic Interview/Sleep History
- For subjects ≥ 65 years: Mini Mental State Examination (MMSE) score of ≥ 25
- Good physical and mental health in the opinion of the investigator
- Female subjects of childbearing age are not pregnant and agree to use acceptable contraception
- Total sleep time of <6.5 hours on at least 3 out of 7 nights each week
- Sleep latency of ≥30 minutes on at least 3 out of 7 nights each week
- ≥1 hour of wakefulness after sleep onset on at least 3 out of 7 nights

- For subjects chronically using a hypnotic or anxiolytic for treatment of insomnia (defined as use of 4 times/week), a 4-week washout (or 5 t½ lives, whichever is greater) is required
- 6.5 to 9 hours nightly in bed on at least 3 out of 7 nights each week during the 4 weeks
- Regular bedtime is between 9 pm (21:00) and 1 am (01:00)
- Subject is willing to refrain from napping
- Willing to limit alcohol to 2 drinks a day and at least 3 hours before going to bed
- Willing to limit caffeine consumption to 5 standard 6-ounce cups of caffeinated beverages a day, or 600 mg caffeine, and avoid caffeine after 4 pm (16:00)
- Willing to limit nicotine.

For those subjects in the PSG cohort, the additional inclusion criteria were:

- Willing to stay overnight at a sleep laboratory for PSG testing visits
- Willing to stay in bed for at least 8 hours each night while at the sleep laboratory
- Willing to refrain from drinking alcohol on all PSG visit days, and at least 24 hours prior to a PSG visit
- Willing to avoid caffeine after 1 pm (13:00) on PSG visit days
- At baseline: LPS > 20 minutes on both Screening and Baseline PSG nights and a mean WASO of≥60 minutes on the combined Screening and Baseline PSG nights, where neither night can be≤45 minutes.

The exclusion criteria were the same as for Study P006.

6.1.1.1.3. Study treatments

The study treatments were:

1. Suvorexant high dose: 40 mg for subjects <65 years and 30 mg for subjects ≥ 65 years
2. Suvorexant low dose: 20 mg for subjects <65 years and 15 mg for subjects ≥ 65 years
3. Placebo

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measures were:

- Sleep maintenance:
  - Suvorexant high dose: Change from baseline in sTST and sWASO[13] on the daily e-diary at Month 1 and Month 3
  - Suvorexant high dose: Change from baseline in wakefulness after persistent sleep onset (WASO) by PSG at Month 1 and Month 3.
- Sleep Onset:
  - Suvorexant high dose: Change from baseline in mean subjective time to sleep onset (sTSOm) by daily e-diary at Month 1 and Month 3
  - Suvorexant high dose: Change from baseline in latency to onset of persistent sleep (LPS) by PSG at Month 1 and Month 3.

[13] Erratum: exploratory end point

The secondary efficacy outcome measures were evaluated for both high dose and low dose:

- Sleep maintenance:
  - Change from baseline in mean subjective total sleep time (sTSTm) on the daily e-diary at Week 1
  - Change from baseline in wakefulness after persistent sleep onset (WASO) by PSG at Night 1
- Sleep onset:
  - Change from baseline in mean subjective time to sleep onset (sTSOm) by daily e-diary at Week 1
  - Change from baseline in latency to onset of persistent sleep (LPS) by PSG at Night 1.

The exploratory outcome measures were[14]:

- Mean subjective number of awakenings (sNAWm)
- Mean subjective sleep quality (sQUALm)
- Mean subjective refreshed upon awakening (sREFRESHEDm)
- Responder analysis endpoints:
  - Percentage of patients achieving ≥ 6 point improvement from baseline in ISI total score
  - Percentage of patients responding to treatment based upon the cumulative frequencies of percent change from baseline in sTSTm on the daily sleep diary
  - Percentage of patients responding to treatment based upon the cumulative frequencies of percent change from baseline in sWASOm on the daily sleep diary
  - Percentage of patients responding to treatment based upon the cumulative frequencies of percent change from baseline in sTSOm on the daily sleep diary
- NREM stage 1 duration (S1) (minutes) from Lights-Off to Lights-On
- NREM stage 1 percent (PS1): defined as S1 divided by TST
- NREM stage 2 duration (S2) (minutes) from Lights-Off to Lights-On
- NREM stage 2 percent (PS2): defined as S2 divided by TST
- NREM stage 3 duration (SWS) (minutes) from Lights-Off to Lights-On
- NREM stage 3 percent (PSWS): defined as S3/4 divided by TST
- REM duration (REM) (minutes): duration of stage R from Lights-Off to Lights-On
- REM percent (PREM): defined as REM divided by TST
- Other PSG sleep parameters:
  - Total sleep time (TST) (minutes)
  - Number of awakenings (NAWPS2E)
  - Rate of awakenings (RNAWPS2E): 100*NAWPS2E/TST.
  - Sleep onset latency (SOL1) (minutes): duration of time measured from lights off to the first epoch of 3 consecutive stage S1 or any epoch of stage S2, SWS, or stage R

[14] Erratum: sWASO was also an exploratory end point.

  - Non-REM epochs to REM (LREM2): number of non-REM sleep epochs from lights off to the first epoch of REM sleep
  - Latency to REM (LREM3): Duration of time measured from onset of sleep (SOL1) to the first epoch of Stage R
  - Number of Arousals (NOA): Number of times – beginning from lights off to lights on– that the patient arouses from Stage S2, SWS, or stage R as evidenced by a shift to Stage S1 or to Stage wake with a duration of less than 2 epochs
  - Rate of Arousals (RNOA): 100*NOA/TST
  - Wakefulness After persistent Sleep Onset (WASO) by hour
  - Duration of wakefulness (minutes) after onset of persistent sleep
  - Wakefulness After persistent Sleep Onset by thirds of night (WASO1T1, WASO1T2, WASO1T3)
- Insomnia Severity Index
- Clinical Global Impressions – Severity of Illness (CGI-S)
- Patient Global Impressions – Severity of Illness (PGI-S)
- Clinical Global Impressions – Improvement (CGI-I)
- Patient Global Impressions – Improvement (PGI-I).

The safety outcome measures were[15]:

- Laboratory evaluations (hematology, chemistry, urinalysis)
- Urine drug screen
- Alcohol breath test (PQ-cohort only)
- Physical examination
- Electrocardiogram (ECG)
- Vital signs
- Tyrer Withdrawal Symptom Questionnaire via the evening e-diary questionnaire
- Digit Symbol Substitution Test (PQ-cohort only)
- Columbia Suicide Severity Rating Scale
- Motor Vehicle Accidents and Violations.

For the PSG cohort, polysomnography was performed at screening, at baseline, on Night 1, at end of Month 1, at end of Month 3 and at run-out.

6.1.1.1.5. Randomisation and blinding methods

Randomisation was performed centrally by IVRS, with stratification by stratified by cohort and by age group (<65 years, ≥ 65 years). Subjects were randomised 3:2:3 to high dose, low dose or placebo. At the end of the treatment phase(s) the suvorexant subjects were re-randomised to either the same dose of suvorexant or placebo.[16] The study was double-blind with in-house blinding through use of matching-image placebo tablets of suvorexant. It would have been

[15] Erratum: rebound insomnia was also a safety outcome measure
[16] Erratum: At the end of the treatment phase(s) the suvorexant subjects remained on the same dose of suvorexant or were switched to placebo in a 1:1 ratio, as determined at Visit 3, during the Run-out phase.

possible for the subjects to discriminate between high dose and low dose groups tablets but not for their respective placebos.

6.1.1.1.6. Analysis populations

The FAS consisted of all randomized patients who received at least one dose of study medication and had any post-randomization efficacy assessment data. The FAS-PSG population consisted of all randomized patients who had at least one post-randomization PSG observation subsequent to administration of at least one dose of study treatment; and Baseline data for those analyses that require baseline data. The e-diary FAS population consisted of all randomized patients who had at least one post-randomization e-diary observation subsequent to administration of at least one dose of study treatment; and Baseline data for those analyses that require baseline data. The safety population was all subjects as treated.

6.1.1.1.7. Sample size

The sample size calculation was based on the effect sizes from Study P006. The sample size calculation assumed a dropout rate of 1% at Night 1, 5% at Week 1, 10% at month 1 and 20% at Month 3. The estimated sample size was 360 subjects in the high dose and placebo groups, and 240 in the low dose group, with 75% subjects in the PSG strata and 25% in the questionnaire alone strata.

6.1.1.1.8. Statistical methods

Hypothesis tests were performed using a longitudinal data analysis model. Multiplicity was addressed by using a Bonferroni approach, within each indication, and a fixed sequential testing procedure was used to move from the first set of primary hypotheses (Month 1) to the next set of primary hypotheses (Month 3).

6.1.1.1.9. Participant flow

A total of 2878 subjects were screened and 1022 randomised to treatment: 254 to low dose, 383 to high dose, and 385 to placebo. Of these subjects 230 (90.6%) low dose, 345 (90.1%) high dose and 341 (88.6%) placebo completed treatment. There were 423 subjects that proceeded into the extension phase: 172 in the high dose group, 100 in the low dose and 151 in the placebo. Of these subjects 377 completed and continued into the run-out phase. A total of 862 subjects entered the run out phase, and only one subject from each treatment group discontinued.

There were 775 (75.8%) subjects randomized to[17] the PSG cohort: 291 to high dose, 193 to low dose and 291 to placebo. One subject in the placebo group did not receive treatment, and there were 774 subjects in the FAS.

6.1.1.1.10. Major protocol violations/deviations

There were 114 subjects identified as protocol violators.

6.1.1.1.11. Baseline data

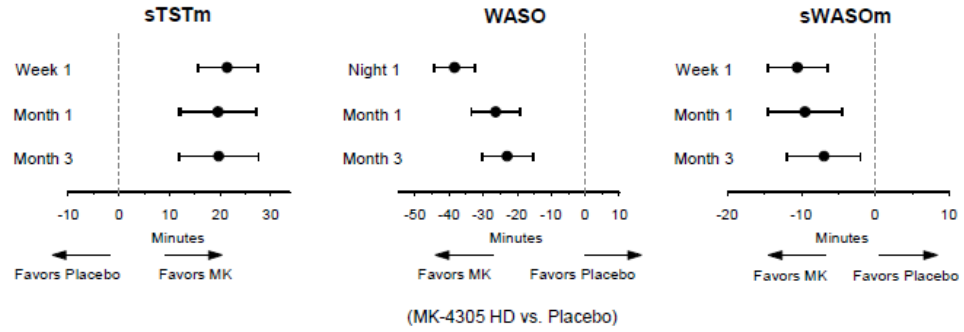
There were 637 (62.4%) females, 384 (37.6%) males and the age range was 18 to 87 years. There were 429 (42.0%) subjects aged ≥ 65 years. The treatment groups were similar in demographic and physical characteristics at baseline. The efficacy measures at baseline were similar for the three treatment groups. There were 301 (78.6%) subjects in the high dose group, 202 (79.5%) in the low dose and 300 (78.1%) in the placebo with a history of prior medical conditions. Prior medication history was similar for the three treatment groups. Concomitant medications were similar for the three groups except for a higher usage of sex hormones and modulators of the genital system in the low dose group.

[17] Erratum: replace 'to' with 'within'

6.1.1.1.12. Results for the primary efficacy outcome

Sleep maintenance was improved by high dose suvorexant in comparison with placebo through to Month 3 (Figure 3). At Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 19.7 (11.9 to 27.6) minutes, p <0.00001, sWASO was -6.9 (-11.9 to -2.0) minutes, p = 0.00565; and WASO was -22.0 (-29.6 to -14.4)[18] minutes, p <0.0001.

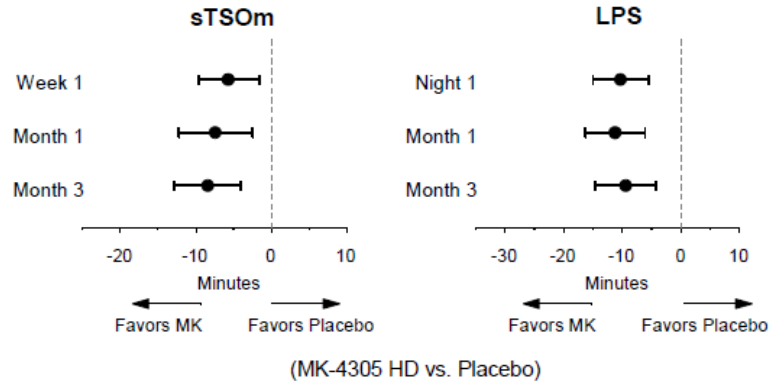
Figure 3. Point Estimates and 95% Confidence Intervals for Sleep Maintenance Efficacy Endpoints MK-4305 High Dose (HD) versus Placebo (LDA / Full Analysis Set / Data-as-Observed)



MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

Sleep onset was improved by high dose suvorexant in comparison with placebo through to Month 3. At Month 3, the improvement in sTSO was -8.4 (-12.8 to -4.0) minutes, p = 0.00019; and in LPS was -9.4 (-14.6 to -4.3), p = 0.00037.

Figure 4. Point Estimates and 95% Confidence Intervals for Sleep Onset Efficacy Endpoints MK-4305 High Dose (HD) versus Placebo (LDA / Full Analysis Set / Data-as-Observed)



MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

The subgroup analysis showed no difference in effect by age group (Figures 5 and 6). In the high dose group in comparison with placebo, for the <65 years age group, at Month 3 the mean (95% CI) improvement in sTST was 21.0 (10.7 to 31.3) minutes, sWASO was -8.0 (-14.4 to -1.5) minutes, WASO was -27.5 (-37.4 to -17.6) minutes, sTSO was -7.8 (-13.5 to -2.0) minutes, and LPS was -7.1 (-13.9 to -0.2) minutes. For the ≥ 65 years age group, at Month 3 the mean (95% CI) improvement in sTST was 18.1 (6.0 to 30.1) minutes, sWASO was -5.6 (-13.1 to 2.0), WASO was -16.9 (-28.3 to -5.4), sTSO was -9.3 (-16.1 to -2.5) minutes, and LPS was -12.4 (-20.3 to -4.4) minutes. There were no subgroup effects for gender or baseline severity. There was greater efficacy for sTST for Whites than non-Whites: 25.9 (16.2 to 35.7) minutes compared with 8.3 (-4.8 to 21.3) minutes for non-Whites; for sWASO -9.9 (-16.0 to -3.7) and -1.5 (-9.7 to 6.7)

[18] Erratum: -22.9 (-30.3 to -15.4)

respectively. In the Asian / Eastern European / Africa region there was actually a deterioration in sTST with high dose suvorexant: -13.5 (-54.4 to 27.5) minutes; and in sWASO 9.5 (-16.0 to 35.0) minutes. However for WASO the improvement was similar for Whites and non-Whites: -19.3 (-27.4 to -11.3) minutes compared with -41.4 (-60.7 to -22.2) minutes for non-Whites; and there was no regional variation. For LPS, the improvement was greater for Whites and non-Whites: -11.1 (-16.6 to -5.5) minutes compared with -3.9 (-17.2 to 9.5) minutes for non-Whites.

Figure 5. Point Estimates and 95% Confidence Intervals for Change from Baseline for Maintenance Endpoints MK-4305 High Dose (HD) versus Placebo at Month 3 by Subgroup Factors (LDA / Full Analysis Set E-Diary / Data-as-Observed)

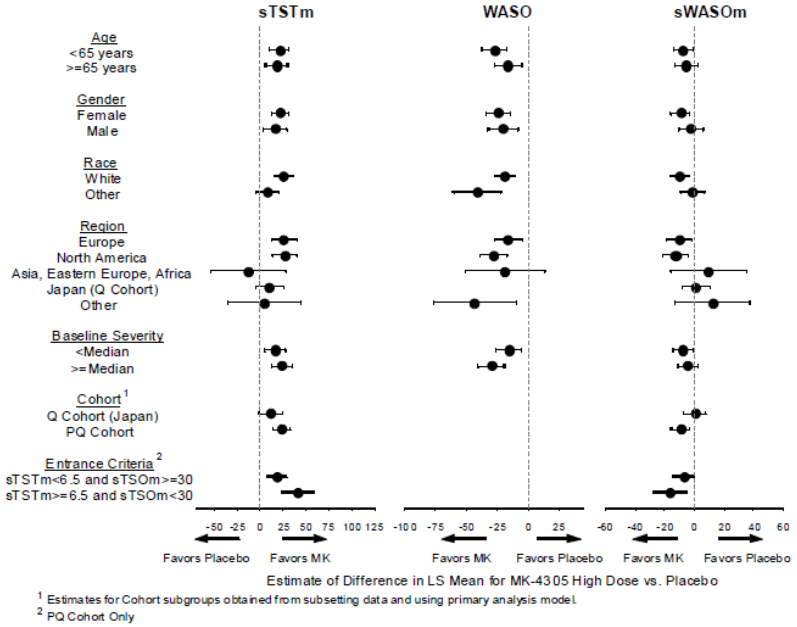
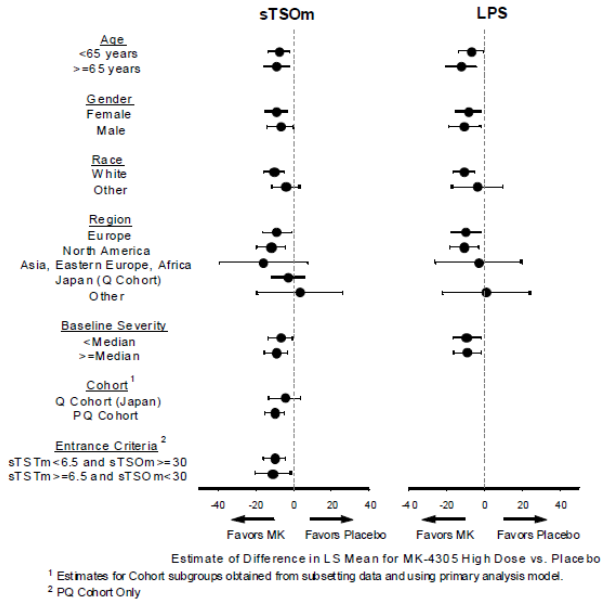


Figure 6. Point Estimates and 95% Confidence Intervals for Change from Baseline for Onset Endpoints MK-4305 High Dose (HD) versus Placebo at Month 3 by Subgroup Factors (LDA / Full Analysis Set E-Diary / Data-as-Observed)



For all the primary efficacy outcome measures there were substantial improvements in the placebo group over time (Figures 7-11). There was little apparent dose effect between the high

dose and low dose groups, particularly for the PSG endpoints. There was also less apparent effect for suvorexant by subjective measures compared to PSG.

Figure 7. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Mean Subjective Total Sleep Time (sTSTm; minutes) by Time Point During the Treatment Phase (Full Analysis Set E-Diary / Data-as-Observed)

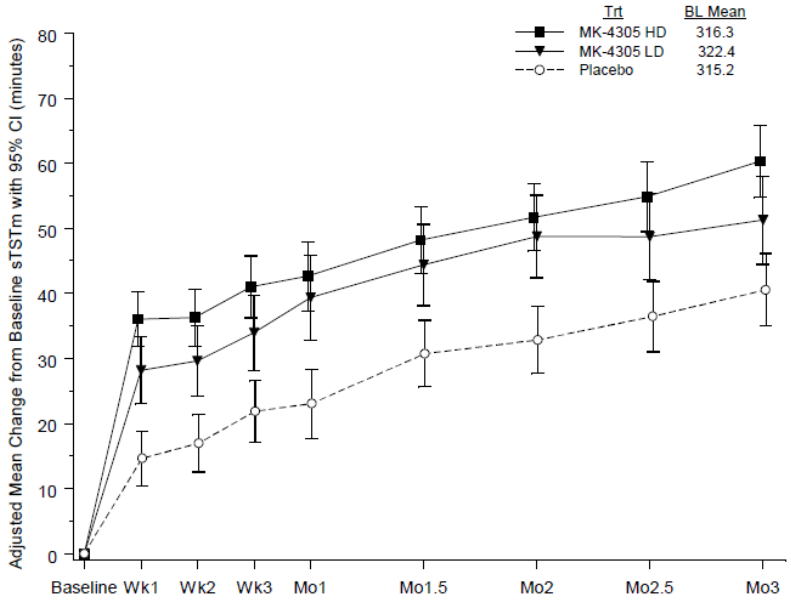


Figure 8. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Mean Subjective Wake Time After Sleep Onset (sWASOm; minutes) by Time Point During the Treatment Phase (Full Analysis Set E-Diary / Data-as-Observed)

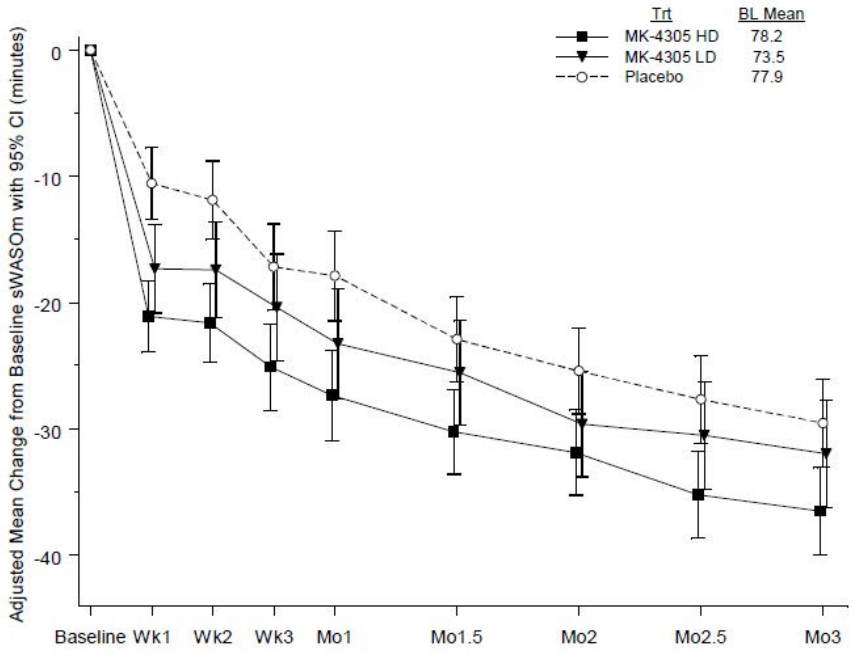


Figure 9. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Wakefulness After Persistent Sleep Onset (WASO; minutes) by Time Point (Full Analysis Set PSG / Data-as-Observed)

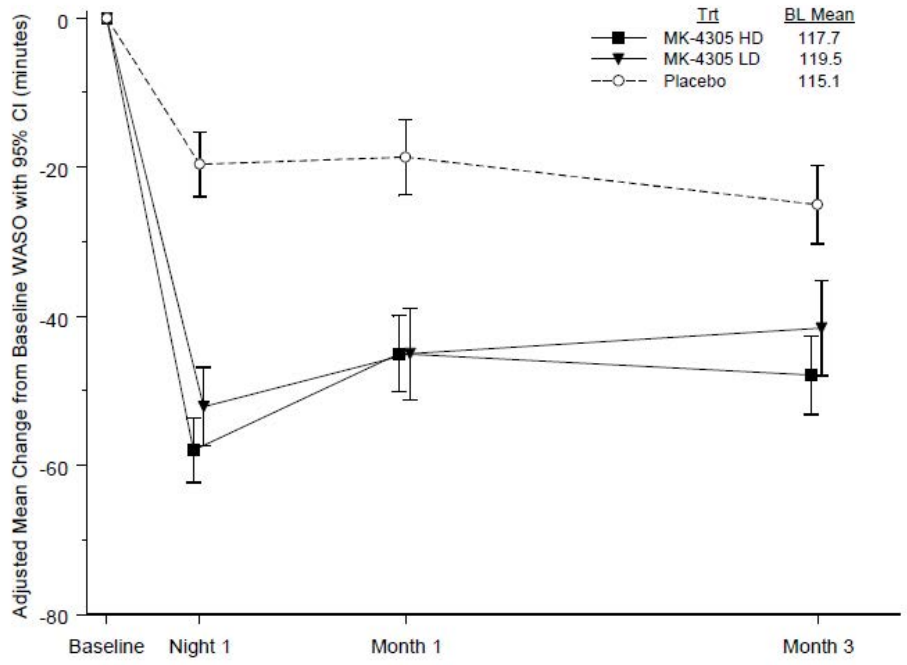


Figure 10. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Mean Subjective Time to Sleep Onset (sTSOm; minutes) by Time Point During the Treatment Phase (Full Analysis Set E-Diary / Data-as-Observed)

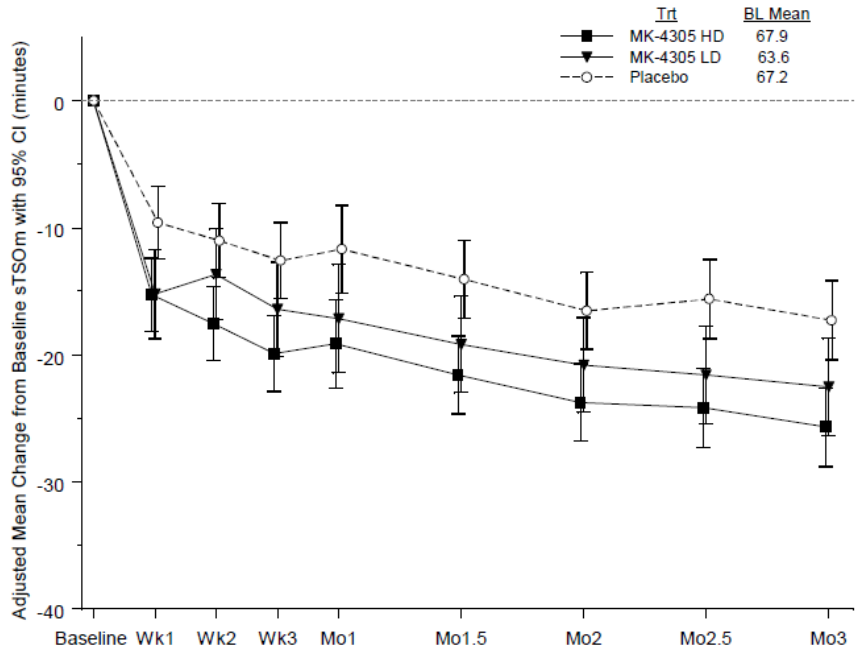
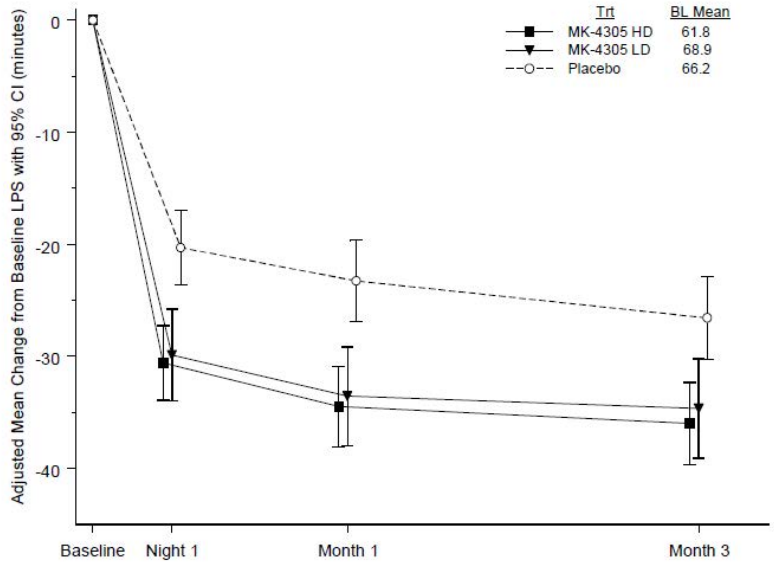


Figure 11. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Latency to Onset of Persistent Sleep (LPS; minutes) by Time Point (Full Analysis Set PSG / Data-as-Observed)



6.1.1.1.13. Results for other efficacy outcomes

Sleep maintenance was initially improved by low dose suvorexant in comparison with placebo but the benefit was not sustained through to Month 3. At Month 3, the improvement in sTST, relative to placebo, was 10.7 (1.9 to 19.5) minutes, p = 0.01711; sWASO was -2.4 (-7.9 to 3.1) minutes, p = 0.38819; and WASO was -16.3 (-24.7 to -7.8)[19].

Sleep onset was not improved to the same extent by low dose suvorexant in comparison with placebo through to Month 3. The improvement in sTSO was approximately 5 minutes and marginally statistically significant: -5.2 (-10.2 to -0.3) minutes, p = 0.03771. The improvement in LPS was -7.3 (-13.0 to -1.5), p = 0.01347[20].

For the remaining secondary efficacy outcome measures:

- There were no significant differences in sNAWm at any time point
- At Month 3, sQUALm was significantly improved in the high dose group compared with placebo: mean (95% CI) 0.08 (0.01 to 0.15), p = 0.02434
- Although there were improvements in sREFRESHED at Month 1, these were not sustained to Month 3
- At Month 3, ISI was significantly improved compared with placebo: mean (95% CI) -1.4 (-2.1 to -0.7), p = 0.00013 for high dose, -1.2 (-1.9 to -0.4), p = 0.00371 for low dose
- At Month 3, CGI-S was significantly improved compared with placebo: mean (95% CI) -0.3 (-0.5 to -0.2), p = 0.0001 for high dose, -0.3 (-0.5 to -0.1), p = 0.00159 for low dose
- At Month 3, CGI-I was significantly improved compared with placebo: mean (95% CI) -0.4 (-0.6 to -0.3), p <0.00001 for high dose; -0.4 (-0.5 to -0.2), p = 0.00002 for low dose
- At Month 3, PGI-S was significantly improved compared with placebo: mean (95% CI) -0.4 (-0.6 to -0.3), p <0.00001 for high dose; -0.3 (-0.5 to -0.1), p = 0.00036 for low dose

[19] Erratum: -16.6 (-24.8 to -8.3) p=0.00009
[20] Erratum: -8.1 (-13.8, -2.3) p=0.00606

- At Month 3, PGI-I was significantly improved compared with placebo: mean (95% CI) -0.5 (-0.6 to -0.3), p <0.00001 for high dose; -0.4 (-0.5 to -0.2), p = 0.00004 for low dose
- The responder analysis for ISI reported a clinically meaningful response at Month 3 in 168 (51.1%) subjects in the high dose group, 115 (52.0%) in the low dose and 129 (39.3%) in the placebo. For sTST, there was a ≥ 15% improvement from baseline in 190 (54.6%) subjects in the high dose group, 102 (44.7%) in the low dose and 143 (42.2%) in the placebo. For sWASO, there was a ≥ 15% improvement from baseline in 266 (76.7%) subjects in the high dose group, 172 (75.4%) in the low dose and 238 (70.2%) in the placebo. For sTSO, there was a ≥ 15% improvement from baseline in 262 (75.3%) subjects in the high dose group, 152 (66.7%) in the low dose and 231 (68.1%) in the placebo
- At Month 3, relative to placebo, there was an increase in NREM Stage 1 duration of 3.8 (1.2 to 6.4) minutes in the high dose group and 3.1 (0.2 to 6.0) minutes in the low dose; NREM Stage 2 duration of 13.3 (6.6 to 20.0) minutes in the high dose group and 13.2 (5.8 to 20.6) minutes in the low dose; REM duration of 12.7 (8.5 to 17.0) minutes in the high dose group and 9.2 (4.4 to 13.9) minutes in the low dose. There was no significant change in Slow Wave Sleep (SWS).

In the extension phase, the improvement in sTST was not sustained through to Month six, and was actually better in the placebo group: 4.3 (-9.2 to 17.9) minutes for high dose and -8.7 (-24.5 to 7.0) for low dose. There was no significant improvement in sWASO: 5.7 (-2.2 to 13.6) minutes for high dose and 6.9 (-2.4 to 16.1) minutes for low dose. At Month 6, the mean (95% CI) change in sTSO relative to placebo was -3.7 (-11.2 to 3.8) minutes for high dose and 0.6 (-8.1 to 9.3) minutes for low dose.

6.1.1.2. Study P029

6.1.1.2.1. Study design, objectives, locations and dates

Study P029 was similar in design to Study P028. It was a multicentre, randomised, parallel group, Phase III study to evaluate safety and efficacy of suvorexant in subjects with primary insomnia. The subjects were also randomized in two cohorts: Questionnaire only and PSG + Qestionnaire. The study was conducted at 114 centres in 19 countries from July 2010 to October 2011. Although there was a run-out phase, unlike Study P028 there was no optional 3 month extension phase.

6.1.1.2.2. Inclusion and exclusion criteria

The inclusion criteria were the same as for Study P028.

The exclusion criteria were the same as for Study P006.

6.1.1.2.3. Study treatments

The study treatments were the same as for Study P028:

1. Suvorexant high dose: 40 mg for subjects <65 years and 30 mg for subjects ≥ 65 years
2. Suvorexant low dose: 20 mg for subjects <65 years and 15 mg for subjects ≥ 65 years
3. Placebo

6.1.1.2.4. Efficacy variables and outcomes

The efficacy and safety outcome measures were similar to those for Study P028:

The primary efficacy outcome measures were:

- Sleep maintenance:
  - Suvorexant high dose: Change from baseline in sTST on the daily e-diary at Month 1 and Month 3

  - Suvorexant high dose: Change from baseline in WASO by PSG at Month 1 and Month 3
- Sleep Onset:
  - Suvorexant high dose: Change from baseline in mean sTSO by daily e-diary at Month 1 and Month 3
  - Suvorexant high dose: Change from baseline in LPS by PSG at Month 1 and Month 3.

The secondary efficacy outcome measures were evaluated for both high dose and low dose[21]:

- Sleep maintenance:
  - Change from baseline in mean subjective total sleep time sTSTm and sWASO[22] on the daily e-diary at Week 1
  - Change from baseline in WASO by PSG at Night 1.
- Sleep onset:
  - Change from baseline in mean sTSO by daily e-diary at Week 1
  - Change from baseline in LPS by PSG at Night 1.

The exploratory outcome measures were:

- Mean subjective number of awakenings (sNAWm)
- Mean subjective sleep quality (sQUALm)
- Mean subjective refreshed upon awakening (sREFRESHEDm)
- Responder analysis endpoints:
  - Percentage of patients achieving ≥ 6 point improvement from baseline in ISI total score
  - Percentage of patients responding to treatment based upon the cumulative frequencies of percent change from baseline in sTSTm on the daily sleep diary
  - Percentage of patients responding to treatment based upon the cumulative frequencies of percent change from baseline in sWASOm on the daily sleep diary
  - Percentage of patients responding to treatment based upon the cumulative frequencies of percent change from baseline in sTSOm on the daily sleep diary
- NREM stage 1 duration (S1) (minutes) from Lights-Off to Lights-On
- NREM stage 1 percent (PS1): defined as S1 divided by TST
- NREM stage 2 duration (S2) (minutes) from Lights-Off to Lights-On
- NREM stage 2 percent (PS2): defined as S2 divided by TST
- NREM stage 3 duration (SWS) (minutes) from Lights-Off to Lights-On
- NREM stage 3 percent (PSWS): defined as S3/4 divided by TST
- REM duration (REM) (minutes): duration of stage R from Lights-Off to Lights-On
- REM percent (PREM): defined as REM divided by TST.
- Other PSG sleep parameters:
  - Total sleep time (TST) (minutes)

[21] Erratum: The secondary efficacy outcome measures were evaluated for high dose.
[22] Erratum: sWASO was an exploratory end point.

  - Number of awakenings (NAWPS2E)
  - Rate of awakenings (RNAWPS2E): 100*NAWPS2E/TST.
  - Sleep onset latency (SOL1) (minutes): duration of time measured from lights off to the first epoch of 3 consecutive stage S1 or any epoch of stage S2, SWS, or stage R
  - Non-REM epochs to REM (LREM2): number of non-REM sleep epochs from lights off to the first epoch of REM sleep
  - Latency to REM (LREM3): Duration of time measured from onset of sleep (SOL1) to the first epoch of Stage R
  - Number of Arousals (NOA): Number of times – beginning from lights off to lights on– that the patient arouses from Stage S2, SWS, or stage R as evidenced by a shift to Stage S1 or to Stage wake with a duration of less than 2 epochs
  - Rate of Arousals (RNOA): 100*NOA/TST
  - Wakefulness After persistent Sleep Onset (WASO) by hour
  - Duration of wakefulness (minutes) after onset of persistent sleep
  - Wakefulness After persistent Sleep Onset by thirds of night (WASO1T1, WASO1T2, WASO1T3)
- Insomnia Severity Index
- Clinical Global Impressions – Severity of Illness (CGI-S)
- Patient Global Impressions – Severity of Illness (PGI-S)
- Clinical Global Impressions – Improvement (CGI-I)
- Patient Global Impressions – Improvement (PGI-I).

The safety outcome measures were[23]:

- Laboratory evaluations (haematology, chemistry, urinalysis)
- Urine drug screen
- Alcohol breath test (PQ-cohort only)
- Physical examination
- Electrocardiogram (ECG)
- Vital signs
- Tyrer Withdrawal Symptom Questionnaire via the evening e-diary questionnaire
- Digit Symbol Substitution Test (PQ-cohort only)
- Columbia Suicide Severity Rating Scale
- Motor Vehicle Accidents and Violations.

For the PSG cohort, polysomnography was performed at screening, at baseline, on Night 1, at end of Month 1, at end of Month 3 and at run-out.

6.1.1.2.5. Randomisation and blinding methods

Randomisation was performed centrally by IVRS, with stratification by stratified by cohort and by age group (<65 years, ≥ 65 years). Questionnaire subjects were randomised 1:1:1; and PSG

[23] Erratum: Rebound insomnia was also included.

subjects were randomised 2:1:2 to high dose, low dose or placebo. At the end of the treatment phase(s) the suvorexant subjects were re-randomised to either the same dose of suvorexant or placebo in a 1:1 ratio[24]. The study was double-blind with in-house blinding through use of matching-image placebo tablets of suvorexant. It would have been possible for the subjects to discriminate between high dose and low dose but not for their respective placebos.

6.1.1.2.6. Analysis populations

The analysis populations were the same as for Study P028.

6.1.1.2.7. Sample size

The sample size calculation was similar to that for Study P028 and was based on the effect sizes from Study P006. The sample size calculation assumed a dropout rate of 1% at Night 1, 5% at Week 1, 10% at month 1 and 20% at Month 3. The estimated sample size was 360 subjects in the high dose and placebo groups, and 240 in the low dose group, with 71% subjects in the PSG strata and 29% in the Questionnaire alone strata.

6.1.1.2.8. Statistical methods

The hypothesis tests were performed in the same manner as for Study P028.

6.1.1.2.9. Participant flow

A total of 2876 subjects were screened and 1019 were randomised to treatment: 240 to low dose, 392 to high dose, and 387 to placebo. Of these subjects 205 (85.4%) low dose, 346 (88.3%) high dose and 330 (85.3%) placebo completed treatment. A total of 876 subjects entered the run out phase, and six (0.7%) subjects discontinued.

There were 751 (73.7%) subjects randomized to[25] the PSG cohort: 302 to high dose, 150 to low dose and 299 to placebo. Five subjects did not receive treatment: three in the high dose group and two in the placebo. A further 21 subjects were excluded from the FAS, leaving 725 (71.1%) subjects: five from the high dose group, five from the low dose and eleven from the placebo.

6.1.1.2.10. Major protocol violations/deviations

There were 116 subjects identified as protocol violators.

6.1.1.2.11. Baseline data

There were 671 (66.5%) females, 338 (33.5%) males and the age range was 18 to 86 years. There were 410 (40.6%) subjects aged ≥ 65 years. The treatment groups were similar in demographic and physical characteristics at baseline. The efficacy measures at baseline were similar for the three treatment groups. There were 309 (79.8%) subjects in the high dose group, 177 (74.1%) in the low dose and 305 (79.6%) in the placebo with a history of prior medical conditions. Prior medication history was similar for the three treatment groups. Concomitant medications were similar for the three groups except for a higher usage of sex hormones and modulators of the genital system in the high dose group.

6.1.1.2.12. Results for the primary efficacy outcome

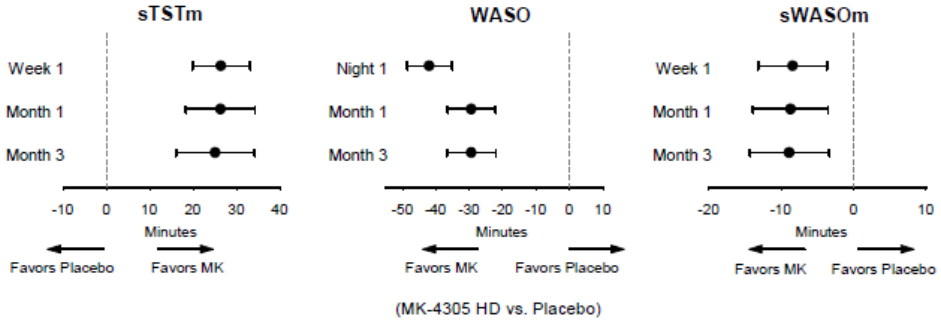
Sleep maintenance was improved by high dose suvorexant in comparison with placebo through to Month 3 (Figure 12). At Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 25.1 (16.0 to 34.2) minutes, p <0.00001, sWASO was -8.9 (-14.4 to -3.4) minutes, p = 0.00167); and WASO was -29.4 (-36.7 to -22.1) minutes, p <0.00001.

Sleep onset was improved by high dose suvorexant in comparison with placebo through to Month 3 (Figure 13). At Month 3, the improvement in sTSO was -13.2 (-19.4 to -7.0) minutes, p = 0.00003; and in LPS was -3.6 (-10.1 to 2.8), p = 0.26510.

[24] see also Study P028.

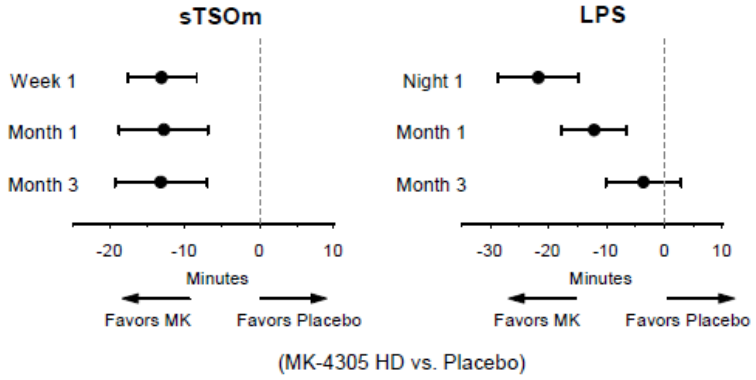
[25] Erratum: replace 'to' with 'within'.

Figure 12. Point Estimates and 95% Confidence Intervals for Sleep Maintenance Efficacy Endpoints MK-4305 High Dose (HD) versus Placebo (LDA / Full Analysis Set / Data-as-Observed)



MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.
sWASOm is a supportive sleep maintenance endpoint

Figure 13. Point Estimates and 95% Confidence Intervals for Sleep Onset Efficacy Endpoints MK-4305 High Dose (HD) versus Placebo (LDA / Full Analysis Set / Data-as-Observed)



MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.
sWASOm is a supportive sleep maintenance endpoint

The subgroup analysis showed no difference in effect by age group. In the high dose group in comparison with placebo, for the <65 years age group, at Month 3 the mean (95% CI) improvement in sTST was 25.7 (13.9 to 37.6) minutes, sWASO was -5.2 (-12.4 to 2.1) minutes, WASO was -27.0 (-36.7 to -17.3) minutes, sTSO was -15.7 (-23.7 to -7.6) minutes, and LPS was -3.8 (-12.3 to 4.7) minutes. For the ≥ 65 years age group, at Month 3 the mean (95% CI) improvement in sTST was 24.1 (10.0 to 38.3) minutes, sWASO was -14.1 (-22.7 to -5.6), WASO was -32.5 (-43.7 to -21.4), sTSO was -9.8 (-19.4 to -0.1) minutes, and LPS was -3.5 (-13.3 to 6.3) minutes. There were no subgroup effects for gender. There was greater effect in subjects with greater severity at baseline for WASO, sWASO and sleep onset.

For all primary efficacy outcome measures there were substantial improvements in the placebo group over time (Figures 14-18). There was little apparent dose effect between the high dose and low dose groups, particularly for the PSG endpoints. There was also less apparent effect for suvorexant by subjective measures compared to PSG. Although at Night 1 there was improvement in sleep onset, there was no apparent benefit at Month 3.

Figure 14. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Mean Subjective Total Sleep Time (sTSTm; minutes) by Time Point During the Treatment Phase (Full Analysis Set E-Diary / Data-as-Observed)

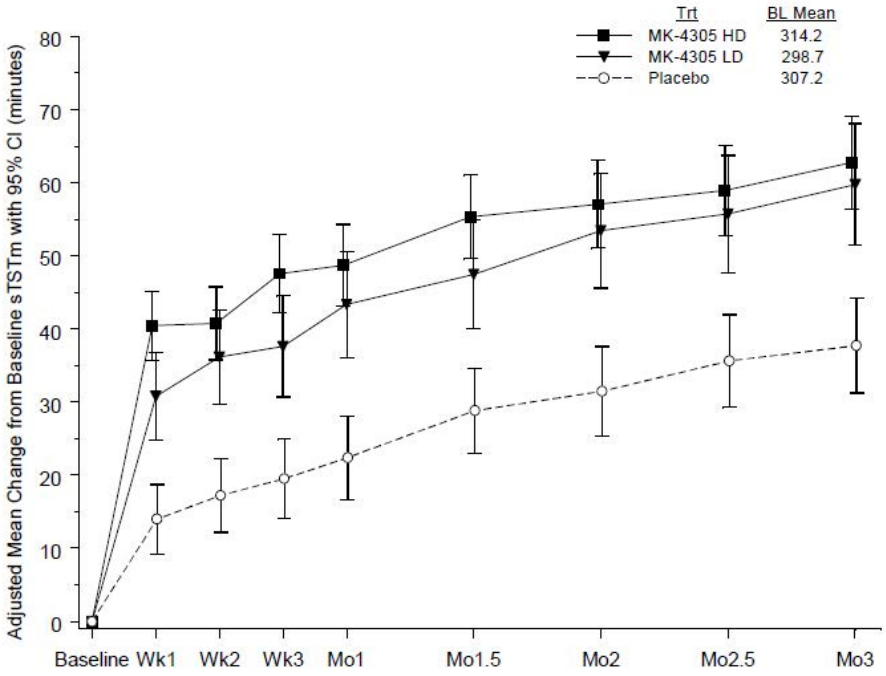


Figure 15. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Mean Subjective Wake Time After Sleep Onset (sWASOm; minutes) by Time Point During the Treatment Phase (Full Analysis Set E-Diary / Data-as-Observed)

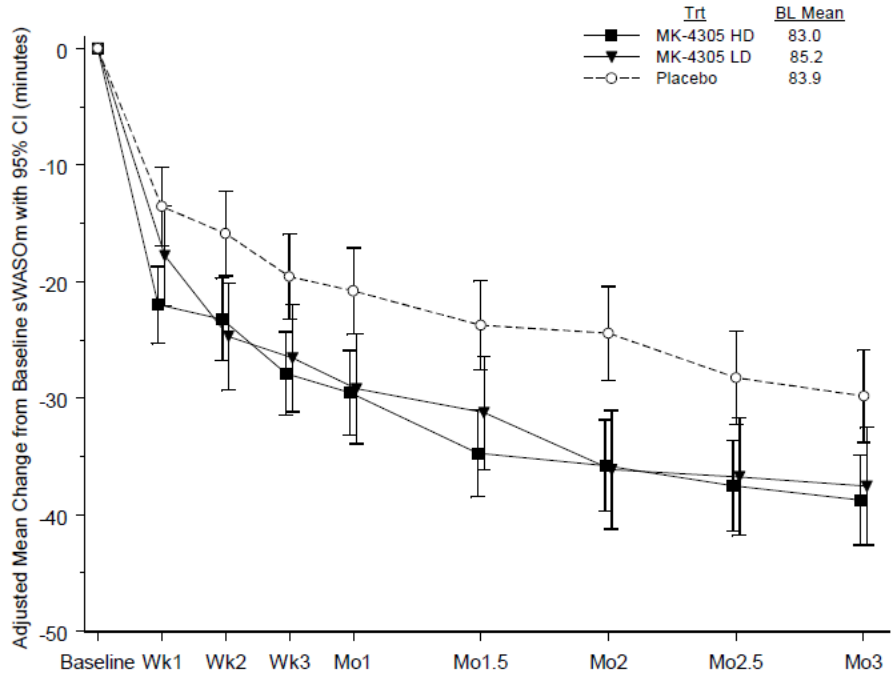


Figure 16. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Wakefulness After Persistent Sleep Onset (WASO; minutes) by Time Point (Full Analysis Set PSG / Data-as-Observed)

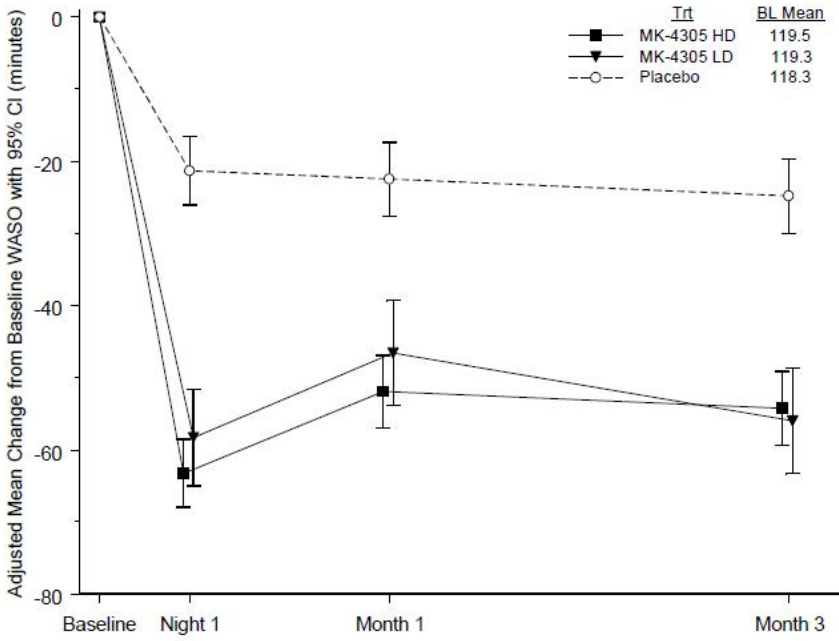


Figure 17. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Mean Subjective Time to Sleep Onset (sTSOm; minutes) by Time Point During the Treatment Phase (Full Analysis Set E-Diary / Data-as-Observed)

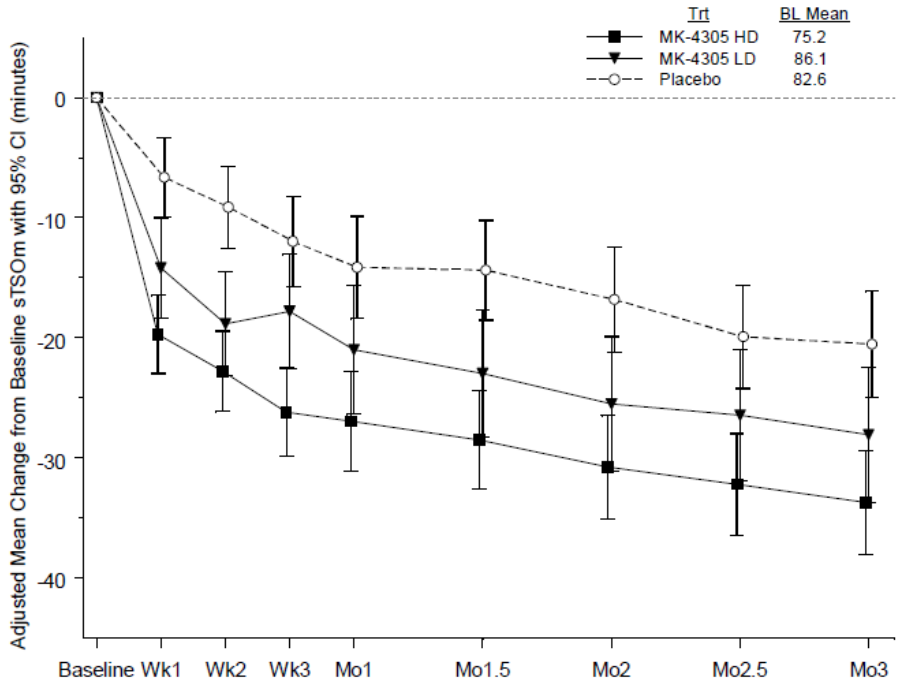
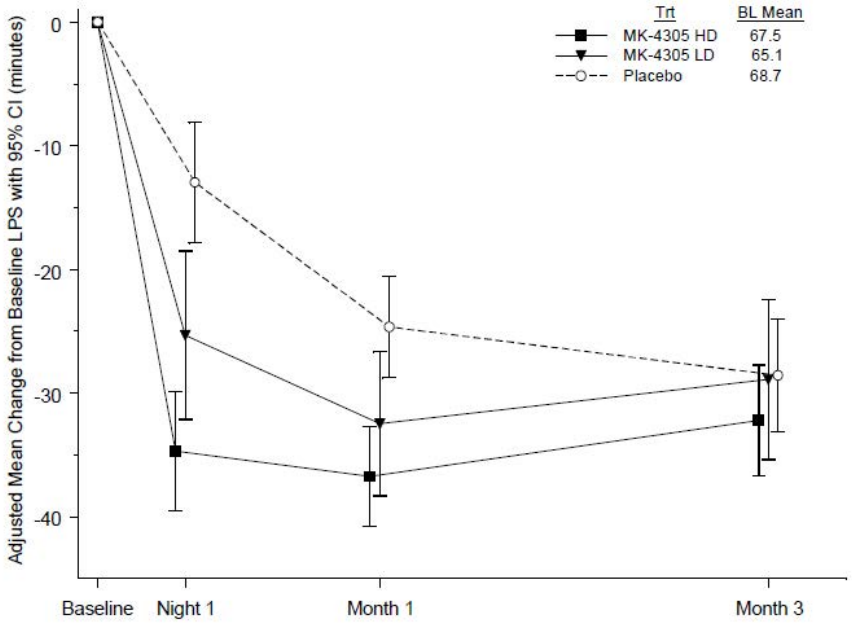


Figure 18. Adjusted Means and 95% Confidence Intervals for Change from Baseline in Latency to Onset of Persistent Sleep (LPS; minutes) by Time Point (Full Analysis Set PSG / Data-as-Observed)



6.1.1.2.13. Results for other efficacy outcomes

Sleep maintenance was initially improved by low dose suvorexant in comparison with placebo but the benefit was not sustained through to Month 3. At Month 3, the improvement in sTST, relative to placebo, was 22.1 (11.5 to 32.6) minutes, p = 0.00004; sWASO was -7.7 (-14.1 to -1.3) minutes, p = 0.01885; and WASO was -31.1 (-40.1 to -22.2).

Sleep onset was not improved to the same extent by low dose suvorexant in comparison with placebo through to Month 3. The improvement in sTSO was approximately 5 minutes[26] and marginally statistically significant: -7.6 (-14.7 to -0.4) minutes, p = 0.03894. The improvement in LPS was -0.3 (-8.3 to 7.6), p = 0.93219.

For the remaining secondary efficacy outcome measures:

- There were no significant differences in sNAWm for suvorexant in comparison with placebo.
- sQUALm was significantly improved compared with placebo at all time points: At Month 3, in comparison with placebo, mean (95% CI) 0.1 (0.1 to 0.2), p = 0.00030 for high dose; 0.1 (0.00 to 0.2), p = 0.00520 for low dose.
- sREFRESHED was also improved in comparison with placebo through to Month 3. At Month 3, in comparison with placebo, mean (95% CI) 0.1 (0.0 to 0.3), p = 0.00510 for high dose; 0.2 (0.00 to 0.3), p = 0.00658 for low dose.
- At Month 3, ISI was significantly improved compared with placebo: mean (95% CI) -2.3 (-3.1 to -1.6) p <0.00001 for high dose, and -1.3 (-2.2 to -0.4) p = 0.00380 for low dose.
- At Month 3, CGI-S was significantly improved compared with placebo: mean (95% CI) -0.6 (-0.8 to -0.4) p <000001 for high dose, and -0.3 (-0.5 to -0.1) p = 0.00304 for low dose.
- At Month 3, CGI-I was significantly improved compared with placebo: mean (95% CI) -0.5 (-0.7 to -0.4) p <000001 for high dose, and -0.4 (-0.6 to -0.3) p <000001

[26] Erratum: 8 minutes

- At Month 3, PGI-S was significantly improved compared with placebo: mean (95% CI) -0.5 (-0.6 to -0.3) p <000001 for high dose, and -0.3 (-0.5 to -0.1) p = 0.00691 for low dose
- At Month 3, PGI-I was significantly improved compared with placebo: mean (95% CI) -0.5 (-0.7 to -0.4) p <000001 for high dose, and -0.3 (-0.5 to -0.1) p = 0.00222 for low dose
- The responder analysis for ISI reported a clinically meaningful response (≥ 6 point improvement) at Month 3 in 192 (58.7%) subjects in the high dose group, 113 (59.5%) in the low dose and 140 (45.2%) in the placebo. For sTST, there was a ≥ 15% improvement from baseline in 182 (54.2%) subjects in the high dose group, 111 (56.3%) in the low dose and 133 (41.3%) in the placebo. For sWASO, there was a ≥ 15% improvement from baseline in 263 (78.5%) subjects in the high dose group, 150 (76.1%) in the low dose and 220 (68.8%) in the placebo. For sTSO, there was a ≥ 15% improvement from baseline in 264 (77.6%) subjects in the high dose group, 145 (73.6%) in the low dose and 207 (63.7%) in the placebo.
- At Month 3, relative to placebo, there was an increase in NREM Stage 1 duration of 6.0 (3.4 to 8.7) minutes in the high dose group and 2.3 (-1.0 to 5.5) minutes in the low dose; NREM Stage 2 duration of 18.5 (11.5 to 25.4) minutes in the high dose group and 18.3 (9.7 to 26.8) minutes in the low dose; REM duration of 11.7 (7.7 to 15.7) minutes in the high dose group and 8.3 (3.4 to 13.3) minutes in the low dose. There was no significant change in Slow Wave Sleep (SWS).

6.1.2. Other efficacy studies

6.1.2.1. Study P009

Study P009 was a multicentre, randomized, double blind (with in-house blinding), placebo controlled, parallel group of suvorexant in subjects with primary insomnia. The study was conducted at 106 centres from December 2009 to August 2011.

The inclusion criteria included:

- Male or female and ≥18 years of age
- DSM-IV-TR diagnosis of Primary Insomnia based on the Investigator's judgment and the patient's sleep history as assessed on the Sleep Diagnostic Interview/Sleep History
- Patient is able to read, understand and complete questionnaires and diaries, including operation of the e-diary
- Subjects ≥65 years of age scores ≥25 on the Mini Mental State Examination (MMSE), to rule out cognitive impairment
- Females who are not pregnant and agree to use acceptable contraception.

The exclusion criteria included:

- Female subjects who are pregnant or lactating
- Patient has a history of hypersensitivity or idiosyncratic reaction to more than two chemical classes of drugs
- History or current evidence of any condition, therapy, lab or ECG abnormality or other circumstances that might confound the results of the study, or interfere with the patient's participation for the full duration of the study
- Recent and/or active history of a confounding neurological disorder, including but not limited to: seizure disorder (other than single episodes of childhood febrile seizures), stroke, transient ischemic attack, multiple sclerosis, cognitive impairment, or significant head trauma with sustained loss of consciousness and residual impairment within the last 10 years

- History within the past 6 months prior to the Screening Visit 1 or current evidence of an unstable or otherwise clinically significant cardiovascular disorder, including but not limited to: acute coronary syndrome; unstable angina; congestive heart failure; cardiogenic syncope; cardiomyopathy; or any symptomatic arrhythmia
- Clinically significant ECG abnormality such as AV conduction disturbance (e.g. second or third degree AV block), sick sinus syndrome, bradycardia, accessory bypass tract (e.g., Wolff-Parkinson-White), or current evidence of long QT syndrome or Torsades de pointe
- Abnormal screening laboratory values including: ALT, AST or bilirubin >1.5xULN or serum creatinine ≥ 2 mg/dL
- Taking, or plans to take, one or more of the following medications (non-inclusive)within the washout periods:
  - Clinically relevant CYP3A4 Inhibitors and Inducers: 2 weeks or 5 t½ lives (whichever is longer)
  - Centrally acting anticholinergics or antihistamines: 2 weeks
  - Melatonin: 2 weeks
  - Anticonvulsants: 2 weeks
  - Antipsychotics: 2 weeks
  - Anxiolytics: 2 weeks
  - Benzodiazepines: 2 weeks or 5 t½ lives (whichever is longer)
  - Hypnotics: 2 weeks or 5 t½ lives (whichever is longer)
  - Any CNS depressants: 2 weeks
  - Over-the-counter medications that could affect sleep (e.g., kava-kava, valerian, Benadryl [diphenhydramine] St. John's Wort): 2 weeks
  - Stimulants: 2 weeks
  - Diet pills: 2 weeks
- Positive screening urine drug screen (e.g., positive for benzodiazepines, cannabinoids, cocaine, etc.).
- Any of the following:
  - A lifetime history of bipolar disorder, a psychotic disorder, or posttraumatic stress disorder;
  - A psychiatric condition requiring treatment with a prohibited medication
  - Other current psychiatric condition that, in the investigator's opinion, would interfere with the patient's ability to participate in the study
  - Evidence of suicidality
- History of substance abuse or dependence
- In the opinion of the Investigator, difficulty sleeping due to tobacco, caffeine, or alcohol use
- History of malignancy 5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer
- History of transmeridian travel (across > 3 time zones or > 3 hour time difference) within the past 2 weeks

- History of shift work (defined as permanent night shift or rotating day/night shift work) within the past 2 weeks or anticipates need to perform shift work during the study
- History or diagnosis of: narcolepsy; cataplexy, Circadian Rhythm Sleep Disorder; parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and REM behaviour disorder; Sleep-related Breathing Disorder (obstructive or central sleep apnea syndrome, central alveolar hypoventilation syndrome); Periodic Limb Movement Disorder; Restless Legs Syndrome; or Primary Hypersomia
- In the opinion of the Investigator, difficulty sleeping due to a confounding medical condition. NOTE: Medical Conditions may include chronic pain syndromes, chronic migraines, cardiac disease, nocturia (>3 times/night), asthma, gastroesophageal reflux disease (GERD), or hot flashes
- BMI > 40 kg/m^2 .

The study treatments were:

1. Suvorexant 40 mg for subjects aged <65 years and 30 mg for subjects aged ≥ 65 years
2. Placebo

The treatments were administered orally at bedtime. Subjects treated with suvorexant were re-randomised in the ratio 1:1 to suvorexant or placebo during the 2 month discontinuation phase.[27] Treatment duration was for 12 months, followed by a 2 month discontinuation phase.

The study was primarily a safety and tolerability study, but the following efficacy outcome measures were obtained:

- Morning e-diary
  - subjective total sleep time (sTST)
  - subjective time to sleep onset (sTSO)
- Clinical Global Impressions-Severity (CGI-S) scale
- Clinical Global Impressions- Improvement (CGI-I) scale
- Patient Global Impressions-Severity (PGI-S) scale
- Patient Global Impressions-Improvement (PGI-I) scale
- Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16)
- Insomnia Severity Index (ISI).

The safety outcome measures were: laboratory evaluations, urine drug screen, physical examination, ECG, vital signs, Columbia Suicide Severity Rating Scale (C-SSRS), rebound insomnia and potential withdrawal symptoms will be assessed using the e-diary containing the morning questionnaire and the Tyrer Withdrawal Symptom Questionnaire (administered in the evening) during the Double-Blind Run-out Phase.

The sample size was determined by regulatory safety requirements in order to have 200 subjects (100 aged <65 years and 100 ≥ 65 years) complete 12 months treatment with suvorexant. The intended sample size was 500 treated with suvorexant and 250 with placebo, with 50% subjects aged <65 years and 50% aged ≥ 65 years.

There were 522 subjects randomized to suvorexant, of whom 322 (61.7%) completed the study. There were 259 subjects randomized to placebo, of whom 162 (62.5%) completed the study.

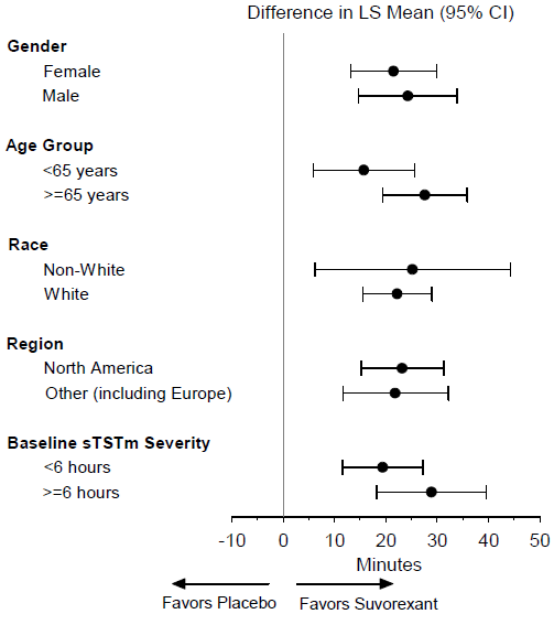
[27] Erratum: Subjects treated with suvorexant during the 12-month Treatment phase received suvorexant or placebo in a 1:1 ration during the following 2-month discontinuation phase, as determined at Visit 2.

There were 44 (8.4%) subjects in the suvorexant group and 28 (10.8%) in the placebo that withdrew because of lack of efficacy. Eight subjects were excluded from the FAS because of absent baseline data. All 322 suvorexant treated subjects that completed 12 months entered the withdrawal phase: 156 randomized to suvorexant and 166 to placebo.

There were 436 (56.0%) females, 343 (44.0%) males and the age range was 18 to 90 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar for efficacy measures at baseline.

Over the first month of treatment there was a significant increase in subjective total sleep time in the suvorexant group: LS mean (95% CI) difference suvorexant-placebo 22.7 (16.4 to 29.0) minutes, p <0.0001. There was no effect for gender, age group, race, region or baseline sTST (Figure 19).

Figure 19. Difference in LS Means (95% CI) between Suvorexant and Placebo for Month 1 (Average of Weeks 1, 2, 3, 4) for sTSTm by Subgroup



Mean subjective Wake After Sleep Onset (sWASO) decreased in the suvorexant group: LS mean (95% CI) difference suvorexant-placebo -9.3 (-13.5 to -5.1) minutes, p <0.0001. Mean subjective Time to Sleep Onset (sTSO) decreased in the suvorexant group: LS mean (95% CI) difference suvorexant-placebo -9.5 (-14.6 to -4.5) minutes, p <0.0002. The improvements in sTST, sWASO and sTSO were maintained to Month 12. At Month 12, the mean (95% CI) improvement in sTST relative to placebo was 27.5 (16.2 to 38.8) minutes p <0.0001, sWASO was -9.7 (-16.5 to -3.0) p = 0.0048, and sTSO was -9.7 (-16.5 to -2.9) p = 0.0055. There was a small increase in the subjective quality of sleep in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), p <0.0001; and at Month 12: 0.1 (0.0 to 0.2) p = 0.0338. There was a small increase in the subjective refreshed upon waking up in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), p <0.0001; and at Month 12: 0.2 (0.0 to 0.3) p = 0.0162. There was an improvement in Insomnia Severity Index that persisted to Month 12: LS mean difference (95% CI) at Month 12: -0.9 (-1.8 to -0.0) p = 0.0390. There was an improvement in Clinical Global Impression of Severity (CGI-S) that persisted to Month 12: LS mean difference (95% CI) at Month 12: -0.4 (-0.6 to -0.2) p = 0.0003. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) at Month 12: -0.5 (-0.7 to -0.3) p <0.0001. There was an improvement in Patient Global Impression of Severity (PGI-S) that persisted to Month 12: LS mean difference (95% CI) at Month 12: -0.3 (-0.5 to -0.1) p = 0.0110. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) at

Month 12: -0.5 (-0.7 to -0.3) p <0.0001. There was no difference between the groups at any time point in Quick Inventory of Depressive Symptomatology (QIDS).

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

A pooled analysis of the Phase 2 and 3 efficacy data (Study 617) estimated that 2/3 of efficacy was preserved at Month 1 and Month 3 relative to Night 1. In the ≥ 65 years age group, there was greater improvement in WASO, but lesser improvement in LPS from baseline compared to subjects <65 years. Gender, race, ethnicity and cohort did not have significant effects on efficacy.

A study that combined the data from Study P028 and P029 (Study 636) calculated a mean (95% CI) improvement from baseline to Month 3 in sTST of 22.1 (17.2[28] to 28.1) minutes for high dose, and 16.0 (9.2 to 22.8) minutes for low dose; in sWASO of -7.8 (-11.5 to -4.1) minutes for high dose, and -4.7 (-8.9 to -0.5) minutes for low dose; and in sTSO of -10.8 (-14.6 to -7.0) minutes for high dose, and -5.9 (-10.2 to -1.6) minutes for low dose. For subjects aged ≥ 75 years the mean (95% CI) improvement from baseline to Month 3 in sTST was 12.8 (-8.9 to 34.5) minutes for high dose, and 16.0 (-9.5 to 41.5) minutes for low dose; in sWASO of -8.8 (-22.1 to 4.5) minutes for high dose, and -10.4 (-26.0 to 5.2) minutes for low dose; and in sTSO of -5.1 (-18.7 to 8.6) minutes for high dose, and -2.6 (-18.6 to 13.5) minutes for low dose.

6.2. Evaluator's conclusions on clinical efficacy for primary insomnia

The efficacy of high dose suvorexant (40 mg for subjects <65 years age and 30 mg for subjects ≥ 65 years age) is supported by the following findings:

- Sleep maintenance was improved by high dose suvorexant in comparison with placebo through to Month 3. In Study P028, at Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 19.7 (11.9 to 27.6) minutes, p <0.00001, sWASO was -6.9 (-11.9 to -2.0) minutes, p = 0.00565; and WASO was -22.0 (-29.6 to -14.4)[29] minutes, p <0.00001. In Study P029, at Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 25.1 (16.0 to 34.2) minutes, p <0.00001, sWASO was -8.9 (-14.4 to -3.4) minutes, p = 0.00167; and WASO was -29.4 (-36.7 to -22.1) minutes, p <0.00001.
- Sleep onset was improved by high dose suvorexant in comparison with placebo through to Month 3. In Study P028, at Month 3, the improvement in sTSO was -8.4 (-12.8 to -4.0) minutes, p = 0.00019; and in LPS was -9.4 (-14.6 to -4.3), p = 0.00037. In Study P029, at Month 3, the improvement in sTSO was -13.2 (-19.4 to -7.0) minutes, p = 0.00003; and in LPS was -3.6 (-10.1 to 2.8), p = 0.26510
- The secondary efficacy outcome measures supported the efficacy of high dose suvorexant.

The efficacy of low dose suvorexant (20 mg for subjects <65 years age and 15 mg for subjects ≥ 65 years age) is supported by the following findings:

- In Study P028, sleep maintenance was initially improved by low dose suvorexant in comparison with placebo but the benefit was not sustained through to Month 3. At Month 3, the improvement in sTST, relative to placebo, was 10.7 (1.9 to 19.5) minutes, p = 0.01711; sWASO was -2.4 (-7.9 to 3.1) minutes, p = 0.38819; and WASO was -16.3 (-24.7 to -7.8)[30]. In Study P029, at Month 3, the improvement in sTST, relative to placebo, was 22.1 (11.5 to 32.6) minutes, p = 0.00004; sWASO was -7.7 (-14.1 to -1.3) minutes, p = 0.01885; and WASO was -31.1 (-40.1 to -22.2) p <0.00001
- In Study P028, sleep onset was not improved to the same extent, as for high dose, by low dose suvorexant in comparison with placebo through to Month 3. The improvement in sTSO

[28] Erratum: 16.1
[29] Erratum: -22.9 (-30.3, -15.4)
[30] Erratum: -16.6 (-24.8 to -8.3) p=0.00009

was approximately 5 minutes and marginally statistically significant: -5.2 (-10.2 to -0.3) minutes, p = 0.03771. The improvement in LPS was -7.3 (-13.0 to -1.5), p = 0.01347.[31] In Study P029, the improvement in sTSO was -7.6 (-14.7 to -0.4) minutes, p = 0.03894. The improvement in LPS was -0.3 (-8.3 to 7.6), p = 0.93219

- The secondary efficacy outcome measures supported efficacy for low dose suvorexant but not as strongly as for high dose.

Efficacy for both high dose and low dose was demonstrated for both the <65 year age group and the ≥ 65 year age group. There were no consistent subgroup effects.

The data from Study P028 did not support efficacy beyond three months duration of treatment for either the low dose or high dose treatment. However, the data from Study P009, which was only for the high dose (40 mg for subjects <65 years and 30 mg for subjects ≥ 65 years) and which was primarily intended as a long-term safety and tolerability study reported the following at Month 12: the mean (95% CI) improvement in sTST relative to placebo was 27.5 (16.2 to 38.8) minutes p <0.0001, sWASO was -9.7 (-16.5 to -3.0) p = 0.0048, and sTSO was -9.7 (-16.5 to -2.9) p = 0.0055. There was a small increase in the subjective quality of sleep in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), p <0.0001; and at Month 12: 0.1 (0.0 to 0.2) p = 0.0338. There was a small increase in the subjective refreshed upon waking up in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), p <0.0001; and at Month 12: 0.2 (0.0 to 0.3) p = 0.0162. There was an improvement in Insomnia Severity Index that persisted to Month 12: LS mean difference (95% CI) -0.9 (-1.8 to -0.0) p = 0.0390. There was an improvement in Clinical Global Impression of Severity (CGI-S) that persisted to Month 12: LS mean difference (95% CI) -0.4 (-0.6 to -0.2) p = 0.0003. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) p <0.0001. There was an improvement in Patient Global Impression of Severity (PGI-S) that persisted to Month 12: LS mean difference (95% CI) -0.3 (-0.5 to -0.1) p = 0.0110. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) p <0.0001.[32]

The subjects included in the pivotal studies (Study P028 and Study P029) did not all have to satisfy PSG criteria[33] for primary insomnia. Those subjects in the Questionnaire only cohorts did not undergo PSG in the screening phase and were included in the study on the basis of self-report. Hence, although some of these subjects may not have satisfied the PSG inclusion criteria the results are still generalisable to the intended treatment group. In clinical practice in Australia, few patients presenting with primary insomnia would undergo polysomnography.

The efficacy endpoints used in the clinical trial were appropriate and measured objective endpoints for sleep maintenance and sleep onset. Subjective measures were used for measuring subject wellbeing. The statistical analyses were appropriate and the studies were well powered up to the Month 3 time point.

In the pivotal studies (Study P028 and Study P029) for all the primary efficacy outcome measures there were substantial improvements in the placebo groups over time, from Baseline to Month 3. Generally, there was little apparent dose effect between the high dose and low dose groups, particularly for the PSG endpoints.[34] There was also less apparent effect for suvorexant by subjective measures compared to PSG. In Study P029, although at Night 1 there was

[31] Erratum: The improvement in LPS was -8.1 (-13.8 to -2.3), p = 0.00606

[32] Erratum: There was an improvement in Patient Global Impression of Improvement (PGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) p <0.0001.

[33] Erratum: The subjects included in the pivotal studies (Study P028 and Study P029) did not all have to satisfy PSG criteria.

[34] Erratum: A dose-response relationship was not demonstrated between low-dose and high-dose suvorexant treatments.

improvement in sleep onset, there was no apparent benefit at Month 3. These results indicate that the natural history of primary insomnia in the study population was to improve over time and also lend support to the selection of the low dose when initiating treatment.

In addition, the subjective and objective (PSG) endpoints did not show the same responses, which may indicate that these outcome measures were measuring different concepts. Patients may perceive their insomnia differently to how it is measured by polysomnography.

In conclusion, the data support the Sponsor's amended dosing recommendations. Although the efficacy data for the low dose (20 mg for subjects <65 years age and 15 mg for subjects ≥ 65 years age) are not as compelling as for the high dose (40 mg for subjects <65 years age and 30 mg for subjects ≥ 65 years age) there are sufficient data to conclude efficacy. However, the efficacy of the low dose (20 mg for subjects <65 years age and 15 mg for subjects ≥ 65 years age) has not been demonstrated for more than 3 months duration. Efficacy has only been demonstrated for primary insomnia and not for any other indication. There are insufficient data to support a 10 mg dose recommendation.

7. Clinical safety

7.1. Studies providing evaluable safety data

In the development program for suvorexant there were 32 Phase 1 studies, one Phase 2 dose-finding study, two Phase 3 efficacy studies and one long term Phase 3 safety study.

7.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs)
- AEs of particular interest, including behavioural sleep disturbance, residual effects, suicidality, abuse potential, withdrawal effects and tolerance
- Laboratory tests, including serum biochemistry and haematology[35].

7.1.2. Pivotal studies that assessed safety as a primary outcome

There were two pivotal efficacy/safety studies and one long term safety study included in the submission.

7.2. Pivotal studies that assessed safety as a primary outcome

Studies P028 and P029 assessed safety as a primary outcome. Study P009 assessed safety as the primary outcome.

7.3. Patient exposure

7.3.1. Phase 1 studies

There were 922 subjects enrolled in the Phase 1 studies, 842 subjects were exposed to at least one dose of suvorexant, of whom 111 were aged ≥ 65 years. There were 575 (62.4%) males and

[35] and ECG test parameters, and vital sign measures (weight, blood pressure , pulse, temperature); Suicidal ideation and behaviour assessed by Columbia Suicidalitiy Severity Rating Scale, Suicidal ideation and behaviour assessed by Columbia Suicidalitiy Severity Rating Scale, Residual effects assessed by Digit Symbol Substitution Test, Withdrawal assessed by Tyrer Withdrawal Symptom Questionnaire (WSQ), Rebound assessed by subjective (sleep diary) and objective (PSG) sleep endpoints

347 (37.6%) females. There were 190[36] subjects exposed to the dose range >40 to 80 mg and 133 exposed to the dose range >80 to 240 mg.

7.4. Phase 2 studies

In Study P006, there were 62 subjects exposed to 10 mg, 62 to 20 mg, 61 to 40 mg and 62 to 80 mg; administered each night for up to 31 days.

7.5. Phase 3 studies

In the combined Phase 3 population (Study P009, Study P028 and Study P029) there were 2,809 subjects: 1,291 treated with high dose suvorexant, 493 with low dose and 1,025 with placebo. There were 1,744 (62.1%) females, 1,065 (37.9%) males, 1,029 subjects aged 65 to 74 years, and 269 subjects aged ≥ 75 years. There were 500 subjects aged 65 to 74 years and 127 aged ≥ 75 years treated with high dose suvorexant.

In Study P009, there were 521 subjects exposed to suvorexant for up to 434 days. There were 324 subjects exposed to the 30 mg dose and 212 to the 40 mg dose.

In Study P028, there were 637 subjects exposed to suvorexant. There were 225 subjects exposed to suvorexant 40 mg, with 161 exposed for over 3 months and 50 for over 6 months. There were 162 subjects exposed to suvorexant 30 mg, with 115 exposed for over 3 months and 37 for over 6 months. There were 147 subjects exposed to suvorexant 20 mg, with 104 exposed for over 3 months and 20 for over 6 months. There were 107 subjects exposed to suvorexant 15 mg, with 72 exposed for over 3 months and 22 for over 6 months.

In Study P029, there were 626 subjects exposed to suvorexant. There were 233 subjects exposed to suvorexant 40 mg, with 137 exposed for over 3 months. There were 158 subjects exposed to suvorexant 30 mg, with 93 exposed for over 3 months. There were 144 subjects exposed to suvorexant 20 mg, with 68 exposed for over 3 months. There were 95 subjects exposed to suvorexant 15 mg, with 46 exposed for over 3 months.

7.6. Adverse events

7.6.1. All adverse events (irrespective of relationship to study treatment)

7.6.1.1. Pivotal studies

In Study P006 TEAEs were reported in eleven (17.7%) subjects in the suvorexant 10 mg group, 12 (19.7%) in the 20 mg, 18 (30.5%) in the 40 mg, 22 (36.1%) in the 80 mg and 50 (20.1%) with placebo. Somnolence was the most common TEAE in the suvovexant group, and the incidence increased with dose: one (1.6%) subject with 10 mg, three (4.9%) with 20 mg, six (10.2%) with 40 mg, seven (11.5%) with 80 mg, and one (0.4%) with placebo. No other TEAE occurred in more than 10% of any group.

In Study P009, TEAEs were reported in the treatment phase in 362 (69.5%) subjects in the suvorexant group and 164 (63.6%) in the placebo. In the treatment phase psychiatric disorders were more common in the suvorexant group: 58 (11.1%) subjects compared with 15 (5.8%) in the placebo. Abnormal dreams, nightmare and depression were more common with suvorexant.[37] Fatigue and peripheral oedema were more common with suvorexant. TEAEs were reported in the discontinuation phase in 35 (22.4%) subjects in the suvorexant group and 38 (22.9%) in the placebo. There were 13 (2.5%) subjects in the suvorexant group and two (0.8%) in the placebo that reported excessive daytime sleepiness. Sleep paralysis was reported in two

[36] Erratum: 224

[37] Erratum: Abnormal dreams and nightmare were more common with suvorexant.

(0.4%) subjects in the suvorexant group and none in the placebo. Falls were reported in twelve (2.3%) subjects in the suvorexant group and eight (3.1%) in the placebo. Motor vehicle accidents or violations were reported in 22 (5.5%) subjects in the suvorexant group and eight (4.1%) in the placebo. In the discontinuation group the pattern of TEAEs was similar for the two groups.

In Study P028, in the 3 month treatment phase TEAEs were reported in 198 (51.7%) subjects in the high dose group, 126 (49.6%) in the low dose and 191 (49.7%) in the placebo. The commonest TEAE was somnolence, occurring in 41 (10.7%) subjects in the high dose group, 13 (5.1%) in the low dose and 13 (3.4%) in the placebo. In the extension phase, TEAEs were reported in 59 (34.3%) subjects in the high dose group, 32 (32.0%) in the low dose and 42 (27.8%) in the placebo. In the run out phase TEAEs were reported in five (3.1%) subjects continuing on high dose, 13 (8.0%) subjects ceasing high dose, six (5.9%) subjects continuing low dose, seven (6.3%) subjects ceasing low dose, and 17 (5.2%) subject continuing placebo. No individual event was reported in ≥ 2% subjects in any group. Overall, there were no reports of complex sleep-related behaviours. There was one subject reported with hypnagogic hallucinations in the low dose group. Sleep paralysis was reported in two (0.5%) subjects in the high dose group and one (0.4%) in the low dose. No events were considered to be cataplexy. Falls were reported in four (1.0%) subjects in the high dose group, three (1.2%) in the low dose and five (1.3%) in the placebo.

In Study P029, TEAEs were reported in 189 (48.8%) subjects in the high dose group, 103 (43.1%) in the low dose and 167 (43.6%) in the placebo. The commonest TEAE was somnolence, occurring in 40 (10.3%) subjects in the high dose group, 20 (8.4%) in the low dose and 12 (3.1%) in the placebo. In the run out phase TEAEs were reported in 16 (9.2%) subjects continuing on high dose, ten (5.8%) subjects ceasing high dose, three (3.1%) subjects continuing low dose, seven (6.5%) subjects ceasing low dose, and 20 (6.1%) subject continuing placebo. No individual event was reported in ≥ 2% subjects in any group in the run-out phase. One subject in the high dose group was reported with complex sleep-related behaviours: parasomnia and sleep walking. Hypnagogic / hypnopompic hallucinations were reported by one subject in the high dose group and one in the low dose. Sleep paralysis was reported in one (0.3%) subject in the high dose group. No events of cataplexy were reported.

The Integrated Summary of Safety did not indicate any differences in rates of TEAEs by gender or age group.

7.6.1.2. Other studies

In the Phase 1 studies, TEAEs were reported in 597 (76.3%) subjects treated with suvorexant, 105 (67.7%) treated with suvorexant plus another drug, 154 (45.8%) treated with other drugs and 166 (41.3%) with placebo. Somnolence was the most commonly reported TEAE with suvorexant and this was attributed to the morning dosing in the majority of the studies.

7.6.2. Treatment-related adverse events (adverse drug reactions)

7.6.2.1. Pivotal studies

In Study P006 treatment related TEAEs were reported in three (4.8%) subjects in the suvorexant 10 mg group, four (6.6%) in the 20 mg, 12 (20.3%) in the 40 mg, 14 (23.0%) in the 80 mg and 17 (6.8%) with placebo. Treatment related TEAEs were significantly more common with the 40 mg and 80 mg dose levels than with placebo: difference (95% CI) 14.7 (5.4 to 27.1) % subjects and 16.1 (6.7 to 28.4) % respectively. The most commonly reported treatment related TEAE was somnolence, reported in no subject with 10 mg, three (4.9%) with 20 mg, seven (11.9%) with 40 mg, six (9.8%) with 80 mg, and one (0.4%) with placebo.

In Study P009 treatment related TEAEs were reported in the treatment phase in 182 (34.9%) subjects in the suvorexant group and 53 (20.5%) in the placebo. There were significantly more treatment related TEAEs in the suvorexant group: difference (95% CI) in % compared with

placebo 14.4 (7.8 to 20.6) %. Somnolence, fatigue and dry mouth were more common with suvorexant. Treatment related TEAEs were reported in the discontinuation phase in six (3.8%) subjects in the suvorexant group and three (1.8%) in the placebo.

In Study P028 in the 3 month treatment phase, treatment related TEAEs were reported in 96 (25.1%) subjects in the high dose group, 51 (20.1%) in the low dose and 53 (13.8%) in the placebo. In the high dose group, somnolence was reported in 38 (9.9%) subjects and headache in eleven (2.9%). In the extension phase, treatment related TEAEs were reported in eleven (6.4%) subjects in the high dose group, three (3.0%) in the low dose and six (4.0%) in the placebo.

In Study P029 treatment related TEAEs were reported in 86 (22.2%) subjects in the high dose group, 58 (24.3%) in the low dose and 63 (16.4%) in the placebo. Somnolence was reported in 36 (9.3%) subjects in the high dose group, 19 (7.9%) in the low dose and eleven (2.9%) in the placebo.

7.6.2.2. Other studies

In the Phase 1 studies, treatment related TEAEs were reported in 549 (70.2%) subjects treated with suvorexant, 97 (62.6%) treated with suvorexant plus another drug, 135 (40.2%) treated with other drugs and 109 (27.1%) with placebo.

7.6.3. Deaths and other serious adverse events

7.6.3.1. Pivotal studies

In Study P006 there were no deaths and no SAEs reported.

In Study P009 there were no deaths reported. SAEs were reported in the treatment phase in 27 (5.2%) subjects in the suvorexant group and 17 (6.6%) in the placebo. There was no clear pattern to the SAEs. One subject in the suvorexant group reported suicidal ideation. SAEs were reported in the discontinuation phase in three (1.9%) subjects in the suvorexant group (positional vertigo, cellulites, squamous cell carcinoma) and one (0.6%) in the placebo (breast cancer in situ).

In Study P028 in the 3 month treatment phase there was one death in the placebo group (cerebrovascular accident). SAEs were reported in no subjects in the high dose group, one (0.4%) in the low dose (pneumonia) and eleven (2.9%) in the placebo. In the extension phase there were no deaths, and SAEs were reported in three (1.7%) subjects in the high dose group (subarachnoid haemorrhage, basal call carcinoma and duodenal ulcer), and no subjects in the low dose or placebo groups. In the run-out phase, one (0.6%) subject in the group ceasing high dose was reported with a SAE (atrial fibrillation).

In Study P029 there was one death in the high dose group (near-drowning / hypoxic-ischaemic encephalopathy). SAEs were reported in six (1.6%) subjects in the high dose group, two (0.8%) in the low dose and five (1.3%) in the placebo. No individual event was reported in more than one subject. In the run-out phase there were no deaths and only one SAE in the group discontinuing low dose (meningitis).

7.6.3.2. Other studies

There were no deaths reported in the Phase 1 studies.

In the Phase 1 studies, SAEs were reported in four (0.5%) subjects treated with suvorexant, none treated with suvorexant plus another drug, none treated with other drugs and none with placebo:

- In Study P013: One subject with appendicitis after 6 days of suvorexant 40 mg daily
- In Study P022: One SAE at 240 mg: chest pain/ myoclonus / sleep paralysis

- In Study P027: pyrexia (febrile illness requiring hospitalisation) 24 days after the last dose of suvorexant 40 mg
- In Study P035: One subject reported an induced abortion.

7.6.4. Discontinuation due to adverse events

7.6.4.1. Pivotal studies

In Study P006, DAE occurred for one (1.6%) subject in the 80 mg group (visual hallucinations), and three (1.2%) with placebo (ALT increased, irritability/ difficulty thinking/ sedation, wide complex tachycardia).

In Study P009, DAE occurred for 61 (11.7%) subjects in the suvorexant group and 22 (8.5%) in the placebo, in the treatment phase. Somnolence was more common in the suvorexant group: 20 (3.8%) subjects compared with two (0.8%) in the placebo. Two subjects in the suvorexant group discontinued because of suicidal ideation. DAE occurred in the discontinuation phase for one (0.6%) subject in the placebo group.

In Study P028 in the 3 month treatment phase DAE occurred for 13 (3.4%) subjects in the high dose group, six (2.4%) in the low dose and eight (2.1%) in the placebo. Nervous system disorders were more common in the high dose group, with somnolence the reason for discontinuation in seven (1.8%) subjects. In the extension phase, DAE was reported for four (2.3%) subjects in the high dose group (hypertensive crisis, amnesia, nightmare, and subarachnoid haemorrhage). In the run-out phase, DAE occurred for one (0.6%) subject in the group ceasing high dose (atrial fibrillation).

In Study P029 DAE occurred for 18 (4.7%) subjects in the high dose group, nine (3.8%) in the low dose and 17 (4.4%) in the placebo. Two subjects in the high dose group ceased due to nightmares, and one in the low dose group because of suicidal ideation. DAE did not occur for any subject during the run-out phase.

7.6.4.2. Other studies

In the Phase 1 studies, SAEs were reported in ten (1.3%) subjects treated with suvorexant, one (0.6%) treated with suvorexant plus another drug, three (0.9%) treated with other drugs and one (0.2%) with placebo. In Study P022 there were two subjects with DAE, both at 240 mg: chest pain/ myoclonus / sleep paralysis; respiratory depression.

7.7. Laboratory tests

7.7.1. Liver function

7.7.1.1. Pivotal studies

In Study P006 two subjects had elevation of ALT with placebo and none with suvorexant.

In Study P009 two (0.4%) subjects in the suvorexant group and one (0.4%) in the placebo had elevation of ALT >3xULN. Three (0.6%) subjects in the suvorexant group and four (1.6%) in the placebo had elevation of AST >3xULN.

In Study P028 in the treatment phase there were two (0.5%) subjects in the high dose group with elevated ALT, one (0.4%) in the low dose and none in the placebo. There was one (0.3%) subject in the high dose group with elevated AST, one (0.4%) in the low dose and none in the placebo. There was one (0.3%) subject in the high dose group with elevated bilirubin, one (0.4%) in the low dose and none in the placebo. In the extension phase there was one subject in the placebo group with elevated ALT and AST.

In Study P029 elevation of ALT >3xULN was reported in three (0.8%) subjects in the high dose group and one (0.4%) in the low dose. There were no significant (>3xULN) elevations in AST.

Bilirubin was elevated by >166.7%xULN in four (1.0%) subjects in the high dose group, one (0.4%) in the low dose and two (0.5%) in the placebo.

7.7.2. Kidney function

7.7.2.1. Pivotal studies

In Study P006, no subject had a clinically significant elevation in serum creatinine.

In Study P009, two (0.4%) subjects in the suvorexant group and three (1.2%) in the placebo had elevation of serum creatinine.

In Study P028, there were no subjects with elevated serum creatinine.

In Study P029, one (0.4%) subject in the low dose group and two (0.5%) in the placebo had elevation of serum creatinine >142.5%xULN.

7.7.3. Other clinical chemistry

There were no other clinically significant abnormalities in clinical chemistry.

7.7.4. Haematology

7.7.4.1. Pivotal studies

In Study P006, there were no clinically significant changes in haematology parameters.

In Study P009, three (0.6%) subjects in the suvorexant group and three (1.2%) in the placebo had neutropenia.

In Study P028, there were three (0.8%) subjects in the high dose group with decreased neutrophil count, two (0.8%) in the low dose and none in the placebo.

In Study P029 decreased neutrophil count was reported in two (0.5%) subjects in the high dose group, three (1.3%) in the low dose and one (0.3%) in the placebo. Decreased platelet count was reported in one (0.4%) subject in the low dose group.

7.7.5. Electrocardiograph

7.7.5.1. Pivotal studies

In Study P006 there were 28 (11.6%) subjects in the suvorexant groups and 30 (12.2%) in the placebo that had QTcB prolongation ≥ 30 msec and ≤60 msec; three (1.2%) in the suvorexant and one (0.4%) in the placebo had prolongation >60 msec and no subject had QTcB >500 msec.

In Study P009 there were 79 (15.4%) subjects in the suvorexant group and 42 (16.5%) in the placebo with prolongation of QTcB, compared to baseline, of ≥ 30 msec and ≤60 msec; three (0.6%) in the suvorexant and four (1.6%) in the placebo with prolongation >60 msec; and one (0.4%) in the placebo with QTcB >500 msec.

In Study P028 prolongation, from baseline, of QTcB ≥ 30 msec and ≤60 msec was reported in 40 (10.5%) subjects in the high dose group, 21 (8.3%) in the low dose and 36 (9.5%) in the placebo. Prolongation >60 msec was reported in one (0.4%) subject in the low dose group and one (0.3%) in the placebo. One subject in the high dose group was reported with a QTc ≥ 500 msec.

In Study P029 prolongation in QTcB from baseline ≥ 30 msec to ≤60 msec was reported in 37 (9.7%) subjects in the high dose group, 27 (11.8%) subjects in the low dose and 43 (11.6%) in the placebo. Prolongation from baseline >60 msec was reported in one (0.3%) subject in the high dose group and four (1.1%) in the placebo. A QTcB of ≥ 500 msec was reported in one (0.3%) subject in the high dose group.

7.7.5.2. Other studies

In Study P001 there was no difference in QTc interval between placebo and a single 120 mg oral dose, over a 12 hour time interval.

7.7.6. Vital signs

7.7.6.1. Pivotal studies

In Study P006 there were no significant changes in the mean values of vital signs. Seven subjects had a decrease in sitting SBP of ≥ 20 mmHg from baseline to Week 4 with suvorexant. Nine (3.7%) subjects in the suvorexant groups had an orthostatic decrease in blood pressure ≥ 20 mmHg at Week 4, compared to 13 (5.2%) in the placebo.

In Study P009 the proportions of subjects with abnormalities in vital signs were similar for suvorexant and placebo.

In Study P028 there were three subjects in the suvorexant high dose group with decreases in SBP and DBP respectively.

In Study P029 the distribution of subjects with changes in vital signs was similar for the three treatment groups.

7.7.7. Rebound insomnia

7.7.7.1. Pivotal studies

In Study P006 there was no consistent indication of rebound insomnia in the suvorexant groups during the washout period.

In Study P009, on treatment withdrawal, there was mean decrease in sTST of 30 minutes that persisted for at least 6 months[38] compared with the group on continuing treatment (Figure 20). However, this change may reflect a return to pre-treatment values rather than rebound. There was an increase in sWASO at Week 1 of 12 minutes that decreased to Week 8 (Figure 21) that may represent a rebound phenomenon. There was mean increase in sTSO of approximately 17 minutes at Week 1 that decreased to approximately 12 minutes by Week 8 (Figure 22).

[38] Erratum: 8 weeks

Figure 20. Adjusted Means and 95% Confidence Intervals for Change from Month 12 in Mean Subjective Total Sleep Time (sTSTm; minutes) During the Randomized Discontinuation Phase (LDA / Full Analysis Set / Data-as-Observed)

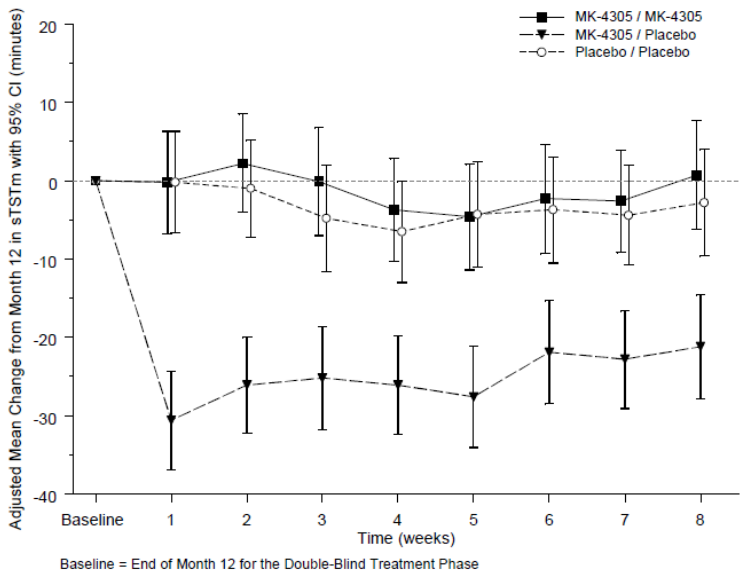


Figure 21. Adjusted Means and 95% Confidence Intervals for Change from Month 12 in Mean Subjective Wake Time After Sleep Onset (sWASOm; minutes) During the Randomized Discontinuation Phase (LDA / Full Analysis Set / Data-as-Observed)

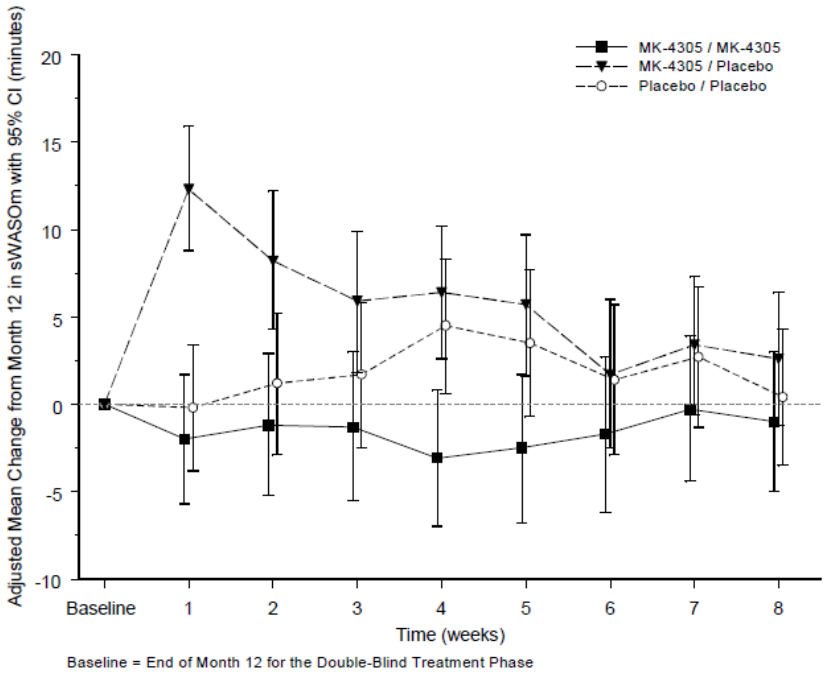
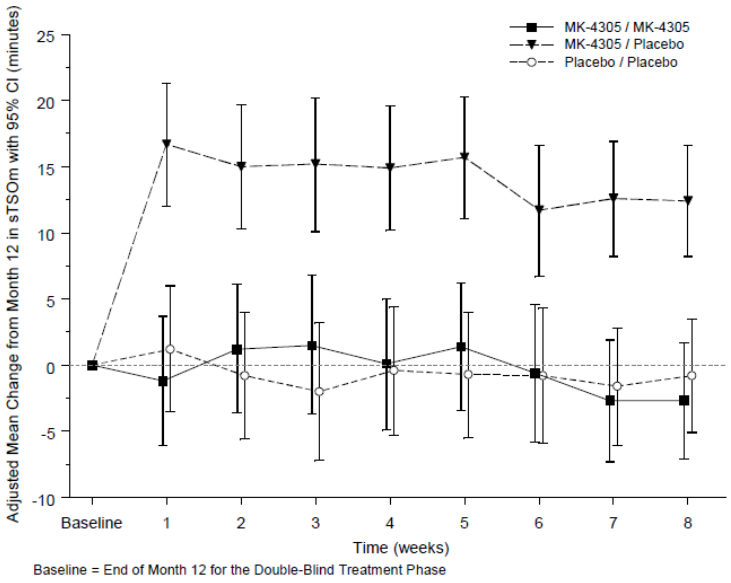


Figure 22. Adjusted Means and 95% Confidence Intervals for Change from Month 12 in Mean Subjective Time to Sleep Onset (sTSOm; minutes) During the Randomized Discontinuation Phase (LDA / Full Analysis Set / Data-as-Observed



In Study P028, rebound by WASO was reported in 29 (34.5%) subjects ceasing high dose, compared to seven (9.1%) continuing; and in 25 (41.0%) subjects ceasing low dose, compared to three (5.0%) continuing. The difference % (95% CI) compared to placebo was 12.9 (1.4 to 24.9) % for high dose and 19.3 (6.1 to 33.1) % for low dose. Rebound by LPS was reported in 19 (22.1%) subjects ceasing high dose, compared to eleven (14.3%) continuing; and in 13 (20.6%) subjects ceasing low dose, compared to four (6.7%) continuing. The difference % (95% CI) compared to placebo was 3.9 (-6.0 to 15.0) % for high dose and 2.4 (-8.0 to 15.0) % for low dose. There was no significant difference between the groups for rebound based on sTST or sTSO. However, based on sWASO, 9.4 (0.1 to 18.8) % more subjects in the high dose group compared to the placebo reported rebound.

In Study P029, rebound effects based on WASO were reported in 42 (33.1%) subjects ceasing high dose, 18 (26.5%) ceasing low dose and 66 (25.8%) on placebo; and based on LPS in 17 (13.3%) subjects ceasing high dose, eleven (16.2%) ceasing low dose and 39 (15.1%) on placebo.

7.7.8. Withdrawal effects

7.7.8.1. Pivotal studies

In Study P006 using the Tyrer Withdrawal Symptom Questionnaire, there did not appear to be withdrawal effects in the suvorexant groups.

In Study P009 in the withdrawal phase in comparison with subjects always on placebo, there was rebound, based on sTST, in 10% of the study group, and based on sTSO in 4.6%.[39,40] There was no significant difference in sWASO. In Study P009 there did not appear to be a significant

[39] Erratum: From Table 12.30 in the CSR for Study P009, for sTST, 10.82% (95% CI: -0.3 to 21.7) of the study group had rebound (on Nights 1, 2 or 3) and this had borderline statistical significance (p = 0.057). From Table 12.32 in the CSR for Study P009, for sTSO, 4.58% (95% CI: -6.3 to 15.3) of the study group had rebound (on Nights 1, 2 or 3) and this was not statistically significant from placebo treatment (p = 0.409).

[40] Erratum: Sentence should be moved to Section 7.7.7.1 *Rebound insomnia* above.

difference between groups in the number of subjects with withdrawal symptoms during the withdrawal phase.

In Study P028 there were no significant differences between the treatment groups in Tyrer Withdrawal Scores.

In Study P029 there was some evidence of withdrawal effect on Night 1 for the high dose group: point difference continuing-ceasing (95% CI) -5.2 (-10.8 to -0.7), p = 0.028. There was no significant difference for the following nights or for the low dose.

7.7.9. Suicidal ideation

In Study P009 four subjects in the suvorexant group experienced suicidal ideation during the treatment phase. Three of the four subjects had a prior history of suicidal ideation and one had made a previous suicide attempt. Using the C-SSRS five subjects in the suvorexant group and none in the placebo experienced suicidal ideation.

In Study P028, one subject in the placebo group reported suicidal ideation. There were no C-CASA events.

In Study P029 two subjects in the high dose group and one in the low dose reported suicidal ideation. Four subjects reported suicidal behaviours or thoughts during the C-SSRS assessment: three in the high dose group (one of whom had a prior history of suicidal thoughts) and one in the low does group (who also had a prior history of suicidal thoughts).

7.7.10. Abuse potential

In Study P009 there were similar proportions of subjects with AEs of potential for abuse liability in the suvorexant, 18 (3.5%) subjects, and placebo, ten (3.9%), groups. However, there were six subjects in the suvorexant group, compared with none in the placebo, with AEs of derealisation and hallucinations.

In Study P028 AEs of potential for abuse were reported in ten (2.6%) subjects in the high dose group, 14 (5.5%) in the low dose and 11 (2.9%) in the placebo.

In Study P029 nine (2.3%) subjects in the high dose group, six (2.5%) in the low dose and eight (2.1%) in the placebo were reported with one or more AEs of potential for abuse.

7.7.11. Overdose

In Study P009 there were five (1.0%) subjects in the suvorexant group and five (1.9%) in the placebo that reported overdose.

In Study P028 there were no clinically significant overdoses.

In Study P029 there were three reports of overdose[41], all of which were accidental and without major sequellae.

7.7.12. Residual effects

Residual effects were more common with suvorexant and included: somnolence in 13.2%, fatigue in 6.5% and amnesia in 0.4%.

In Study P028 excessive daytime sleepiness was reported in four subjects in the high dose group, one in the low dose and one in the placebo. Traffic accidents were reported in four (1.5%) subjects in the high dose group, three (1.7%) in the low dose and five (1.9%) in the placebo. Traffic citations were reported in four (1.5%) subjects in the high dose group, four (2.2%) in the low dose and seven (2.7%) in the placebo. There was no significant differences between the treatment groups in next day digit substitution test.

[41] One event was reported in each of the 3 treatment groups.

In Study P029 excessive daytime sleepiness was reported in three (0.8%) subjects in the high dose group and two (0.8%) in the low dose. Somnolence was reported in 40 (10.3%) subjects in the high dose group, 20 (8.4%) in the low dose and 12 (3.1%) in the placebo. Motor vehicle accidents were reported in two (0.7%) subjects in the high dose group, one (0.6%) in the low dose and two (0.7%) in the placebo. Traffic citations were reported in five (1.7%) subjects in the high dose group, four (2.5%) in the low dose and one (0.4%) in the placebo. There were no differences between groups in DSST.

7.8. Post-marketing experience

7.8.1. Post-marketing data

No post-marketing data were included in the submission.

7.9. Evaluator's overall conclusions on clinical safety

The most common TEAE with suvorexant is somnolence, which in the dose finding study was reported in one (1.6%) subject with 10 mg, three (4.9%) with 20 mg, six (10.2%) with 40 mg, seven (11.5%) with 80 mg, and one (0.4%) with placebo. In Study P028 somnolence occurred in 41 (10.7%) subjects in the high dose group, 13 (5.1%) in the low dose and 13 (3.4%) in the placebo. In Study P029 somnolence occurred in 40 (10.3%) subjects in the high dose group, 20 (8.4%) in the low dose and 12 (3.1%) in the placebo. In the clinical trials somnolence was commonly attributed to suvorexant.

Sleep paralysis was reported with suvorexant in <1% subjects in Study P028 and Study P029.

Two deaths were reported during the development program. Neither appears to have been related to suvorexant (cerebrovascular accident and near-drowning / hypoxic-ischaemic encephalopathy).[42] SAEs were uncommon and did not appear to be related to suvorexant. DAEs were also uncommon. There were at least two DAEs related to suicidal ideation. Somnolence and nightmare were more common reasons for DAE in the suvorexant groups.

In the pivotal studies elevations of ALT and/or AST were rare, but occurred more commonly with suvorexant. There was no separate listing of subjects that would have conformed to Hy's Law.[43]

Renal dysfunction was not associated with suvorexant. Suvorexant was not associated with prolongation of the QT interval, including in a thorough QT study. Clinically significant changes in vital signs were uncommon with suvorexant.

Rebound insomnia appears to be common with suvorexant. In Study P028 rebound by WASO was reported in 29 (34.5%) subjects ceasing high dose, compared to seven (9.1%) continuing; and in 25 (41.0%) subjects ceasing low dose, compared to three (5.0%) continuing.

Withdrawal effects as measured by the Tyrer Withdrawal Score are uncommon, and occur mainly on the first night following ceasing treatment. Suicidal ideation was uncommon with suvorexant. Abuse potential for suvorexant was similar to that for placebo.

There were no clinically significant overdoses during the clinical development program. Hence, the effects of suvorexant in overdose are important missing information.

Although the pharmacodynamic studies indicated significant residual effects, the clinical studies did not indicate an increased risk for traffic accidents or cognitive impairment. In the

[42] Two deaths were reported during the development program: one patient in the placebo group (cerebrovascular accident) and one patient in the suvorexant high-dose group (near-drowning/hypoxic ischaemic encephalopathy). The latter did not appear related to suvorexant treatment.
[43] Erratum: There were no subjects that conformed to Hy's Law.

Pharmacodynamic studies the time course of single dose suvorexant was examined in four PD studies at doses up to 240 mg. There did not appear to be persistence of effect beyond 8 hours for the 10 mg dose level, some persistence for the 20 mg and definite persistence for the 40 mg. The rate of next-day somnolence was estimated to be 7.9% with 20 mg, 10.6% with 40 mg and 14.2% with the 80 mg dose level. At high doses (>100 mg) the effects persisted for up to 24 hours. There was lesser abuse potential compared with zolpidem. There was significant next day driving impairment with suvorexant, similar to that for zopiclone, in non-elderly subjects but no significant impairment in elderly subjects. In Study P009 motor vehicle accidents were slightly more common with suvorexant than placebo: 22 (5.5%) subjects in the suvorexant group and eight (4.1%) in the placebo[44], but there was no increase in the rate of accidents in Study P028 or Study P029.

The Pharmacodynamic studies also investigated sleep safety. Suvorexant did not impair sleep safety in normal volunteers, subjects with chronic obstructive pulmonary disease or subjects with obstructive sleep apnoea. Suvorexant and alcohol exhibited a significant additive effect on impairment in cognitive function that lasted for up to 9 hours post-ingestion.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The efficacy of high dose suvorexant (40 mg for subjects <65 years age and 30 mg for subjects ≥ 65 years age) is supported by the following findings:

- Sleep maintenance was improved by high dose suvorexant in comparison with placebo through to Month 3. In Study P028, at Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 19.7 (11.9 to 27.6) minutes, p <0.0001, sWASO was -6.9 (-11.9 to -2.0) minutes, p = 0.00565; and WASO was -22.0 (-29.6 to -14.4)[45] minutes, p <0.00001. In Study P029, at Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 25.1 (16.0 to 34.2) minutes, p <0.00001, sWASO was -8.9 (-14.4 to -3.4) minutes, p = 0.00167; and WASO was -29.4 (-36.7 to -22.1) minutes, p <0.00001
- Sleep onset was improved by high dose suvorexant in comparison with placebo through to Month 3. In Study P028, at Month 3, the improvement in sTSO was -8.4 (-12.8 to -4.0) minutes, p = 0.00019; and in LPS was -9.4 (-14.6 to -4.3), p = 0.00037. In Study P029, at Month 3, the improvement in sTSO was -13.2 (-19.4 to -7.0) minutes, p = 0.00003; and in LPS was -3.6 (-10.1 to 2.8), p = 0.26510
- The secondary efficacy outcome measures supported the efficacy of high dose suvorexant.

The efficacy of low dose suvorexant (20 mg for subjects <65 years age and 15 mg for subjects ≥ 65 years age) is supported by the following findings:

- In Study P028, sleep maintenance was initially improved by low dose suvorexant in comparison with placebo but the benefit was not sustained through to Month 3. At Month 3, the improvement in sTST, relative to placebo, was 10.7 (1.9 to 19.5) minutes, p = 0.01711; sWASO was -2.4 (-7.9 to 3.1) minutes, p = 0.38819; and WASO was -16.3 (-24.7 to -7.8)[46]. In Study P029, at Month 3, the improvement in sTST, relative to placebo, was 22.1 (11.5 to

[44] Erratum: The clinical evaluator has cited the patients in the study population (Treatment phase) who had one or more motor vehicle accidents or violations (MVAV). The number of patients who had motor vehicle accidents were 7 (1.8%) for the suvorexant group and 3 (1.5%) for the placebo treatment.
[45] Erratum: -22.9(-30.3, -15.4)
[46] Erratum: -16.6 (-24.8 to -8.3)

32.6) minutes, p = 0.00004; sWASO was -7.7 (-14.1 to -1.3) minutes, p = 0.01885; and WASO was -31.1 (-40.1 to -22.2) p <0.00001

- In Study P028, sleep onset was not improved to the same extent by low dose suvorexant in comparison with placebo through to Month 3. The improvement in sTSO was approximately 5 minutes and marginally statistically significant: -5.2 (-10.2 to -0.3) minutes, p = 0.03771. The improvement in LPS was -7.3 (-13.0 to -1.5)[47], p = 0.01347.[48] In Study P029, the improvement in sTSO was -7.6 (-14.7 to -0.4) minutes, p = 0.03894. The improvement in LPS was -0.3 (-8.3 to 7.6), p = 0.93219
- The secondary efficacy outcome measures supported efficacy for low dose suvorexant but not as strongly as for high dose.

Efficacy for both high dose and low dose was demonstrated for both the <65 year age group and the ≥ 65 year age group. There were no consistent subgroup effects.

The data from Study P028 did not support efficacy beyond three months duration of treatment for either the low dose or high dose treatment. However, the data from Study P009, which was only for the high dose (40 mg for subjects <65 years and 30 mg for subjects ≥ 65 years) and which was primarily intended as a long-term safety and tolerability study reported the following at Month 12 the mean (95% CI) improvement in sTST relative to placebo was 27.5 (16.2 to 38.8) minutes p <0.0001, sWASO was -9.7 (-16.5 to -3.0) p = 0.0048, and sTSO was -9.7 (-16.5 to -2.9) p = 0.0055. There was a small increase in the subjective quality of sleep in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), p <0.0001; and at Month 12: 0.1 (0.0 to 0.2) p = 0.0338. There was a small increase in the subjective refreshed upon waking up in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), p <0.0001; and at Month 12: 0.2 (0.0 to 0.3) p = 0.0162. There was an improvement in Insomnia Severity Index that persisted to Month 12: LS mean difference (95% CI) -0.9 (-1.8 to -0.0) p = 0.0390. There was an improvement in Clinical Global Impression of Severity (CGI-S) that persisted to Month 12: LS mean difference (95% CI) -0.4 (-0.6 to -0.2) p = 0.0003. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) p <0.0001. There was an improvement in Patient Global Impression of Severity (PGI-S) that persisted to Month 12: LS mean difference (95% CI) -0.3 (-0.5 to -0.1) p = 0.0110. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) p <0.0001.

The subjects included in the pivotal studies (Study P028 and Study P029) did not all have to satisfy PSG criteria for primary insomnia. Those subjects in the Questionnaire only cohorts did not undergo PSG in the screening phase and were included in the study on the basis of self-report. Hence, although some of these subjects may not have satisfied the PSG inclusion criteria the results are still generalisable to the intended treatment group. In clinical practice in Australia, few patients presenting with primary insomnia would undergo polysomnography.

The efficacy endpoints used in the clinical trial were appropriate and measured objective endpoints for sleep maintenance and sleep onset. Subjective measures were used for measuring subject wellbeing. The statistical analyses were appropriate and the studies were well powered up to the Month 3 time point.

In the pivotal studies (Study P028 and Study P029) for all primary efficacy outcome measures there were substantial improvements in the placebo groups over time, from Baseline to Month 3. There was little apparent dose effect between the high dose and low dose groups, particularly for the PSG endpoints. Generally there was also less apparent effect for suvorexant by subjective measures compared to PSG. In Study P029, although at Night 1 there was improvement in sleep

[47] Erratum: -8.1 (-13.8, -2.3)
[48] Erratum: 0.00606

onset, there was no apparent benefit at Month 3. These results indicate that the natural history of primary insomnia in the study population was to improve over time and also lend support to the selection of the low dose when initiating treatment.

In addition, the subjective and objective (PSG) endpoints did not show the same responses, which may indicate that these outcome measures were measuring different concepts. Of note, there was discordance between sWASO and WASO. Patients may perceive their insomnia differently to how it is measured by polysomnography.

In conclusion, the data support the Sponsor's amended dosing recommendations. Although the efficacy data for the low dose (20 mg for subjects <65 years age and 15 mg for subjects ≥ 65 years age) are not as compelling as for the high dose (40 mg for subjects <65 years age and 30 mg for subjects ≥ 65 years age) there are sufficient data to conclude efficacy. However, the efficacy of the low dose (20 mg for subjects <65 years age and 15 mg for subjects ≥ 65 years age) has not been demonstrated for more than 3 months duration. Efficacy has only been demonstrated for primary insomnia and not for any other indication. There are insufficient data to support a 10 mg dose recommendation.

8.2. First round assessment of risks

The most common TEAE with suvorexant is somnolence, which in the dose finding study was reported in one (1.6%) subject with 10 mg, three (4.9%) with 20 mg, six (10.2%) with 40 mg, seven (11.5%) with 80 mg, and one (0.4%) with placebo. In Study P028 somnolence occurred in 41 (10.7%) subjects in the high dose group, 13 (5.1%) in the low dose and 13 (3.4%) in the placebo. In Study P029 somnolence occurred in 40 (10.3%) subjects in the high dose group, 20 (8.4%) in the low dose and 12 (3.1%) in the placebo. In the clinical trials somnolence was commonly attributed to suvorexant.

Sleep paralysis was reported with suvorexant in <1% subjects in Study P028 and Study P029.

Two deaths were reported during the development program. Neither appears to have been related to suvorexant (cerebrovascular accident and near-drowning / hypoxic-ischaemic encephalopathy). SAEs were uncommon and did not appear to be related to suvorexant. DAEs were also uncommon. There were at least two DAEs related to suicidal ideation. Somnolence and nightmare were more common reasons for DAE in the suvorexant groups.

In the pivotal studies elevations of ALT and/or AST were rare, but occurred more commonly with suvorexant. There was no separate listing of subjects that would have conformed with Hy's Law.

Renal dysfunction was not associated with suvorexant. Suvorexant was not associated with prolongation of the QT interval, including in a thorough QT study. Clinically significant changes in vital signs were uncommon with suvorexant.

Rebound insomnia appears to be common with suvorexant. In Study P028 rebound by WASO was reported in 29 (34.5%) subjects ceasing high dose, compared to seven (9.1%) continuing; and in 25 (41.0%) subjects ceasing low dose, compared to three (5.0%) continuing.

Withdrawal effects as measured by the Tyrer Withdrawal Score are uncommon, and occur mainly on the first night following ceasing treatment. Suicidal ideation was uncommon with suvorexant. Abuse potential for suvorexant was similar to that for placebo. There was also lesser abuse potential compared with zolpidem.

There were no clinically significant overdoses during the clinical development program. Hence, the effects of suvorexant in overdose are important missing information.

Although the pharmacodynamic studies indicated significant residual effects, the clinical studies did not indicate an increased risk for traffic accidents or cognitive impairment. In the Pharmacodynamic studies the time course of single dose suvorexant was examined in four PD

studies at doses up to 240 mg. There did not appear to be persistence of effect beyond 8 hours for the 10 mg dose level, some persistence for the 20 mg and definite persistence for the 40 mg. The rate of next-day somnolence was estimated to be 7.9% with 20 mg, 10.6% with 40 mg and 14.2% with the 80 mg dose level. At high doses (>100 mg) the effects persisted for up to 24 hours. There was significant next day driving impairment with suvorexant 40 mg in Study P035, similar to that for zopiclone, in non-elderly subjects but no significant impairment in elderly subjects in Study P039. In Study P035 SDLP was impaired to a similar extent with suvorexant 40 mg compared with zopiclone 7.5 mg, but for suvorexant 20 mg SDLP was similar to placebo for elderly subjects at both Day 2 and Day 9, and for non-elderly subjects at Day 9.[49] In Study P009 motor vehicle accidents were slightly more common with suvorexant than placebo: 22 (5.5%) subjects in the suvorexant group and eight (4.1%) in the placebo, but there was no increase in the rate of accidents with suvorexant in Study P028 or Study P029.

The problems with residual effects may be related to the half-life of suvorexant, which was estimated to be from 8.9 hours to 13.5 hours. Steady state is achieved at approximately Day 3 of treatment. These PK characteristics are not optimal for a hypnotic and a shorter half-life would be more desirable.

The Pharmacodynamic studies also investigated sleep safety. Suvorexant did not impair sleep safety in normal volunteers, subjects with chronic obstructive pulmonary disease or subjects with obstructive sleep apnoea. Suvorexant and alcohol exhibited a significant additive effect on impairment in cognitive function that lasted for up to 9 hours post-ingestion.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of suvorexant is unfavourable given the proposed usage, but would become favourable if the amended dosing recommendations, as stated below, are adopted by the Sponsor.

For dosage in non-elderly adults (<65 years) and elderly adults (≥ 65 years):

Use the lowest dose effective for the patient. The recommended initial dose is 20 mg for non-elderly adults and 15 mg for elderly adults. For patients whose symptoms (onset and/or maintenance) persist and who do not experience next day somnolence or other residual effects, a dose increase to 40 mg for non-elderly adults or 30 mg for elderly adults may be considered.

For use with moderate CYP3A inhibitors:

For non-elderly and elderly patients taking concomitant moderate CYP3A inhibitors, the recommended dose is 15 mg and should not be exceeded.

9. First round recommendation regarding authorisation

The Evaluator is unable to recommend approval of the following indication:

> *Belsomra is indicated for the treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.*

The data presented in the submission are supportive of efficacy, at the proposed amended dosing recommendations, for treatment duration of up to 3 months. In addition, all the clinical trials were for primary insomnia, hence this should be reflected in the indication.

The Evaluator would have no objection to the approval of suvorexant for the indication:

[49] Erratum: In Study P035 SDLP was impaired to a similar extent with suvorexant 40 mg as with zopiclone 7.5 mg, but for suvorexant 20 mg SDLP was similar to placebo on Day 9. In Study P039 SDLP was similar to placebo with suvorexant 15 and 30 mg on Days 2 and 9 in the elderly.

Belsomra *is indicated for the short term (up to 3 months) treatment of primary insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.*

10. Clinical questions

10.1. Pharmacokinetics

1. What is the proposed mechanism for the decrease in absolute bioavailability with increasing dose?
2. What is the mechanism of absorption for suvorexant?
3. Is the decreased bioavailability with dose explained by the poor water solubility or is there an active transport process involved in absorption?

10.2. Pharmacodynamics

The Clinical Evaluator does not have any questions relating to pharmacodynamics.

10.3. Efficacy

The Clinical Evaluator does not have any questions relating to efficacy.

10.4. Safety

The Sponsor should provide a listing of subjects with elevations of ALT, AST and bilirubin conforming to Hy's Law.

11. Second round evaluation of clinical data submitted in response to questions

The Sponsor has responded to the following questions arising from the Clinical Evaluation:

11.1. Pharmacokinetics

What is the proposed mechanism for the decrease in absolute bioavailability with increasing dose?

What is the mechanism of absorption for suvorexant?

Is the decreased bioavailability with dose explained by the poor water solubility or is there an active transport process involved in absorption?

The Sponsor has responded that suvorexant appears to be primarily absorbed by passive diffusion. The Sponsor does not expect that active, intestinal uptake by transporters plays an important role in suvorexant absorption. The less than proportional increase in suvorexant exposure observed in the oral dose proportionality study P018 is believed to be due to solubility limitations.

In the opinion of the Evaluator, this response is satisfactory and is consistent with the PK of drugs with similar poor solubility.

Does variability in CYP2C19 or UGT alleles affect clearance?

The Sponsor has responded that when extrapolating data from *in vitro* studies "at the intended clinical doses, the fraction of suvorexant metabolized by CYP2C19 is expected to be less than 20% based on *in vitro* CYP phenotyping studies. Further, as the predominant elimination pathway of suvorexant is oxidative metabolism, UGTs are not involved in the elimination of suvorexant. As a result, variability in CYP2C19 or UGT expression is not expected to impact suvorexant clearance."

In the opinion of the Evaluator, this response is satisfactory.

11.2. Safety

Please provide a listing of subjects with elevations of ALT, AST and bilirubin conforming to Hy's Law.

The Sponsor has responded that there were no subjects with elevations of ALT, AST and bilirubin conforming to Hy's Law in the development program for suvorexant.

In the opinion of the Evaluator, this response is satisfactory.

11.3. Additional questions from delegate

Results for the primary efficacy endpoint for the low dose vs. placebo comparison are exploratory and not controlled for multiplicity effects. The current evidence for efficacy of the proposed revised dose regimen (your letter dated 17 July) is based on exploratory analyses. Because of this deficiency in the pivotal studies requests the following additional questions:

Please provide a combined analysis of efficacy for studies P028 and P029 that examines the primary efficacy endpoints for both high dose (HD) and low dose (LD) suvorexant i.e.

Maintenance: Change from baseline at Months 1 and 3 for:

- *Mean subjective total sleep time (sTSTm) on the daily e-diary*
- *Wakefulness after persistent sleep onset (WASO) by PSG*

Onset: Change from baseline at Months 1 and 3 for:

- *Mean subjective time to sleep onset (sTSOm) by daily e-diary*
- *Latency to persistent sleep (LPS) by PSG*

This will be a post hoc analysis. Please provide a statistical plan for this analysis including an assessment of any adjustments performed to account for multiplicity effects.

The Sponsor has provided a post hoc analysis of efficacy for the low dose groups using the pooled data from Study P028 and Study P029. Multiplicity was addressed by using a Bonferroni approach to account for the evaluation of the two distinct indications, and there was a hierarchical approach to the hypothesis tests, where the comparison between low dose and placebo must be significant at Month 1 in order to proceed to the comparison at Month 3.

Based on this analysis, there were the following results:

LS mean (95% CI) difference in change from baseline in sTSTm, active – placebo:

- Week 1: 23.7 (19.2 to 28.2) min ($p < 0.00001$) for HD and 15.0 (10.0 to 20.1) min ($p < 0.0001$) for LD
- Month 1: 22.7 (17.2 to 28.2) min ($p < 0.00001$) for HD and 18.4 (12.2 to 24.7) min ($p < 0.0001$) for LD

- Month 3: 22.1 (16.1 to 28.1) min (p <0.00001) for HD and 16.0 (9.2 to 22.8) min (p <0.0001) for LD

LS mean (95% CI) difference in change from baseline in WASO, active – placebo:

- Night 1: -39.9 (-44.4 to -35.4) min (p <0.00001) for HD and -34.6 (-39.8 to -29.3) min (p <0.0001) for LD
- Month 1: -27.6 (-32.7 to -22.6) min (p <0.00001) for HD and -25.4 (-31.3 to -19.5) min (p <0.0001) for LD
- Month 3: -25.9 (-31.2 to -20.7) min (p <0.00001) for HD and -23.1 (-29.2 to -17.0) min (p <0.0001) for LD

LS mean (95% CI) difference in change from baseline in sTSOm, active – placebo:

- Week 1: -9.4 (-12.5 to -6.2) min (p <0.00001) for HD and -6.1 (-9.7 to -2.5) min (p = 0.0081) for LD
- Month 1: -10.1 (-14.0 to -6.3) min (p <0.00001) for HD and -5.6 (-9.9 to -1.2) min (p = 0.01209) for LD
- Month 3: -10.8 (-14.6 to -7.0) min (p <0.00001) for HD and -5.9 (-10.2 to -1.6) min (p = 0.00675) for LD

LS mean (95% CI) difference in change from baseline in LPS, active – placebo:

- Night 1: -15.8 (-19.9 to -11.6) min (p <0.00001) for HD and -11.2 (-16.1 to -6.4) min (p <0.00001) for LD
- Month 1: -11.4 (-15.3 to -7.6) min (p <0.00001) for HD and -9.1 (-13.6 to -4.6) min (p = 0.00007) for LD
- Month 3: -6.4 (-10.5 to -2.3) min (p = 0.00235) for HD and -4.6 (-9.3 to 0.2) min (p = 0.06205) for LD

In the opinion of the Evaluator, these data support efficacy for LD suvorexant, and also support the Sponsor's proposed approach to dosing. Using LD suvorexant as the starting dose would be expected to minimise adverse effects, and still enable those patients who do not achieve a response to have the dose increased to the HD level.

The Sponsor also provided a pooled analysis of sTSTm up to the 6 month time point. At the 6 month time point there was loss of effect for suvorexant LD. These data do not support long-term use. There was similar loss of effect for suvorexant low dose as measured by sTSOm.

Given the concern expressed by the FDA regarding the effect of the suvorexant high dose regimen on driving ability, are there data on the effect of a 10 mg dose on next day driving ability?

The Sponsor responded: "The Sponsor did not evaluate 10 mg of suvorexant in the model on the road driving platform, nor were motor vehicle accidents or violations prospectively assessed at this dose level in insomnia patient studies. However, based on the lack of effects on driving performance at 15 mg and the apparent dose responsiveness of the SDLP measurement, an effect of 10 mg suvorexant on driving performance as measured by SDLP would not be expected."

In the opinion of the Evaluator, this response is satisfactory.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of suvorexant in the proposed usage are unchanged from those identified in Section 8.1.

12.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of suvorexant in the proposed usage are unchanged from those identified in Section 8.2.

12.3. Second round assessment of benefit-risk balance

As previously stated in Section 8.3: the benefit-risk balance of suvorexant is unfavourable given the proposed usage, but would become favourable if the amended dosing recommendations, as stated below, are adopted by the Sponsor.

For dosage in non-elderly adults (<65 years) and elderly adults (≥ 65 years):

Use the lowest dose effective for the patient. The recommended initial dose is 20 mg for non-elderly adults and 15 mg for elderly adults. For patients whose symptoms (onset and/or maintenance) persist and who do not experience next day somnolence or other residual effects, a dose increase to 40 mg for non-elderly adults or 30 mg for elderly adults may be considered.

For use with moderate CYP3A inhibitors:

For non-elderly and elderly patients taking concomitant moderate CYP3A inhibitors, the recommended dose is 15 mg and should not be exceeded.

Although the FDA has requested resubmission of CMC data for 5 mg and 10 mg tablets the currently available data do not support efficacy for this dose level.

13. Second round recommendation regarding authorisation

The Evaluator is unable to recommend approval of the following indication:

> *Belsomra is indicated for the treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.*

The data presented in the submission are supportive of efficacy, at the proposed amended dosing recommendations, for treatment duration of up to 3 months. In addition, all the clinical trials were for primary insomnia, hence this should be reflected in the indication.

The Evaluator would have no objection to the approval of suvorexant for the indication:

Belsomra is indicated for the short term (up to 3 months) treatment of primary insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au