In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

Division: Worldwide Development
Retention Category: GRS019
Information Type: Clinical Study Report

Title:	A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study to Evaluate the Effects of GW679769 (30mg and 90mg) on Sleep Continuity, PSG Sleep Recordings, Subjective Sleep Assessment, and Daytime Cognitive Function in Subjects with Primary Insomnia

Phase: II

Compound Number: GW679769

Effective Date: 29-AUG-2006

Description: This was a randomized, double-blind, placebo-controlled, cross-over study in subjects with a primary diagnosis of primary insomnia, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV) criteria (307.42), and symptoms for at least 3 months. This study showed an effect of both doses of GW679769 over placebo on the main PSG endpoints. Wake after Sleep Onset (WASO), the primary endpoint of the study, was significantly less after treatment with GW679769 at both doses. Significant effects on Total Sleep Time (TST) and Latency to Persistent Sleep (LPS) over placebo were also demonstrated. Treatment with GW679769 was generally well tolerated.

Subject: Insomnia, GW679769

Author(s): [redacted]

Indication Studied: Primary Insomnia

Initiation Date:	30 July 2004
Completion Date:	30 August 2005
Date of Report:	August 2006

Sponsor Signatory: [redacted] M.D.
(and Medical Officer) VP, Clinical Molecular Imaging Translational Medicine and Genetics and Acting Head, Psychiatry CPDM

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

Synopsis

Identifier: ZM2005/00173/00 **Study Number:** GW679769/903

Title: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study to Evaluate the Effects of GW679769 (30mg and 90mg) on Sleep Continuity, PSG Sleep Recordings, Subjective Sleep Assessment, and Daytime Cognitive Function in Subjects with Primary Insomnia

Investigator(s): [redacted] MD; [redacted] MD MS; [redacted] PhD.; [redacted] DO; [redacted] Ph.D; [redacted] Ph.D.

Study center(s): This study was performed at 6 centers in the United States.

Publication(s): None at the time of this report.

Study Period: The first subject first visit was performed on 06 August 2004, and the last subject last visit was conducted on 29 July 2005.

Phase of Development: II

Objectives:

Primary:

- To evaluate the acute efficacy of GW679769 taken at bedtime on sleep continuity in adults with Primary Insomnia as determined objectively by polysomnography (PSG).

Secondary:

- To study the changes induced by GW679769 on various PSG sleep parameters.
- To investigate the effects of GW679769 on daytime cognitive functioning on the morning following dosing, including tests of alertness, memory, attention and fine motor control.
- To investigate the effects of GW679769 on subjective sleep quality using self reported Post-Sleep Questionnaires.
- To investigate the safety and the pharmacokinetic (PK) profile of GW679769 in subjects with Primary Insomnia after two consecutive days of oral administration.
- To investigate the potential effects on memory associated with REM sleep.
- To investigate the relationship between plasma concentrations of GW679769 and all the sleep or cognitive parameters and to develop a pharmacokinetic/pharmacodynamic (PK/PD) model.

Methodology:

This was a randomized, double-blind, placebo-controlled, cross-over study using a complete set of orthogonal Latin Squares. Potential subjects participated in a screening period consisting of a clinical screening visit and a two-night PSG recording session in the sleep laboratory. Subjects with primary insomnia that qualified for the study participated in three separate two-night PSG sessions in which they were randomized to receive placebo or GW679769 (30mg or 90mg) sixty minutes prior to bedtime (lights out), one treatment for each session in a balanced order. Each treatment session was separated by a minimum of 12 days of washout and occurred on the same day of the week (± 1 day).

Number of subjects:

Forty-eight subjects provided data from at least one treatment session: 43 completed the three treatment sessions as planned (47 subjects provided data after placebo, 45 subjects after GW679769 30mg and 45 subjects after 90mg).

	All Subjects
Number of Subjects Planned, N	48
Randomized, N	48
Completed, n (%)	43 (90)
Total Number Subjects Withdrawn, n (%)	5 (10)
Withdrawn Due to Serious Adverse Events, n (%)	0
Withdrawn Due to Adverse Events, n (%)	0
Withdrawn for Other Reasons, n (%)	5 (10)

Diagnosis and main criteria for inclusion:

Male and female subjects, 18 to 64 years of age (inclusive), with a primary diagnosis of primary insomnia, as defined by Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) criteria 307.42, who had symptoms for at least three months, were considered eligible for the study.

Treatment and administration:

All active and placebo medications were provided as tablets and were identical in appearance. GW679769 30mg and 45mg were provided as white to off-white, film-coated, round tablets containing 30mg and 45mg of GW679769X (as the mesylate salt, GW679769B). Placebo tablets visually matched the active GW679769 tablets.

The batch numbers of the study medications used were Batch 1271 for GW679769 30mg, Batch 1273 for GW679769 45mg, and Batch 041032528 for placebo to match GW679769.

Single-blind placebo medication and double-blind GW679769 (30mg or 90mg) and placebo were administered orally for two consecutive evenings at approximately 60 minutes prior to lights out.

Criteria for evaluation:

Primary

- Wake time after sleep onset (WASO) derived from polysomnographic (PSG) recording.

Secondary

- Objective PSG measures of sleep continuity including: Total Sleep Time (TST), latency to persistent sleep (LPS), wake during sleep (WDS), wake after sleep (WAS), and number of awakenings during sleep.
- Objective PSG measures of sleep structure: Non-REM sleep time, Slow-Wave Sleep (SWS) time (Stage 3 and 4), Stage 2 non-REM sleep time; REM sleep time, REM activity, REM density.
- Spectral analysis of electroencephalogram (EEG) output.
- Subjective Post-Sleep Questionnaire: TST, WASO, SOL, number of awakenings, and sleep quality (SQ) to be applied on each morning following PSG recording.
- Daytime cognitive function data on the morning following dosing, including tests of alertness, memory, attention and fine motor control (i.e. Romberg test, heel-to-toe gait test, VAS for sleepiness/alertness, DSST, and immediate and delayed word recall (HVLT-R).
- Changes of TST, SOL, SQ, WAS and number of awakenings measured with the Post-Sleep Questionnaire score collected on specified mornings at home during the 3-day period following each 2-night PSG sessions.
- Plasma concentration of GW679769 and its major metabolite (GSK525060).

Statistical methods:

Sample size was based on the primary efficacy end-point "wake time after sleep onset (WASO)". In a previous study (NKD10014) a within-subjects standard deviation of about 14 minutes was observed. Assuming a difference vs. placebo of at least 10 minutes, 43 subjects completing the study were expected to provide a 90% power to detect a difference between active drugs and placebo.

Main analyses were based on mean values over the two nights of each session, analyzed using a mixed effect model with session and treatment as fixed effect and subject as random effect.

Additional analyses were performed to investigate the carry-over effect (effect of the treatment received in the previous period), the treatment by period interaction and the centre effect and the treatment by centre interaction. For each of these analyses a specific additional term was added to the original model. Tests of significance were performed at the 5% level. Least square mean values were evaluated for each treatment. Estimates for treatment differences expressed in pair-wise basis were calculated together with 95% corresponding confidence intervals. Error diagnostics from the residuals were examined

to ensure that the model did not depart from the assumptions underlying analysis of variance.

Summary:

Demographics:

Demographic data for the subjects in the safety population are summarized below:

Demography Detail	All Subjects (N = 48)
Gender n (%)	
Female	37 (77%)
Male	11 (23%)
Race n (%)	
White/Caucasian	27 (56%)
Black	19 (40%)
American Hispanic	1 (2%)
East and Southeast Asian	1 (2%)
Age (Years)	
Mean	40
Standard Deviation	10.1
Minimum	21
Maximum	61
Weight (Kg)	
Mean	74.9
Standard Deviation	13.11
Minimum	46.8
Maximum	99.1
Height (cm)	
Mean	167
Standard Deviation	7.8
Minimum	151
Maximum	185

Efficacy:

- This study showed an effect of both doses of GW679769 over placebo on the main PSG endpoints. WASO, the primary endpoint of the study, was significantly less after treatment with GW679769 at both doses. In addition, significant effects on TST and LPS over placebo were demonstrated.
- Assessment of sleep architecture showed a significantly greater duration and percentage of total time spent in Stage 2 sleep with a significantly shorter duration and lower percentage of time spent in Slow Wave Sleep for both doses of GW679769 versus placebo, with no statistically significant difference in percentage of time or total time spent in Stage 1 Sleep and no reduction in REM sleep.

- Statistically significant differences between active treatment and placebo were also observed for the Getting to Sleep domain of the LSEQ scale for both doses, the Quality of Sleep domain of the LSEQ scale at the 30mg dose, subjectively measured TST and WASO at the 30mg dose, and sleep quality at the 90mg dose.
- Cognitive tests performed on the morning following treatment showed no residual effect on psychomotor /attention and verbal memory tasks as assessed by the Digit Symbol Substitution Test (DSST) and the Hopkins Verbal Learning Test (HVLT).
- No consistent differences on the main PSG or cognitive endpoints were detected between the 30mg and the 90mg dose of GW679769.

Safety:

Treatment emergent adverse events are described below:

Adverse Event (AE)	Placebo N = 47[1] n (%)	GW679769 30mg N = 45 n (%)	GW679769 90mg N = 45 n (%)
Total Number of Subjects with AEs	13 (27.7)	6 (13.3)	7 (15.6)
Headache	4 (8.5)	3 (6.7)	0 (0)
Nausea[1]	2 (4.3)	2 (4.4)	0 (0)
Drug Screen Positive[2]	2 (4.3)	0 (0)	0 (0)
Abdominal Pain Upper	1 (2.1)	0 (0)	0 (0)
Back Pain	1 (2.1)	0 (0)	0 (0)
Blood Bilirubin Increased	1 (2.1)	0 (0)	0 (0)
Blood Cholesterol Increased	1 (2.1)	0 (0)	0 (0)
Blood Triglycerides Increased	1 (2.1)	0 (0)	0 (0)
Disorientation	1 (2.1)	0 (0)	0 (0)
Dizziness	1 (2.1)	0 (0)	0 (0)
Eczema	1 (2.1)	0 (0)	0 (0)
Feeling Abnormal	1 (2.1)	0 (0)	0 (0)
Herpes Simplex	1 (2.1)	0 (0)	0 (0)
Hypoglycemia	1 (2.1)	0 (0)	0 (0)
Lymphocyte Count Increased	1 (2.1)	0 (0)	0 (0)
Neutrophil Count Decreased	1 (2.1)	0 (0)	2 (4.4)
Rash macular	1 (2.1)	0 (0)	0 (0)
Vaginitis bacterial	1 (2.1)	0 (0)	0 (0)
Allergy to Arthropod Sting	0 (0)	1 (2.2)	0 (0)
Chills	0 (0)	1 (2.2)	0 (0)
Diarrhea	0 (0)	1 (2.2)	1 (2.2)
Feeling Hot and Cold	0 (0)	1 (2.2)	0 (0)
Rash	0 (0)	1 (2.2)	1 (2.2)
Somnolence	0 (0)	1 (2.2)	0 (0)
Vertigo	0 (0)	1 (2.2)	0 (0)
Blood Glucose Decreased	0 (0)	0 (0)	1 (2.2)
Contusion	0 (0)	0 (0)	1 (2.2)
Flushing	0 (0)	0 (0)	1 (2.2)
Influenza like illness	0 (0)	0 (0)	1 (2.2)
Neutrophil Count Increased	0 (0)	0 (0)	1 (2.2)
Neutrophil Percentage Decreased	0 (0)	0 (0)	1 (2.2)
Pharyngolaryngeal Pain	0 (0)	0 (0)	1 (2.2)
Sinusitis	0 (0)	0 (0)	1 (2.2)
Throat Irritation	0 (0)	0 (0)	1 (2.2)
Toothache	0 (0)	0 (0)	1 (2.2)
White Blood Cell Count Decreased	0 (0)	0 (0)	1 (2.2)

- Treatment with GW679769 30mg and 90mg was generally well tolerated.
- There were no deaths, non-fatal Serious Adverse Events, or pregnancies reported during the conduct of this study.
- The most common adverse events were headache and nausea (4-8%). These events were observed only in the placebo and GW679769 30mg groups.
- Most events reported were mild in intensity. One event of somnolence was described as severe for the GW679769 30mg treatment group and was reported as resolved.

- No subject withdrew from the study due to an adverse event. Five subjects withdrew from the study for protocol deviations (including non-compliance).
- There were no significant changes or consistent trends in clinical laboratory assessments (hematology, clinical chemistry or urinalysis), vital signs (heart rate, respiration rate, systolic or diastolic blood pressure) or ECG values of potential clinical concern following any treatment.

Conclusions:

- In summary, this study showed an effect of both doses of GW679769 over placebo on the main PSG endpoints, WASO, TST, and LPS. In addition, treatment with GW679769 (30mg and 90mg) in subjects with primary insomnia was generally well tolerated.

Date of Report: August 2006

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Abbreviations

AE	Adverse Event
AFS	Awakening From Sleep
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvate transaminase)
AST (SGOT)	Aspartate amino-transferase (serum glutamic oxaloacetic transaminase)
BFW	Behavior Following Wakefulness
BP	Blood Pressure
BUN	Blood urea nitrogen
C_{max}	Maximum observed concentration
CIB or IB	Clinical investigator brochure or Investigator brochure
CK	Creatine phosphokinase
CL/F	Apparent plasma clearance
CL_R	Renal clearance
C_{mean}	Mean Concentration
CNS	Central nervous system
CPK	Clinical Pharmacokinetics
CPSP	Clinical Pharmacology Statistics and Programming
CRF	Case Report Form
CTM	Clinical Trial Material
CVLT	California Verbal Learning Test
HVLT-R	Hopkins Verbal Learning Test - Revised
D1	Day one
dL	Deciliter
DNA	Deoxyribonucleic Acid
DSM–IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
EEG	Electroencephelogram
EISR	Expedited Investigator Safety Report
fL	femtoliter
fT_3	Free triiodothyronine
fT_4	Free thyroxine
FTI	Free thyroxine index
FTIH	First time in humans
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
g/dL	Grams per deciliter
GGT	Gamma glutamyltransferase
GSK	GlaxoSmithKline
GTS	Getting to Sleep
Hb	Hemoglobin

HCG	Human Chorionic Gonadotropin
H	Hour
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IU/L	International Units Per Liter
IUD	Intra–uterine device
IV	Intravenous
kg	Kilogram
L	Liter
HDL	High density lipids
LHD	Lactate Dehydrogenase
LDL	Low density lipids
LFT	Liver function test
LOCF	Last observation carried forward
LPS	Latency to Persistent Sleep
LSEQ	Leeds Sleep Evaluation Questionnaire
MAOI	Monoamine oxidase inhibitor
MCHC	Mean Corpuscular Hemoglobin Content
MCV	Mean Corpuscular Volume
MedRA	Medical Dictionary for Drug Regulatory Activities
mEq	Milliequivalents
MSDS	Material safety data sheet
Msec	Milliseconds
mg	Milligram
min	Minute
mL	Milliliter
N1	Night one
ng	nanograms
NK	Neurokinin
NOAEL	No observable adverse effect level
NREM	non-REM
NSAID	Non-Steroidal Anti-Inflammatory Drug
OC	Observed case
od	Once daily
OTC	Over the counter
oz	Ounce
P450 3A4	Cytochrome P-450 3A4
PCV	Packed cell volume/hematocrit
PET	Positron emission tomography
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PLMS	Periodic Limb Movements
PP	per protocol

PSG	Polysomnography
PUD	Peptic Ulcer Disease
QC	Quality Control
QOS	Quality of Sleep
R	Resting
RBC	Red Blood Cell
REM	Rapid Eye Movement
RR	Respiratory Rate
SAE	Serious adverse event
SD	Standard deviation
SFA	Spindle Frequency Activity
SNP	Single Nucleotide Polymorphism
SNRI	Serotonin and Neurepinephrine Reuptake Inhibitors
SOL	Sleep Onset Latency
SP	Substance P
SQ	Sleep Quality
SSRI	Selective serotonin reuptake inhibitor
SSS	Stanford Sleepiness Scale
SWS	Slow Wave Sleep
t1/2	Terminal phase half-life
T3U	T3 Uptake
TCA	Tricyclic Antidepressant
t_{max}	First time of occurrence of Cmax
TSH	Thyroid stimulating hormone
TST	Total Sleep Time
ug	Microgram
ULRR	Upper limit of reference range
V1	Visit one
VAS	Visual Analogue Scale
WAS	Wake After Sleep
WASO	Wake After Sleep Onset
WBC	White Blood Cell
WDS	Wake During Sleep

Trademark Information

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1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board.

1.2. Ethical Conduct of the Study

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, and, the guiding principles of the Declaration of Helsinki.

1.3. Subject Information and Consent

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. Case report forms were provided for each subject's data to be recorded.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This was a multicenter study conducted at six centers in the United States.

Investigators participating in this study included: [redacted] MD; [redacted] MD MS; [redacted] PhD.; [redacted] DO; [redacted] Ph.D.; [redacted] Ph.D.

The sponsor was responsible for all administrative aspects of the study, including packaging and labeling of study medication supplies, management of protocol clarifications, data review and cleaning and data analysis and reporting.

Site Monitoring was completed by the SRG Woolf Group, Durham, North Carolina, USA.

Central clinical laboratory services were completed by Quest Diagnostics Inc., Van Nuys, California, USA.

ECG reading was completed at the individual sites using local ECG equipment and readers.

Polysomnography (PSG) was read centrally by [redacted] MD.

3. INTRODUCTION

The neurokinin-1 (NK1) receptor is one of the three 7-transmembrane receptors that bind tachykinins, a family of peptide neurotransmitters than include substance P, neurokinin A, and neurokinin B. Both tachyikinins and NK1 receptors are expressed in mammalian brains in various sub-cortical and cortical structures involved in emotional control and mood regulation [Kramer, 1998].

Emerging data suggests that substance P and neurokinin receptors can also be involved in the control of arousal and sleep. Substance P is known to be released by several brain structures [Carrasco, 2003], and is liberated as a result of exposure to environmental stressors. It is also known to reduce the total sleep time in preclinical species and humans [Hetta, 2002]. In particular, substance P (acting through NK1 receptor) is active on locus coeruleus and raphe nuclei, both structures involved in REM sleep regulation [Sakai, 1991; Ma, 2002; Kohlmeier, 2002]. The awakening effects of an infusion of substance P were recently studied in healthy volunteers, showing a decreased total sleep time and increased sleep onset latency [Lieb, 2002]. NK1 antagonists, like benzodiazepines, also show anxiolytic-like effects in several preclinical models [File, 1997; Rupniak, 1994; van der Hart, 2002]. In humans, repeated administration of an NK1 antagonist, GW205171, has been associated with anxiolytic effects in patients suffering from Social Anxiety Disorders [see report for study NKD10013], and the substance P antagonist aprepitant (MK-0869) has been shown to have antidepressant effects in patients with recurrent depression [Kramer, 1998]. These effects on mood were associated with improvement in insomnia, suggesting possible efficacy of NK1 antagonists in sleep disorders [Holsboer, 2003].

The theory that NK1 antagonists may be of potential benefit for primary insomnia and act through a novel mechanism, different from benzodiazepines or related GABA-α receptor modulators is supported by data from a recent study using an investigational NK1 antagonist (GW597599; study NKD10014). When administered at 15 mg and 25 mg, GW597599 produced transient pharmaco-EEG consisting of increases in delta and theta waves and decreases in alpha and beta rhythms modifications primarily in the first 2 hours after dosing in resting conditions when compared with placebo. Overall, the electroencephalograph pattern transiently produced by GW597599 was interpreted as reduced vigilance.

At both doses, GW597599 improved sleep continuity, the sleep efficiency index and the Total Sleep Time. The sleep onset time and the time spent in non-REM sleep were found unchanged. However, the sleep architecture was altered, with stage 2 non-REM sleep being augmented at the expense of slow wave sleep (SWS). In particular, time spent in SWS stage 3 and 4 was significantly decreased. These effects were mostly observed during the first third of the night. On the contrary, time in REM sleep was increased up to 20%, REM latency was shortened and REM activity and density were increased.

To further investigate the potential hypnotic effects of NK1 antagonists, the present study assessed GW679769, a piperadine analogue that has high affinity for the NK1 receptor

with a 30,000 fold selectivity over other G-coupled receptors, ion channels and transporters. It has rapid brain penetration and allows for full central receptor occupancy.

4. STUDY OBJECTIVE(S)

4.1. Primary

- To evaluate the acute efficacy of GW679769 on sleep continuity in adults with Primary Insomnia as determined objectively by polysomnography (PSG).

4.2. Secondary

- To study the changes induced by GW679769 on various PSG sleep parameters.
- To investigate the effects of GW679769 on daytime cognitive functioning on the morning following dosing, including tests of alertness, memory, attention and fine motor control.
- To investigate the effects of GW679769 on subjective sleep quality using self reported Post-Sleep Questionnaires.
- To investigate the safety and the pharmacokinetic (PK) profile of GW679769 in subjects with primary insomnia after two consecutive days of oral administration.
- To investigate the potential effects on memory associated with REM sleep.
- To investigate the relationship between plasma concentrations of GW679769 and all the sleep or cognitive parameters and to develop a pharmacokinetic/pharmacodynamic (PK/PD) model.

4.3. ENDPOINT(S)

4.3.1. Primary

- Wake time after sleep onset (WASO) derived from polysomnographic (PSG) recording.

4.3.2. Secondary

- Objective PSG measures of sleep continuity including: Total Sleep Time (TST), latency to persistent sleep (LPS), wake during sleep (WDS), wake after sleep (WAS), and number of awakenings during sleep.
- Objective PSG measures of sleep structure: Non-REM sleep time, Slow-Wave Sleep (SWS) time (stage 3 and 4), Stage 2 non-REM sleep time; REM sleep time, REM activity, REM density.
- Spectral analysis of EEG output.

- Subjective Post-Sleep Questionnaire: TST, WASO, SOL, number of awakenings, and sleep quality (SQ) to be applied on each morning following PSG recording.
- Daytime cognitive function data on the morning following dosing, including tests of alertness, memory, attention and fine motor control (i.e. Romberg, VAS for sleepiness/alertness, DSST, and immediate and delayed word recall).
- HVLT-R (verbal memory tests).
- Changes of TST, SOL, SQ, WAS and number of awakenings measured with the Post-Sleep Questionnaire score collected on specified mornings at home during the 3-day period following each 2-night PSG sessions.
- Plasma concentration of GW679769 and its major metabolite (GSK525060).

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design - Description

This was a randomized, double-blind, placebo-controlled, cross-over study using a complete set of orthogonal Latin Squares. Potential subjects participated in a screening period consisting of a clinical screening visit and two-night PSG recording in the sleep laboratory. Subjects with primary insomnia that qualified for the study participated in three separate two-night PSG sessions in which they were randomized to receive placebo or GW679769 (30mg or 90mg) one hour before bedtime (lights out), one treatment for each session in a balanced order. Each session was separated by a minimum of 12 days and occurred on the same day of the week (± 1 day).

A schedule of visits and procedures is depicted in Table 1.

Table 1 Time and Events Table

Procedures and Assessments	Screen Visit	Pair of Screening PSG Nights				Pairs of Double-Blind Treatment Sessions												Early Withdrawal or F/U Visit
						First				Second				Third				
	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9		
		N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	
Informed Consent	X																	
Inclusion/Exclusion Criteria Review	X	X		X														
Medical/Surgical/Psychiatric/ Sleep History	X	X		X														
Prior Medication History[1]	X																	
Concomitant Med Review		X		X		X		X		X		X		X		X		X
Adverse Events Inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep-habit Changes Review						X		X		X		X		X		X		
Physical Examination	X						X		X		X		X		X		X	X
12-lead ECG[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sitting Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests	X																X	X
PK Sample Collection						X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacogenetic Sampling[4]						X												
Pregnancy Test[5]	X	X				X				X				X			X	X
Urine Illicit Drug Screen	X	X		X		X		X		X		X		X		X		

1. Within past 30 days; including sleep medication
2. 30 min, 60 min, and 10 hours after single- or double-blind dosing.
3. Blood pressure, heart rate, respiratory rate, oral temperature
4. Pre-dose
5. Serum test at V1, V9/D2, and Early W/D or F/U; for all other visits, serum or urine test

Table 1 Time and Events Table (continued)

Procedures and Assessments	Screen Visit	Pair of Screening PSG Nights				Pairs of Double-Blind Treatment Sessions												Early Withdrawal or F/U Visit
						First				Second				Third				
	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9		
		N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	
Alcohol Breath Test	X	X		X		X		X		X		X		X		X		
Pre-sleep Questionnaire		X		X		X		X		X		X		X		X		
Study Drug Administration[6]		X		X		X		X		X		X		X		X		
Nocturnal PSG		X		X		X		X		X		X		X		X		
Post-sleep Questionnaire			X		X		X		X		X		X		X		X	X
DSST			X		X		X		X		X		X		X		X	
Memory HVLT-R List[7]		X	X		X	X	X		X	X	X		X	X	X		X	
Leeds Sleep Evaluation Questionnaire			X		X		X		X		X		X		X		X	
Stanford Sleepiness Scale			X		X		X		X		X		X		X		X	
Romberg/Heel-to-toe Tests			X		X		X		X		X		X		X		X	
Masking Question					X		X		X		X		X		X		X	
Subject Diaries (*Dispensed and/or Collected*)[8]					X				X				X				X	
Schedule Next Clinic Visit[9]	X		X		X		X		X		X		X		X		X	

6. 60 minutes before lights-out
7. HVLT-R form to be completed dictated by HVLT Randomization List
8. Completion required, starting on the evening of this visit, and concluding on the morning, three days later
9. 2-10 days between V1 and V3; 7 days (± 1 day) between V3/N2 and V4/N1; 12 days minimum (± 1 day) between V5 and V6 and between V7 and V8; and 14 days (± 3 days) for F/U visit completion after V9/D2

5.2. Protocol Amendment(s)

The first draft of the protocol was approved on 29 April 2004. Since that date, there was one protocol amendment to the study protocol which was applied to all centers. This amendment is briefly described below.

On 26 October 2004 (Amendment 1), the protocol underwent changes regarding:

- Clarification of study procedures to be performed and the times of their completion.
- Re-definition of the "visit window" between Visits 3 and 4.
- Refinement of the "Time and Events Table," so as to reflect the clarified study procedures and to improve the table's utility.

5.3. Selection of Study Population

Approximately 48 subjects were to be enrolled in the study. A minimum of 43 evaluable subjects were required to complete the study, covering a maximum drop-out rate of 10%. Subjects were to be recruited from approximately 5-7 sites in the United States.

5.3.1. Inclusion/Exclusion Criteria

5.3.1.1. Inclusion Criteria

A subject was considered eligible for inclusion into this study only if all of the following criteria applied:

1. The subject must have been able to read and understand the informed consent form and provide written informed consent, indicating the subject's understanding of the purpose of the study and willingness to comply with all study procedures described in the protocol, including all sleep-laboratory restrictions and procedures.
2. The subject was required to be 18 through 64 years (inclusive).
3. Diagnosis of primary insomnia, as defined by Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) criteria 307.42. A complaint of difficulty initiating or maintaining sleep or of non-restorative sleep, which lasts for at least three months along with clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance in sleep did not occur exclusively during the course of another sleep disorder or occur exclusively during the course of another mental disorder. Lastly, the disturbance was not due to the direct physiological effects of a substance or a general medical condition.
4. The subject's self-reported sleep history included at least three months of a usual total sleep time (TST) of less than 6.5 hours, sleep onset latency (SOL) of at least 30 minutes and at least three awakenings per night in at least three nights per week.
5. On two screening PSGs (on single-blinded placebo administration at each night):

- TST between 240 and 420 minutes on both nights.
- Mean latency to persistent sleep (LPS) of 30 minutes or more, but not < 20 minutes on either night.
- Mean wake after sleep onset (WASO) of 30 minutes or more, with neither night < 20 minutes.

6. Time in bed between 6.5 and 9 hours for at least five nights per week over the preceding three months.
7. Bed time between 21.00 and 24.00 hours that did not vary by more than ±1 hour.
8. Women of childbearing potential must have been able to commit to consistent and correct use of an acceptable method of birth control; GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of a physician, were as follows:

    a Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal. For purposes of this study, postmenopausal was defined as one year without menses); or,

    b child-bearing potential, had a negative serum pregnancy test result at screen and a negative urine dipstick pregnancy test at baseline (prior to study drug administration), and agreed to one of the following:

    - Male partner who was sterile prior to the female subject's entry into the study and was the sole sexual partner for that female subject,
    - Oral contraceptives (either combined or progestogen only),
    - Double-barrier method of contraception consisting of spermicide with either condom or diaphragm;
    - Intra-uterine device (IUD) with a documented failure rate of less than 1% per year; or
    - Complete abstinence from intercourse for two weeks before exposure to the study drug, throughout the clinical trial, and for a period after the trial to account for elimination of the drug (minimum of three days, equivalent to five half lives).

9. If subjects indicated that they would remain abstinent during the period described above, they must have agreed to follow GSK guidelines for the consistent and correct use of an acceptable method of birth control should they become sexually active.
10. The subject was in good health as determined by medical and psychiatric history, physical examination, ECG, and serum chemistry, hematology, serology, and urinalysis results.
11. Subjects with a medical history of peptic ulcer disease with a known etiology were required to provide documentation from a gastroenterologist of the etiology of the Peptic Ulcer Disease (PUD) and that effective treatment was provided with full eradication of ulcers and symptoms. Also, that all steps have been taken to minimize reoccurrence risk (i.e. if NSAID induced that subject is no longer taking NSAIDs, if

cause was H. Pylori, then subject was required to have a negative antibody or breath test).

5.3.1.2. Exclusion Criteria

A subject was considered ineligible for inclusion in this study if any of the following criteria applied:

1. Any clinically significant unstable medical or surgical condition (treated or untreated).
2. Any history of a clinically significant abnormality of the neurological system (including cognitive disorders or significant head injury) or any history of seizure (including febrile seizure).
3. Subject had a history of depression, anxiety or other Axis I or II disorders.
4. Current or recent (within six months) documented gastrointestinal disease; a history of malabsorption, esophageal reflux, or irritable bowel syndrome; frequent (more than once a week) occurrence of heartburn, or any surgical intervention (e.g. cholecystectomy) which would have been expected to influence the absorption of drugs.
5. Subjects with active PUD and/or history of PUD of an unknown etiology, except as indicated in inclusion criterion number 11.
6. Subject had an unstable medical disorder; or a disorder that would interfere with the action, absorption, distribution, metabolism, or excretion of GW679769; or interfere with the accurate assessment of safety or efficacy.
7. Subjects having clinically significant abnormalities in hematology, blood chemistry, ECG, urinalysis, physical exam, vital signs, or other protocol-specified screening test which were not resolved by the baseline visit.
8. Subjects with a history of clinically significant hepatic, cardiac (e.g. including myocardial infarction), renal, neurologic (e.g. including seizures), cerebrovascular, metabolic or pulmonary disease.
9. Known seropositivity for human immunodeficiency virus (HIV), Hepatitis B, or Hepatitis C.
10. Women having a positive serum HCG pregnancy test at Screening Visit, a positive urine pregnancy dipstick or serum pregnancy test at Baseline Visit (Randomization), or who were lactating or planning to become pregnant within the three months following the Screening Visit.
11. Any clinically significant psychiatric disorder other than primary insomnia as defined by DSM-IV-TR.
12. History of alcohol, narcotic, benzodiazepine, or other substance abuse or dependence (with the exception of tobacco use) within the past 12 months as defined by DSM-IV-TR.
13. Symptoms/signs which were consistent with any primary sleep disorder other than primary insomnia.

14. Body mass index of 34 or more.
15. Apnea-hypopnea index of 10 or more/hour of sleep on screening PSG.
16. Movement arousal index of 10 or more/hour of sleep on screening PSG.
17. Nightshift or rotating-shift work within the last two work weeks or during the study period.
18. Planned travel across more than three time zones during the study or in the two weeks prior to screening.
19. Consumption of 300 mg or more per day on average of xanthine-containing beverages (e.g. coffee, cola, tea, chocolate) over the preceding 1 month [NOTE: 12 oz soda = ~50 mg, 7 oz coffee or 2 oz espresso = ~100 mg, 7 oz tea = ~75 mg of caffeine].
20. Smoking more than one pack of cigarettes per day on average over the preceding one month, or inability to stop smoking during the sleep study.
21. Typical consumption of more than 14 alcoholic units in any week, or more than 5 alcoholic units in any single day, over the preceding 1 month [NOTE: 1 unit = 8 oz beer, 3 oz wine, or 1 oz hard liquor].
22. LFTs elevated above the reference range at pre-study screening that remain elevated with a repeat LFT (to be discussed with the sponsor, if necessary).
23. Subjects who were not euthyroid as evidenced by normal thyroid stimulating hormone (TSH). Subjects maintained on thyroid medication must have been euthyroid for a period of at least six months prior to the screening visit; with no dose changes.
24. Subjects with a history or with evidence of clinically significant renal impairment (serum creatinine > 1.4mg/dL) not resolved by the baseline visit.
25. Subjects with anemia and low Mean Corpuscular Volume (<80fL) at the screening visit (to avoid entering subjects with iron deficiency anemia).
26. Use of any psychotropic medications or other medications, including over-the-counter (OTC) and herbal products, that may affect sleep/wake function within 1 week or 5 half-lives (whichever is longer) prior to screening or need to use any of these medications at any time during the study.
27. Subjects (i.e. asthmatics) who have used systemic corticosteroids within one week or five half-lives (whichever is longer) prior to the screening visit.
28. All other (non-psychotropic) drugs metabolized via the P450 3A4 pathway must have been discontinued from baseline visit and are not allowed until completion of Session 3.
29. Use of any investigational drug within 30 days or five half-lives of the study compound prior to the Screening Visit.
30. Positive urine drug screen (i.e., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, or opiates).
31. Exhibited intolerance to NK1 antagonists.

32. Any serious medical disorder or condition that would in the Investigator's opinion, have precluded the administration of study medication.
33. Subjects who, in the opinion of the investigator, would have been noncompliant with the visit schedule or study procedures.

5.3.1.3. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the Investigator was required to refer to the following document for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product being used in this study:

- The CIB or equivalent documentation for GW679769

5.3.1.4. Lifestyle Guidelines/Other Restrictions

The following lifestyle guidelines and other restrictions were in place during the study:

- Subjects were required to arrive in the unit before dosing and to stay in the unit until all assessments were completed during each study related visit.
- Participants were instructed to refrain from grapefruit and grapefruit juice for 48 hours prior to and throughout each visit to the clinic.
- Subjects were instructed to refrain from alcohol and caffeine- or xanthine-containing products for six hours prior to and throughout each visit to the clinic. Subjects' use of tobacco products was forbidden only during subjects' stay in the sleep unit.
- Water was allowed *ad libitum*.
- Subjects were required to refrain from taking any other medication (either prescribed or over the counter) starting 12 hours before each visit to the clinic.
- Subjects were required to refrain from activities that have the potential to change circadian rhythm (i.e. travel covering more than three time zones, occasional shift work, etc.).

5.3.2. Predetermined Criteria for Subject Withdrawal

A withdrawal was defined as any subject who had been dispensed randomized study medication but did not complete the full treatment phase (i.e., through Session 3).

5.3.2.1. Subject withdrawal from the investigational product

For all subjects who were prematurely withdrawn during the treatment phase of the study, the early withdrawal visit was to be scheduled as soon as possible following the discontinuation of study medication.

The End of Study Record page of the CRF was to be completed and the medication records were to be brought up to date as far as possible. A safety Follow-up Visit was to be scheduled to take place 14 days following the early termination visit for all subjects.

5.3.2.2. Subject withdrawal from the study

A subject who did not complete the full treatment phase was to be considered prematurely discontinued from the study. Subjects who were prematurely discontinued from the study were not replaced.

A subject could voluntarily discontinue participation in this study at any time. The Investigator could also, at his or her discretion, discontinue the subject from participating in this study at any time. The Investigator was to notify the Sponsor if a subject was withdrawn due to a hepatic adverse event (e.g. any LFT elevation, hepatomegaly, jaundice, hepatitis, etc.). If a subject was prematurely discontinued from participation in the study for any reason, the Investigator was to make every effort to perform the evaluations listed for the Early Withdrawal Visit in the Time and Events Table (Table 1).

The reason for termination was required to be recorded on the End of Study Record page of the CRF. A subject could withdraw (or be withdrawn) from the study prematurely for the following reasons:

1. Voluntary withdrawal of informed consent
2. Adverse event (Adverse Event section was required to be completed)
3. Insufficient therapeutic effect
4. Protocol deviation (including non compliance)
5. Lost to follow-up
6. Other (must have been specified)

In the event that a subject was prematurely discontinued from the study at any time due to an Adverse Event (AE) or Serious Adverse Event (SAE), as defined in the protocol, the procedures stated in the protocol were required to be followed.

The Investigator was required to notify the Sponsor if a subject was withdrawn due to an adverse event.

5.4. Investigational Product(s)

5.4.1. Description of Investigational Product(s)

The physical, chemical and pharmaceutical properties and characteristics of GW679769 are provided in the Clinical Investigator's Brochure [VH1002/00006/03].

All active and placebo medications were provided as tablets and were identical in appearance. Clinical supplies in this trial consisted of GW679769 30 and 45mg tablets and placebo. GW679769 30mg and 45mg were provided as white to off-white, film-coated, round tablets containing 30mg and 45mg of GW679769X (as the mesylate salt, GW679769B). Placebo tablets visually matched the active GW679769 tablets. A summary of the investigational product is reported in Table 2.

Table 2 Description of Investigational Product

Product Description	Reference No.	Batch No.	Date of Manufacture	Date of Approval
GW679769 30mg	SF.615.1207	1271	January 2004	March 2004
GW679769 45mg	SF.615.1209	1273	January 2004	March 2004
Placebo	LNB100329	041032528	June 2004	June 2004

5.4.2. Dosages and Administration

GW679769 was administered by mouth at 30mg/day or 90mg/day for two consecutive evenings at approximately 60 minutes prior to lights out.

Placebo was administered by mouth for two consecutive evenings at approximately 60 minutes prior to lights out for both the single-blind and double-blind treatment sessions.

5.4.3. Dose Rationale

Concentration-dependent effects on REM sleep and on sleep continuity in healthy volunteers were seen using 25mg of GW597599, an NK1 antagonist (Study NKD10014). Exposures following a 30mg dose of GW679769 (Cmean 14-62ng/mL) are similar to those obtained following a 25mg dose of GW597599 (Cmean = 16-40ng/mL). Therefore, a 30mg dose of GW679769 was used in this study in order to obtain exposures and, as a result, NK1 receptor occupancy similar to that following administration of 25mg GW597599.

GW679769 and GW597599 show a similar brain penetration (1.2 for both drugs from I.V. administration) and occupy NK1 receptors with similarly high affinity (pKi = 10.20 for both) and have similar protein binding (about 99%). However, the GW679769 PK profile indicated higher exposure than GW597599 per milligram dose. For example, 5mg GW679769 occupies about 75% of NK1 receptors in the temporal cortex as does 15mg GW597599. It was concluded that the plasma concentration following a single dose of 30mg GW679769 (Cmean 14-62 ng/mL) will approximate the receptor occupancy delivered by the higher concentration of the single dose 25mg GW597599 (Cmean = 16-40ng/mL).

The selection of the 90mg dose for GW679769 represents the near maximal tolerated dose under acute or sub-acute administration. According to the Phase I studies using Positron Emission Tomography (PET) 90mg GW679769 would deliver full (95-100%) occupancy of NK1 receptor in the brain. In addition, according to the results of the Phase I studies both compounds were safe and well tolerated when administered at these doses from 1 up to 28 days [VH1002/00006/03].

5.4.4. Blinding

The randomization numbers for each subject was provided to the Site by GlaxoSmithKline. Medication dispensed during the screening period was single-blind.

The study medication taken during the randomized treatment phase was double-blind. GW679769 30mg and 45mg tablets and placebo tablets were identical in appearance as off-white film-coated round tablets. Labels on the packaging identified the container and randomization numbers for each subject. The randomization schedule was not to be broken until the study was completed and all data queries were resolved in order to maintain the study blind.

Only in the case of an emergency, when knowledge of the investigational product was essential for the clinical management or welfare of the subject, the Investigator could unblind a subject's treatment assignment. If the blind was broken for any reason, the Investigator was required to notify GSK immediately of the unblinding incident without revealing the subject's study treatment assignment. In addition, the Investigator was to record the date and reason for revealing the blinded treatment assignment for that subject in the appropriate CRF.

In no case was the blind broken during the conduct of the study.

5.4.5. Treatment Assignment

Subjects were assigned to study treatment in accordance with the randomization schedule generated by GSK Clinical Pharmacology Statistics and Programming (CPSP).

5.4.6. Assessment of Compliance

Study medication was administered under the supervision of study personnel. The oral cavity of each subject was to be examined following dosing to assure that study medication was taken.

5.4.7. Treatment of Investigational Product Overdose

An overdose was defined as an excessive dose taken by a subject, either accidentally or intentionally, irrespective of whether it involved study medication or non-study medication. Overdose may have been suspected or confirmed and may or may not have been associated with clinical signs and symptoms.

It would definitely include, but not be limited to those events which based on the investigators clinical judgement were considered to be of medical concern and/or require clinical observation and/or medical intervention.

As a guide, an overdose would include any dose greater than the highest daily dose included in the protocol.

Deviations to study drug administration (i.e. resulting from poor subject compliance) was required to be recorded in the study medication compliance section of the CRF.

GlaxoSmithKline did not recommend specific treatment of overdose. Treatment of any suspected or confirmed overdose with GW679769 was therefore symptomatic.

Supportive care, as per the clinical judgment of the Investigator, was recommended by the protocol where overdose was suspected.

There were no cases of overdose with GW679769 or placebo during the conduct of the study.

5.5. Prior and Concomitant Medications and Non-Drug Therapies

5.5.1. Permitted Medications

All concomitant medications taken during the study were recorded in the CRF.

In addition, all prior medications were recorded at the screening visit in the CRF with indication, dose information, and dates of administration.

The Clinical Investigator Brochure was to be consulted for information relating to possible drug interactions.

5.5.2. Prohibited Medications

Prohibited medications included the following:

- The concomitant use of other psychotropic medications including antidepressants, sedatives, hypnotics and herbal treatments, was not permitted.
- Subjects were not permitted to take psychotropic drugs or antidepressants (including monoamine oxidase inhibitors, MAOIs) within the time frames specified below prior to the Screening visit until completion of the follow-up visit:
    - At least 12 weeks: depot neuroleptics.
    - At least four weeks: MAOIs or Fluoxetine.
    - At least 14 days or five half-lives (whichever is longer): hypnotics, benzodiazepines, and all other sedatives (including sedating antihistamines).
    - At least 14 days: Antidepressants other than MAOIs or fluoxetine (e.g. TCAs, SSRIs, SNRIs), lithium and oral antipsychotics.
    - At least 14 days: Any CNS-active herbal/natural supplement or preparation known or thought to have any psychoactive effects.
- Systemic corticosteroids were not permitted to be used for at least one week or five half-lives prior to the screening visit until completion of the final follow-up visit.
- All other (non-psychotropic) drugs metabolized via the P450 3A4 pathway were required to be discontinued from baseline visit and were not allowed until completion of the final study session.
- Use of any other investigational drugs within 30 days or five half-lives of the study compound prior to the Screening Visit was not permitted until completion of the final follow-up visit.

5.6. Study Assessments and Procedures

5.6.1. Demographic and Baseline Assessments (Visit 1 and Visit 2/3)

Visit 1:

The following assessments were performed at the Screening Visit in order to determine subject eligibility after obtaining written informed consent:

- Inclusion/Exclusion Criteria review.
- Medical/Surgical/Psychiatric history.
- Sleep history.
- Prior medication history review (within past 30 days).
- Full previous sleep medication history review (with detailed account of all medications within 30 days prior to screening).
- Physical examination.
- 12-lead ECG.
- Sitting Vital signs (blood pressure, heart rate, respiratory rate, oral temperature).
- Clinical laboratory tests.
- Serum Pregnancy Test.
- Urine illicit drug screen.
- Alcohol breath test.

Subjects who met the screening criteria above returned for up to two consecutive nights of PSG screening (PSG 1 and PSG 2) within 2 to 10 days of the initial Screening visit.

Visit 2/3:

At the first PSG screening visit (Visit 2), the following were performed:

- Inclusion/exclusion criteria review.
- Concomitant medication review.
- Adverse events inquiry.
- Medical/Surgical/Psychiatric/Sleep history update.
- Alcohol Breath Test.
- Urine or serum pregnancy test.
- Urine illicit drug screen.
- 12-lead ECG (approximately 30 minutes before single-blind dose).

- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature).
- Pre-sleep questionnaire.
- Memory HVLT-R list.
- Single-blind placebo administration (60 minutes before lights-out).

Lights-out occurred at approximately 21:00 hours to 00:00 hours (midnight).

Approximately 60 minutes after this single-blind placebo administration, the following were also performed:

- 12-lead ECG (just before lights-out).
- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature).
- Nocturnal PSG.

At Visit 2/Day 1 (V2/D1) – the morning after V2/N1 – the following were performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes).
- Psychometric testing (about 35 minutes [± 15 minutes] after lights-on):
  a Digit Symbol Substitution Test (DSST).
  b Memory HVLT-R list.
- Scales for sleepiness/alertness (about 35 minutes [± 15 minutes] after lights-on):
  a Leeds Sleep Evaluation Questionnaire.
  b Stanford Sleepiness Scale.
- 12-lead ECG (approximately 10 hours after single-blind dose).
- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature, collected about 10 hours after single-blind dose).
- Adverse events inquiry (last activity before Romberg, heel-to-toe tests).
- Romberg test, heel-to-toe test.

Subjects were allowed to leave the sleep laboratory at V2/D1 and throughout the study, once they were able to perform the Romberg and heel-to-toe gait tests at a performance level that confirmed to the clinician that no residual effects existed. Residual effects, present to the extent that subjects were unable to leave the sleep laboratory, were to be recorded as adverse events.

The PSG at Visit 2 was used to exclude subjects with sleep-related breathing disorders or PLMS or both. Subjects without such breathing disorders or PLMS were to return for the second Screening PSG night, Visit 3/Night 2 (V3/N2), if the following:

- LPS was greater than or equal to 20 minutes;

- WASO was greater than or equal to 20 minutes; and
- TST was between 240 and 420 minutes.

At Visit 3/Night 2 (V3/N2) – later in the day of V2/D1 – the following procedures were performed:

- Inclusion/exclusion criteria review.
- Concomitant medication review.
- Adverse events inquiry.
- Medical/Surgical/Psychiatric/Sleep history update.
- Alcohol Breath Test.
- Urine illicit drug screen.
- 12-lead ECG (approximately 30 minutes before single-blind dose).
- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature).
- Pre-sleep questionnaire.
- Single-blind placebo administration (60 minutes before lights-out).

Approximately 60 minutes after this single-blind placebo administration, the following were also performed:

- 12-lead ECG (just before lights-out).
- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature).
- Nocturnal PSG.

At Visit 3/Day 2 (V3/D2) – the morning after V3/N2 – the following were performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes).
- Psychometric testing (about 35 minutes [± 15 minutes] after lights-on):
  a Digit Symbol Substitution Test (DSST).
  b Memory HVLT-R list.
- Scales for sleepiness/alertness (about 35 minutes [± 15 minutes] after lights-on):
  a Leeds Sleep Evaluation Questionnaire.
  b Stanford Sleepiness Scale.
- Question about the kind of treatment they received (unmasking/masking effects).
- 12-lead ECG (approximately 10 hours after single-blind dose).

- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature, collected about 10 hours after single-blind dose).
- Adverse events inquiry (last activity before Romberg, heel-to-toe tests).
- Romberg test, heel-to-toe test.

As always, subjects were free to leave the sleep laboratory in the morning following PSG nights, once the Romberg and heel-to-toe gait tests confirmed that no residual effects existed. Residual effects that prevented subjects from promptly leaving the sleep laboratory were to be recorded as adverse events.

All subjects who qualified for the study were scheduled to return a minimum of seven (7) days (± 1 day) after the V2/N1 date, for the first double-blind treatment period. Subjects who do not qualify for the double-blind portion of the study were notified not to return.

Those subjects scheduled to return for the first double-blind treatment period were required to complete a subject diary. The diary consisted of three sets of each of the following items:

- One pre-sleep questionnaire.
- One post-sleep questionnaire.
- One Leeds Sleep Evaluation Questionnaire.
- One Stanford Sleepiness Scale.

Starting on the night of V3/D2 and continuing on each of the succeeding two nights, subjects completed three sets of forms, as are identified, immediately above. Subjects were required to return the completed diaries to the clinic at Visit 4/Night 1 (V4/N1) for study-record maintenance. However, diary data were not analyzed.

5.6.2. Double-Blind Treatment Period (Visits 4/5, 6/7, and 8/9)

If all screening criteria were met, subjects were required to return to the sleep laboratory for 3 sessions, each consisting of two consecutive nights of polysomnographic recording (PSG3 - PSG8). Each session was separated by a minimum of 12 days of washout and was to occur on the same day of the week (± 1 day).

Subjects were required to report to the sleep laboratory in sufficient time to complete the pre-dose assessments and to maintain the appropriate sleep schedule.

At each of the following study visits:

Visit 4/Night 1 (V4/N1)

Visit 5/Night 2 (V5/N2)

Visit 6/Night 1 (V6/N1)

Visit 7/Night 2 (V7/N2)

Visit 8/Night 1 (V8/N1)

Visit 9/Night 2 (V9/N2)

The study procedures, below, were to be performed prior to dosing:

- Concomitant medication review.
- Adverse events inquiry.
- Review of changes in subject's sleep habits.
- Alcohol breath test.
- Urine or serum pregnancy test.
- Urine illicit drug screen.
- Blood sample for Pharmacogenetics (V4/N1 only).
- PK sample collection.
- 12-lead ECG (approximately 30 minutes before study-drug administration).
- Pre-sleep questionnaire.
- Memory HVLT-R list (only at V4/N1, V6/N1, V8/N1). Note that the recall of the N1/N2 twelve-word list on the next morning was not done as planned (See Section 5.6.6.8).

Double-blind study-drug administration was to occur 60 minutes before lights-out. As with all PSG visit nights in this study, lights out was at approximately 21:00 hours to 00:00 hours (midnight).

Approximately 60 minutes after the double-blind study-drug administration, the following were also performed:

- 12-lead ECG (just before lights-out).
- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature).
- Nocturnal PSG.

At each of the following study visits:

Visit 4/Day 1 (V4/D1)

Visit 5/Day 2 (V5/D2)

Visit 6/Day 1 (V6/D1)

Visit 7/Day 2 (V7/D2)

Visit 8/Day 1 (V8/D1)

The assessments, below, were performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes).

- Psychometric testing (about 35 minutes [± 15 minutes] after lights-on):
  - a Digit Symbol Substitution Test (DSST).
  - b Memory HVLT-R list (Recall of the N1/N2 twelve-word list on the next morning was not done as planned [See Section 5.6.6.8]).
- Scales for sleepiness/alertness (about 35 minutes [± 15 minutes] after lights-on):
  - a Leeds Sleep Evaluation Questionnaire.
  - b Stanford Sleepiness Scale.
- Question about the kind of treatment they received (unmasking/masking effects) (only V5/D2, V7/D2, and V9/D2).
- 12-lead ECG (approximately 10 hours after single-blind dose).
- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature; collected about 10 hours after double-blind dose).
- PK blood sample (10 hours from time of dosing the night before).
- Adverse events inquiry (last activity before Romberg, heel-to-toe tests).
- Romberg test, heel-to-toe test.

At Visit 9/Day 2 (V9/D2), the following additional assessments were performed upon awakening (approximately 8 hours after lights-out):

- Physical examination.
- Laboratory tests.
- Serum Pregnancy Test.

Subjects were permitted to leave the sleep laboratory once they are able to perform the Romberg and heel-to-toe gait testing at a level of performance to indicate to the clinician that there are no residual effects. Residual effects, present to the extent that the subject was unable to leave the sleep laboratory, were to be recorded as adverse events.

As after Visit 3, subjects were also required to complete a subject diary after each of Visits 5, 7, and 9. Like that completed after Visit 3, the diary consists of three sets of each of the following items:

- One pre-sleep questionnaire.
- One post-sleep questionnaire.
- One Leeds Sleep Evaluation Questionnaire.
- One Stanford Sleepiness Scale.

Starting on the night of V5/D2, V7/D2, and V9/D2 and continuing on each of the succeeding two nights, subjects were to complete the diary as identified immediately above. Similarly, subjects completed a subject diary, starting on each of the nights of V7/D2 and V9/D2. Subjects were required to return the completed diaries to the clinic at

their next study visit for study-record maintenance. However, diary data were not analyzed.

During the 12 days between sessions, no other drugs were allowed, in particular hypnotics. In addition, no changes of life-style or extreme exercise were allowed.

5.6.3. Early Withdrawal Visit Assessment

For subjects who were withdrawn from the study the following assessments were performed:

- Post-Sleep Questionnaire.
- Physical examination.
- 12-lead ECG.
- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature).
- Concomitant medications.
- Adverse events inquiry. (The Investigator was to contact the medical monitor regarding any gastric AEs regardless of relationship to study drug).
- Thyroid function tests.
- Serum pregnancy test.
- Blood draw for clinical labs (in particular for LFTs) and pK. Any significant abnormal results were to be repeated until resolution.

5.6.4. Follow-up Visit(s) Assessments

A follow-up visit was to be conducted 14 days (± 3 days) after the last night of the PSG recording (Visit 9). The following assessments were to be performed at the follow-up visit:

- Post-Sleep Questionnaire.
- Leeds Sleep Evaluation Questionnaire; Stanford Sleepiness Scale.
- Physical examination.
- 12-lead ECG.
- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature).
- Concomitant medications.
- Adverse events inquiry. (The Investigator was to contact the medical monitor regarding any gastric AEs regardless of relationship to study drug).
- Thyroid function tests.
- Serum Pregnancy Test.

- Clinical laboratory tests. (Any significant abnormal result from the end of study visit (Visit 9) was to be repeated until resolution).

5.6.5. Efficacy Assessment

The chosen efficacy measurements are well substantiated in the literature. Polysomnographic (PSG) and subjective sleep questionnaires are routinely used to assess the hypnotic properties of pharmaceutical compounds. The principal end-points for efficacy were TST, WASO, and LPS as measured with PSG. Correlation with the corresponding subjective scores of the Sleep Questionnaire on the same sleep parameters was assessed.

5.6.5.1. Primary efficacy endpoint

The primary efficacy endpoint was wake time after sleep onset (WASO) derived from polysomnographic (PSG) recording (See Attachment 1: Definition of PSG Variables).

The primary comparison of interest was GW679769 90mg vs placebo, and GW679769 30mg vs placebo.

Another comparison of interest was GW679769 90mg vs GW679769 30mg.

5.6.5.2. Secondary efficacy endpoint(s)

Secondary endpoints included the following:

1. Objective PSG measures of sleep continuity including: Total Sleep Time (TST), latency to persistent sleep (LPS), wake during sleep (WDS), wake after sleep (WAS), and number of awakenings during sleep (See Attachment 1: Definition of PSG Variables).
2. Objective PSG measures of sleep structure: Non-REM sleep time, Slow-Wave Sleep (SWS) time (stage 3 and 4), Stage 2 non-REM sleep time; REM sleep time, REM activity, REM density (See Attachment 2: Sleep Staging).
3. Spectral analysis of EEG output.
4. Subjective Post-Sleep Questionnaire: TST, WASO, SOL, number of awakenings, and sleep quality (SQ) to be applied on each morning following PSG recording.
5. Daytime cognitive function data on the morning following dosing, including tests of alertness, memory, attention and fine motor control (i.e. Romberg test, heel-to-toe gait test, VAS for sleepiness/alertness, DSST, and immediate and delayed word recall (HVLT-R).
6. HVLT-R (verbal memory tests).
7. Changes of TST, SOL, SQ, WAS and number of awakenings measured with the Post-Sleep Questionnaire score collected on specified mornings at home during the 3-day period following each 2-night PSG sessions.
8. Plasma concentration of GW679769 and its major metabolite (GSK525060).

5.6.6. Safety Assessments

Safety assessments were obtained as detailed in the Time and Events Table (Table 1). The definition and assessment of all adverse events, serious adverse events and pregnancies are detailed in the study protocol and are further summarized in this section.

The Investigator, or medically-qualified delegate, was responsible for reviewing safety data on an ongoing basis throughout the study. The Investigator exercised his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant and reported to the sponsor, as appropriate.

5.6.6.1. Adverse events

An adverse event (AE) was defined as:

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Examples of an AE included:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).

Examples of an AE did not include a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

AEs could also include pre- or post-treatment events that occurred as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

All AEs occurring after administration of the first dose of study medication (beginning of placebo run-in), and on or before the final visit were reported on the Adverse Event form in the CRF. All adverse events were to be recorded irrespective of whether they are considered drug related.

The methods used for coding and tabulating adverse events (AEs) were as follows: Adverse events occurring after the first dose of study medication during each PSG session and up to the time of first dose in the next treatment session (i.e. including the 12-Day washout period) were assigned to treatment in the first treatment session. Adverse events were assigned to treatment in the last treatment session if they occurred during or after the treatment session, up to 30 days following the last dose of study medication. If an event occurred more than 30 days following the last dose of study medication it was attributed to the last treatment session. Thus, the reporting period for adverse events after the last treatment session was longer than the first two treatment sessions.

5.6.6.2. Serious adverse events

A serious adverse event was defined as any untoward medical occurrence that, at any dose:

a Results in death.

b Is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the Patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e Is a congenital anomaly/birth defect.

f Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Serious Adverse Events were required to be reported to GSK within 24 hours.

SAEs that were related to study participation (e.g. procedures, invasive tests, a change from existing therapy) or were related to a concurrent medication were to be collected and recorded from the time the subject consented to participate in the study until he/she was discharged. All other AEs and SAEs were to be collected from the time of administration of study medication until discharge from the study.

5.6.6.3. Pregnancies

A serum pregnancy test was required to be completed for women of childbearing potential at the Screen Visit and again at the 14-Day Follow-up Visit. Serum samples were processed through the designated laboratory. Urine dipstick pregnancy tests or serum pregnancy tests were to be obtained prior to dosing on the first evening of each session and the morning following the final dose of study medication.

Pregnancies reported after administration of the first dose of randomized study medication and on or before the final scheduled study visit (14-Day Follow-up Visit) were required to be reported using the Pregnancy Notification Form in the CRF.

In the event a subject was to become pregnant during the reporting period, study drug for that subject was to be stopped immediately.

The investigator, or his/her designee, was required to collect pregnancy information on any female subject who became pregnant while participating in this study. The investigator, or his/her designee, was required to record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject was also required to be followed to determine the outcome of the pregnancy. Information on the status of the mother and child was to be forwarded to GSK. Generally, follow-up would be no longer than 6 to 8 weeks following the

estimated delivery date. Any premature termination of the pregnancy was required to be reported.

5.6.6.4. Clinical laboratory evaluations

Laboratory samples were sent by courier to a central laboratory (Quest Diagnostics). Full guidance, training and materials for storage and transportation of samples were provided to all centers by the sponsor. Normal values, methods and quality control used for the above tests were provided for the sponsor by Quest Diagnostics.

Routine hematological parameters and blood chemistry were assessed at screening, after treatment (i.e. following participation in all three cross-treatment arms of GW679769 30mg, 90mg and placebo) and at the follow-up visit (14 +/- 2 days after the last dose).

Serum chemistry consisted of sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, calcium, magnesium, phosphorus, uric acid, total and conjugated bilirubin, total protein, albumin, cholesterol, triglycerides, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase.

Hematology consisted of hemoglobin, hematocrit, RBC, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count, WBC count and differential count, polymorphonuclear leukocytes (neutrophils), lymphocytes, eosinophils, monocytes, basophils, atypical lymphocytes, and Pepsinogen I and II.

Urinalysis consisted of testing for protein, glucose, ketones, blood (hemoglobin), pH, specific gravity, bilirubin, nitrites, microscopic: bacteria, red blood cells (RBC), white blood cells (WBC) casts, and crystals.

Other clinical laboratory tests included the following:

- Urine drug screen: including a means to detect the presence of drugs prohibited according to the protocol, including opiates, cocaine, amphetamine, cannabinoids, barbiturates, benzodiazepines, phencyclidine, methadone, propoxyphene, antidepressants, phenothiazines, and methaqualone. A positive result for any of the above drugs, without explanation, would preclude the subject from enrollment or continued participation in the study.
- Pregnancy Test (serum at screening and follow-up and urine or serum prior to the first dose in each session and the morning following the last dose of study medication).
- HIV, Hepatitis B & C (screening only).
- Thyroid Stimulating Hormone (Screening Visit, Early Withdrawal Visit or Follow-up Visit).

5.6.6.5. Other safety assessments

5.6.6.6. Vital Signs

Vital signs were measured at the initial Screening visit, and approximately 30 minutes before, 60 minutes after, and 10 hours after dosing (either single-or double-blind) on Screening PSG and treatment PSG nights. Vital signs to be measured included the following:

- Sitting blood pressure.
- Heart rate.
- Respiratory rate.
- Oral temperature.

Before blood pressure and heart rate were measured, the subject was required to be in a seated position and resting for at least five minutes. (The same position was to be used each time vital signs were measured for a given subject). Any vital sign value that was judged by the Investigator as a clinically significant change (worsening) when compared to a baseline value would be considered an adverse event, recorded on the CRF, and monitored until the event resolved or stabilized.

5.6.6.7. Electrocardiography

A 12-lead ECG was conducted at the following times with respect to nocturnal PSG performance in Study GW679769/903:

- Thirty (30) minutes before dosing (either single- or double-blind).
- Approximately 60 minutes after dosing (either single- or double-blind).
- Approximately ten (10) hours after dosing (either single- or double-blind).

Electrocardiograms were not read centrally. A qualified physician was responsible for providing interpretation of the electrocardiogram. Any electrocardiogram finding that was judged by the Investigator as a clinically significant change (worsening) when compared to a baseline value would be considered an adverse event, recorded on the CRF, and monitored until the event resolved or stabilized.

5.6.6.8. Assessment of Morning Residual Effects

Residual effects relative to morning attention, memory and psychomotor function were measured by the use of two psychometric tests (DSST and HVLT-R) and two instruments for sleepiness/alertness (Leeds Sleep Evaluation Questionnaire and Stanford Sleepiness Scale). These assessments were made on mornings (D1 and D2) following the two nights spent in the sleep laboratory. The HVLT-R was also completed at V2/N1, V4/N1, V6/N1, and V8/N1. There was a slight discrepancy in the administration of the HVLT-R during the conduct of the trial. The HVLT-R was administered at the times dictated in the protocol as listed above. However, on Day 1sites administered the whole HVLT-R (with the same list of words as the night before), including the three

learning trials, instead of administering only the free delayed recall of the list that subjects received on N1.

The two instruments for sleepiness/alertness and the psychometric tests were to be completed approximately 35 minutes (±15 minutes) after lights on. The HVLT-R tests to be completed at V2/N1, V4/N1, V6/N1, and V8/N1 could have been completed at anytime prior to single- or double-blind dosing.

After each night, subjects were permitted to leave the sleep laboratory once they were able to perform the Romberg and heel-to-toe gait testing at a level of performance to indicate to the clinician that there are no residual effects. Residual effects that were present to the extent that the subject was unable to leave the sleep laboratory were to be recorded as adverse events.

5.6.6.9. Hepatic Safety Monitoring

In the case of hepatic clinical findings detected during Early Withdrawal, at the End of the study (Visit 9) or during the Follow-Up visit, the following procedure was to be followed:

If a liver function test (LFT) elevation [including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyltransferase (GGT), direct bilirubin or total bilirubin] greater than or equal to twice the upper limit of the reference range (ULRR) occurred in any subject, weekly LFT monitoring was to be performed for that subject until the results were within the normal range. Measurement of creatine kinase (CK) isoenzymes could be performed on isolated AST values to rule out a muscular origin if deemed clinically necessary by the medical monitor or the investigator. Individuals with isolated elevations in indirect bilirubin and no reason to suspect hemolysis likely had Gilbert's syndrome and may have been kept in the study after repeat testing confirmed the absence of hemolysis (stable Hemoglobin, Hematocrit, and RBC morphology in peripheral smear, platelet count, LHD, haptoglobin and reticulocyte count are all normal) and persistent normality of liver enzymes. Isolated elevations in direct bilirubin were not expected and were to be reported to the sponsor.

The investigator was to notify the sponsor in the event of a hepatic adverse event (e.g. LFT elevations less than three times ULRR), hepatomegaly, jaundice, hepatitis, etc…

5.6.6.10. Peptic Ulcer Disease

All subjects were asked to report any peptic ulcer symptoms to the investigating physician.

If, during the course of the study, a subject with a history of PUD reported peptic ulcer symptoms, the subject was to be referred to a gastroenterologist for evaluation with the possibility that an endoscopy and biopsy may be recommended. In the event of any of the above, termination of study drug was also to be considered.

The investigator was required to inform GSK of all such cases within 24 hours of learning of the peptic ulcer symptoms.

During the course of the study, pepsinogen levels were measured. In the event of a drop in pepsinogen (either within or outside the laboratory reference range), the GSK Medical Monitor was required to be notified within 24 hours to assess appropriate follow-up. Subjects were to be considered for withdrawal from the study if the circulating levels of Pepsinogen I were below the lower limit of the normal range on two consecutive readings performed at least four days apart. Such subjects were to continue to be followed and should have been offered to undergo further evaluation, namely gastric biopsy.

5.7. Data Quality Assurance

Subject data were collected by the investigator or designee using the Case Report Form (CRF) defined by GSK. Subject data necessary for analysis and reporting was entered/transmitted into a validated database or data system. Clinical data management was performed in accordance with applicable GSK standards and data cleaning procedures. Database freeze occurred after data management quality control procedures were completed. Original CRFs were required to be retained by GSK, while the investigator also was required to retain a copy.

This report was also subject to a quality review.

5.8. Data Analysis Methods

SAS V8 on Windows was used for carrying out the statistical analyses.

5.8.1. Timings of Planned Analyses

5.8.1.1. Interim analyses and data monitoring

An interim analysis was carried-out on the PSG data collected on the first 28 subjects enrolled into the study. The analysis was performed by an independent statistician.

The focus of this interim analysis was limited to the total sleep time (TST) and the Latency to Persistent Sleep (LPS) which are parameters more sensitive of WASO.

To maintain the blind, only aggregate data were released to GSK personnel and were not communicated to any study site. The study team and the investigators remained blinded throughout the entire study. The result of the interim analysis did not affect the conduct of the remainder of the study and there was no plan to terminate the study after the Interim Analysis due to superior efficacy.

5.8.1.2. Changes in the conduct of the study or planned analyses

Analyses were carried out according to the Reporting and Analysis Plan issued on 03MAR05 and its amendment issued on 08AUG05 [See Attachment 3: Reporting and Analysis Plan and Attachment 4: Reporting and Analysis Plan (Amendment 1)].

Sleep parameters collected by diary on specific mornings at home during the 3-day period following each 2-night PSG sessions were not included in the data-base and therefore were not analyzed.

Derived Plasma PK Parameters were not calculated so no listing or summary tables of GW679769 or GSK525060 (metabolite of GW679769) were produced.

Recall of the N1 HVLT-R word list on D1 was not done as planned. Instead, the complete HVLT-R task (immediate recall and delayed recall) were performed on D1 as on D2. As a result, the effect of treatment on HVLT-R performance was determined by analysis of D2 data only.

The mixed effect model utilized to analyze HVLT-R data was slightly modified (removing the subject*session random effect) due to the presence of negative variance components.

5.8.2. Sample Size Considerations

The final sample size was based on the primary efficacy end-point "wake time after sleep onset (WASO)". In a previous study (NKD10014) a within subjects standard deviation of about 14 min was observed. So assuming a difference vs. placebo of at least 10 min, 43 subjects completing the study would provide a 90% power to detect a difference between active drugs and placebo.

A greater power was expected on the most important of the secondary endpoint (TST) where, in the previous study, a within subjects standard deviation of about 17 min was observed and where differences vs placebo of at least 20 min were expected.

5.8.3. Analysis Populations

The populations identified in the analysis plan included:

- Safety Population: including all subjects dosed at least once.
- Intent-to-Treat Population (ITT): including all subjects dosed at least once, with efficacy or PD measures available for at least one night in the double-blind phase.
- Per-Protocol Population: consisting of all subjects of the ITT who did meet inclusion criteria five. In PSG analyses, nights with any technical problem in PSG recordings were removed.

- Interim Analysis Population: including all subjects dosed at least once, with efficacy measures for at least one night in the double-blind phase included in the Interim Analysis.
- Non-Interim Analysis Population: including subjects not included in the Interim Analysis.

5.8.4. Treatment Comparisons

The primary comparisons of interest were:

- GW679769 90mg vs placebo.
- GW679769 30mg vs placebo.

Another comparison of interest was:

- GW679769 90mg vs GW679769 30mg.

5.8.5. General Considerations for Data Analyses

5.8.5.1. Multicenter studies

In the primary analysis the potential presence of a centre by treatment interaction was investigated.

5.8.6. Data Handling Conventions

5.8.6.1. Premature discontinuation and missing data

Subjects who withdrew from the study were reported and the reason for withdrawal was described.

Appropriate mixed effects models able to use incomplete data were used [See Attachment 3: Reporting and Analysis Plan and Attachment 4: Reporting and Analysis Plan (Amendment 1)]. This approach is suitable for mildly unbalanced data when cases are missing at random

5.8.6.2. Derived and transformed data

For each session and subject, mean values over the two nights were obtained for PSG and other measures collected during the two nights. Mean values were obtained even when PSG data are available for just one night.

Sleep quality answers were classified as follows:

Very poor = 1, Poor = 2, Average=3, Good=4, Very Good=5.

Leeds Sleep Questionnaire (LSEQ)

The Leeds Sleep Evaluation Questionnaire (LSEQ) has been used to monitor subjectively perceived changes in sleep during psychopharmacological investigation involving a variety of psychoactive agents. The questionnaire contains ten self-rating 100-mm-line analogue questions pertaining to four consecutive aspects of sleep: getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS) and behavior following wakefulness (BFW).

Scores on the four LSEQ subscales vary between 100 (the largest possible positive change experienced after drug administration) and 0 (the largest possible negative change experienced after drug administration). In this placebo-controlled study, drug effects were assessed both in absolute terms and with reference to a placebo value, by subtracting scores obtained after placebo administration. In this latest case, scores vary from –100 to +100 with positive values showing a drug induced improvement.

- GTS domain was derived as mean value of the items # 1,2,3
- QOS domain was derived as mean value of the items # 4,5
- AFS domain was derived as mean value of the items # 6,7
- BFW domain was derived as mean value of the items # 8,9,10

The presence of missing data prevented the calculation of the corresponding domain score.

Digit Symbol Substitution Test (DSST)

The DSST is a widely used measure of performance impairment. It is a typical test of association involved in substituting symbols for digits over a period of time. The number of correct signs substituted is taken as the score. Subjects marked a geometric pattern associated with one of the digits displayed on a computer screen. Subjects had 90 seconds to match as many geometric patterns as possible. The dependent measure was the number of patterns the subject was able to mark correctly (i.e., number of trials correct). For each test this measure was reported on the CRF.

HVLT-R

For each test, 4 scores were derived and reported on the CRFs:

Total Recall, Delayed Recall, Retention and Recognition Discrimination Index.

Raw scores (without any adjustment for age or type of form) were considered in the analyses.

5.8.6.3. Assessment windows

Nominal times were used in the main analyses.

5.8.6.4. Values of clinical concern

5.8.6.4.1. Laboratory Values

Table 3 shows the criteria by which clinical laboratory analytes were considered to be of potential clinical concern.

Table 3 Laboratory Data Ranges of Study GW679769/903

Parameter	Gender	Age (Years)	Reference Range	Clinical Concern Thresholds	Units
Hematology					
Hemoglobin	Female	18-64	12-15.6	10.5-16.1	g/dL
	Male	18-64	13.8-17.2	12-18	g/dL
Hematocrit	Female	18-64	35-46	31-51	%
	Male	18-64	41-50	36-54	%
White Cells	Female	18-99	3.8-10.8	2.8-13.8	10^9/L
	Male	18-99	3.8-10.8	2.8-13.8	10^9/L
Red Cells	Female	18-64	3.9-5.2		10^12/L
	Male	18-64	4.4-5.8		10^12/L
Mean Cell Volume	Female	18-64	80-100		fL
	Male	18-64	80-100		fL
Mean Cell Hemoglobin Concentration	Female	18-99	32-36		%
	Male	18-99	32-36		%
Platelets	Female	18-99	130000-400000	80000-500000	10^6/L
	Male	18-99	130000-400000	80000-500000	10^6/L
Neutrophils	Female	18-99	1.8-8		10^9/L
	Male	18-99	1.8-8		10^9/L
Neutrophils %	Female	18-99	40-75		%
	Male	18-99	40-75		%
Eosinophils	Female	18-99	0.05-0.55		10^9/L
	Male	18-99	0.05-0.55		10^9/L
Eosinophils %	Female	18-99	0.0-7.0		%
	Male	18-99	0.0-7.0		%
Basophils	Female	18-99	0-0.2		10^9/L
	Male	18-99	0-0.2		10^9/L
Basophils %	Female	18-99	0-2		%
	Female	18-99	0-2		%
Monocytes	Female	18-99	0.2-1.1		10^9/L
	Male	18-99	0.2-1.1		10^9/L
Monocytes %	Female	18-99	0.0-12		%
	Male	18-99	0.0-12		%
Lymphocytes	Female	18-99	0.85-4.1		10^9/L
	Male	18-99	0.85-4.1		10^9/L
Lymphocytes %	Female	18-99	16.0-46.0		%
	Male	18-99	16.0-46.0		%
Pepsinogen I	Female	18-99	40-140		ug/L
	Male	18-99	40-140		ug/L
Pepsinogen II	Female	18-99	0-22		ng/mL
	Male	18-99	0-22		ng/mL

Parameter	Gender	Age (Years)	Reference Range	Clinical Concern Thresholds	Units
Biochemistry					
Sodium	Female	18-99	135-146	130-151	mEq/L
	Male	18-99	135-146	130-151	mEq/L
Potassium	Female	18-99	3.5-5.3	3-5.8	mEq/L
	Male	18-99	3.5-5.3	3-5.8	mEq/L
Chloride	Female	18-99	95-108		mEq/L
	Male	18-99	95-108		mEq/L
Total Carbon Dioxide	Female	13-99	20-32		mEq/L
	Male	13-99	20-32		mEq/L
Total Calcium	Female	18-99	8.5-10.3	7.2-12	mg/dL
	Male	18-99	8.5-10.3	7.2-12	mg/dL
Inorganic Phosphate	Female	18-64	2.5-4.5	1.7-5.5	mg/dL
	Male	18-64	2.5-4.5	1.7-5.5	mg/dL
Magnesium	Female	18-99	1.2-2.0		mEq/L
	Male	18-99	1.2-2.0		mEq/L
Blood Urea Nitrogen	Female	18-64	7-25	0-37.5	mg/dL
	Male	18-64	7-25	0-37.5	mg/dL
Creatinine	Female	18-99	0.5-1.4	0-1.8	mg/dL
	Male	18-99	0.5-1.4	0-1.8	mg/dL
Glucose	Female	18-49	70-115	59-124	mg/dL
	Female	50-99	70-125	59-124	mg/dL
	Male	18-49	70-115	59-124	mg/dL
Uric Acid	Female	18-99	2.5-7.5	0-10.9	mg/dL
	Male	18-99	4.0-8.5	0-10.9	mg/dL
Gamma Glutamyltransferase	Female	18-64	0-45	0-90	IU/L
	Male	18-64	0-65	0-130	IU/L
Aspartate Aminotransferase	Female	18-64	0-42	0-84	IU/L
	Male	18-64	0-42	0-84	IU/L
Alanine Aminotransferase	Female	18-99	0-48	0-96	IU/L
	Male	18-99	0-48	0-96	IU/L
Alkaline Phosphatase	Female	18-99	20-125	0-187.5	IU/L
	Male	18-99	20-125	0-187.5	IU/L
Total Bilirubin	Female	18-99	0.0-1.3	0-1.95	mg/dL
	Male	18-99	0.0-1.3	0-1.95	mg/dL
Direct Bilirubin	Female	18-99	0.0-0.4		mg/dL
	Male	18-99	0.0-0.4		mg/dL
Indirect Bilirubin	Female	18-99	0.0-1.3		mg/dL
	Male	18-99	0.0-1.3		mg/dL
Total Proteins	Female	18-64	6.0-8.5	5-9.5	g/dL
	Male	18-64	6.0-8.5	5-9.5	g/dL
Albumin	Female	18-99	3.2-5.0	2.7-5.5	g/dL
	Male	18-99	3.2-5.0	2.7-5.5	g/dL
Cholesterol	Female	18-99	0-199		mg/dL

Parameter	Gender	Age (Years)	Reference Range	Clinical Concern Thresholds	Units
	Male	18-99	0-199		mg/dL
Triglycerides	Female	18-99	0-199		mg/dL
	Male	18-99	0-199		mg/dL
Thyroid Stimulating Hormone	Female	18-99	0.4-5.5		uIU/mL
	Male	18-99	0.4-5.5		uIU/mL
Urinalysis					
Specific Gravity	Female	18-99	1.001-1.035		
	Male	18-99	1.001-1.035		
pH	Female	18-99	4.6-8.0		
	Male	18-99	4.6-8.0		
Protein	Female	18-99	-		
	Male	18-99	-		
Urine Bilirubin	Female	18-99	-		
	Male	18-99	-		
Ketone	Female	18-99	-		
	Male	18-99	-		
Blood	Female	18-99	-		
	Male	18-99	-		
Nitrite	Female	18-99	-		
	Male	18-99	-		
RBCs -Microscopy	Female	18-99	0-3		
	Male	18-99	0-3		
WBCs - Microscopy	Female	18-99	0-10		
	Male	18-99	0-5		

Data Source: Table DS18

5.8.6.4.2. Vital Signs

The following criteria presented in Table 4 were used to determine whether a subject's vital signs (blood pressure and heart rate) lie outside of a pre-determined clinically important range and had a change from baseline of potential clinical importance.

Table 4 Vital Signs Flagging Ranges

Parameter	Flagging Reason
Systolic Blood Pressure	>30mmHg decrease or >30mmHg increase from baseline
Diastolic Blood Pressure	>20mmHg decrease or >20mmHg increase from baseline
Pulse	<35 Beats Per Minute or >120 Beats Per Minute

Data Source: Table DS12

5.8.6.4.3. Electrocardiographic Data

The following criteria presented in Table 5 were used to determine whether a subject's ECG findings lie outside of a pre-determined clinically important range.

Table 5 ECG Flagging Ranges

Parameter	F3 Flagging Reason (Milliseconds)
PR Interval	> 219 msec
QRS Interval	>119 msec
QTc Interval	>470 msec (male) >470 msec (female) >480 msec (female)

Data Source: Table DS15

5.8.7. Study Population

5.8.7.1. Disposition of subjects

A listing of subject number, treatment number, planned treatment allocation and actual treatment received was provided. All subjects who withdrew from the study were described.

5.8.7.2. Protocol deviations

Compliance with Inclusion criterion five (listed below) was not met for some subjects.

On two screening PSGs (on single-blinded placebo administration at each night):

- *TST between 240 and 420 minutes on both nights.*
- *Mean LPS of 30 minutes or more, but not < 20 minutes on either night.*
- *Mean WASO of 30 minutes or more, with neither night < 20 minutes.*

A list of the subjects who did not meet these criteria was provided (See Table 9).

5.8.7.3. Demographic and baseline characteristics

Demographic characteristics (age, gender, race, height, weight, and body mass index) were listed and summarized (Table DS1).

Any prior and concomitant medication recorded was listed, Medical History was described. Results of pre-sleep questionnaires were listed (Table DS37).

PSG measures (Table DS43), results of subjective post–sleep questionnaires (Table DS38, Table DS40, Table DS42) and cognitive tests (Table DS41, Table DS44) related to the screening period were summarized.

5.8.7.4. Treatment compliance

A listing of the actual treatments was produced (Table DS2).

5.8.8. Efficacy Analyses

5.8.8.1. Primary efficacy measure(s)

WASO measures (mean over the two nights) were analyzed using a mixed effects model with session and treatment as fixed effects and subject as random effect.

Additional analyses were performed to investigate the carry-over effect (effect of the treatment received in the previous period), the treatment by period interaction and the centre effect plus the treatment by centre interaction. For each of these analyses a specific additional term was added to the original model. Tests of significance were performed at the 5% level. Least squares mean values were evaluated for each treatment. Estimates for treatment differences expressed in pair-wise basis were calculated together with 95% corresponding confidence intervals. Error diagnostics from the residuals were examined to ensure that the model did not depart from the assumptions underlying analysis of variance. When the assumptions were seriously violated, transformations of the data or nonparametric methods had been considered.

The presence of a first night effect was investigated by fitting a model on single nights values with treatment, session, night and treatment night as fixed effects and subject and subject*session as random effects.

5.8.8.2. Secondary efficacy measure(s)

Secondary efficacy measures were analyzed using the same approach described for the primary analysis. This analysis was performed for the following parameters:

- Objective efficacy PSG measures: Total Sleep Time (TST), Latency to Persistent Sleep (LPS), Wake during sleep (WDS), Wake after sleep (WAS), number of Arousals per hour of sleep, number of Micro-Arousals per hour of sleep and number of one minute awakenings (See Attachment 1: Definition of PSG Variables).
- Subjective post-sleep questionnaire (PSG nights) : LSEQ domains, SSS, TST, WASO, Sleep Onset Latency (SOL), number of awakenings and Sleep Quality (SQ).

5.8.9. Safety Analyses

A list of the codes used for adverse event management was provided. All adverse events were summarized and listed by treatment period according to MedDra coding dictionary. Total numbers of adverse events by treatment and relationship with study drug were tabulated.

A list of laboratory values of potential clinical concern was reported. A complete list of labs data, flagged as ‘H’, ‘L’ (High, Low), ‘A’,’B’ (above/below potential clinical concern threshold) was presented. Finally normal ranges and potential clinical concerns ranges were given.

Vital signs and ECG data were listed by subject and time. Summary statistics of vital signs and ECG by treatment group were presented.

6. STUDY POPULATION RESULTS

This section presents study population data and includes the number and distribution of subjects by treatment group, and subject disposition (i.e. completers, withdrawals). Also described here are baseline and demographic characteristics.

The first subject was screened on 06 August 2004 (study start); the last follow up visit was on 29 July 2005.

6.1. Disposition of Subjects

This was a multicenter study carried out at six centers in the United States.

Table 6 shows the disposition of subjects in the study. Forty-eight subjects provided data from at least one blinded session: 43 completed the three treatment sessions as planned (47 subjects provided data after placebo, 45 subjects after GW679769 30mg and 45 subjects after 90mg).

Five subjects were withdrawn from the study for protocol deviations (including non-compliance; see Section 6.2).

Table 6 Subject Disposition

	All Subjects
Number of Subjects Planned, N	48
Randomized, N	48
Completed, n (%)	43 (90)
Total Number Subjects Withdrawn, n (%)	5 (10)
Withdrawn Due to Serious Adverse Events, n (%)	0 (0)
Withdrawn Due to Adverse, n (%)	0 (0)
Withdrawn for Other Reasons[1], n (%)	5 (10)

Data Source: Table DS1 and Table DS3

1. Other = Protocol violation

6.2. Protocol Deviations

As summarized in Section 6.4.2.1, six randomized subjects did not meet inclusion criterion five for the following reasons (Table DS3):

On two screening PSGs (on single-blinded placebo administration at each night):

- TST between 240 and 420 minutes on both nights.
- Mean LPS of 30 minutes or more, but not < 20 minutes on either night.
- Mean WASO of 30 minutes or more, with neither night < 20 minutes.

6.3. Populations Analyzed

The following analysis populations have been defined:

Safety Population: including all subjects receiving double-blind study medication at least once (48 subjects, 137 sessions). This population was used for all safety analyses.

Intent-to-Treat Population: including all subjects dosed at least once, with efficacy or PD measures available for at least one night in the double-blind phase (consisting of the same 48 subjects and 137 sessions of the safety population). This population was used as primary population for all efficacy and PD analyses.

Per-Protocol Population: consisting of all subjects of the ITT who did meet inclusion criterion five. In PSG analyses, nights with any technical problem in PSG recordings were removed. Per-Protocol population includes 42 subjects and 120 sessions. In PSG analyses, 119 sessions were considered, because technical problems in PSG recordings were observed in both of the nights for subject # 11, session 2.

Interim Analysis Population: consisting of all subjects of the ITT included in the Interim analysis (28 subjects, 77 sessions).

Non-Interim Analysis Population (ie subjects not included in the Interim Analysis): consisting of 20 subjects and 60 sessions.

Analyses concerning the objective PSG measures of sleep continuity (WASO, TST, LPS, WDS, WAS, number of arousals/micro-arousals per hour of sleep, and number of one minute awakenings) were carried out on four Populations (Intent-to-treat, Interim Analysis Population, Subjects not included in the Interim, and Per-Protocol), while other efficacy and PD analyses were carried out only on the Intent-to-Treat population.

6.4. Demographics and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Table 7 shows the number of subjects by gender, race and age group. The mean age of the study population was 40 years and approximately 77% of all subjects were female. Fifty-six percent of the population was White/Caucasian, 40% were Black, 2% were American Hispanic, and 2% were East and South East Asian.

Demographic characteristics for the Safety Population are detailed in Table DS1.

Table 7 Number (%) of Subjects by Gender, Race and Age Group

Demography Detail	All Subjects (N=48)
Gender n (%)	
Female	37 (77%)
Male	11 (23%)
Race n (%)	
White/Caucasian	27 (56%)
Black	19 (40%)
American Hispanic	1 (2%)
East and Southeast Asian	1 (2%)
Age (Years)	
Mean	40
Standard Deviation	10.1
Minimum	21
Maximum	61
Weight (Kg)	
Mean	74.9
Standard Deviation	13.11
Minimum	46.8
Maximum	99.1
Height (cm)	
Mean	167
Standard Deviation	7.8
Minimum	151
Maximum	185

Data Source: Table DS1

6.4.2. Baseline Characteristics

6.4.2.1. Baseline Objective PSG Efficacy Measures

A summary of key pre-treatment PSG measures obtained at the PSG screening session is presented in Table 8 (See Attachment 1: Definition of PSG Variables).

Details of subjective pre-sleep questionnaires are detailed in Table DS37, and sleep history data in Table DS49.

The Leeds Sleep Questionnaire and Stanford Sleepiness Questionnaire are detailed in Table DS40 and Table DS42. PSG data is listed in Table DS43.

Table 8 Summary of Pre-Treatment PSG Efficacy Measures –Mean over the Two Screening Nights (All Subjects, ITT Population)

PSG Measure	N	Mean	Standard Deviation
WASO (min)	48	69.02	35.88
TST (min)	48	356.75	42.61
LPS (min)	48	59.06	21.04
WDS (min)	48	60.58	33.82
WAS (min)	48	8.44	12.66
No. of 1 Min Awakenings	48	10.40	3.62

Data Source: Table 6.1

As summarized in Section 5.3.1 (Inclusion/Exclusion Criteria), subjects were eligible for inclusion in the study if during the two PSG screening nights (on single blind placebo administration) the following Inclusion Criteria (Criteria #5) were met:

- TST between 240 and 420 minutes on both nights
- Mean LPS of 30 minutes or more, but not <20 minutes on either night
- Mean WASO of 30 minutes or more, with neither night < 20 minutes

Table 9 provides a summary of the six randomized subjects who did not meet the criteria as outlined above. These subjects were excluded from the per protocol population (see Section 6.3).

Table 9 Listing of Subjects Who Did Not Meet Inclusion Criteria Number Five

[redacted]

Data Source: Attachment 5, Listing 3
1. Reason for exclusion

6.4.2.2. Baseline Subjective Post Sleep Questionnaires

A summary of the pre-treatment subjective post-sleep questionnaires are presented in Table DS38 and Table 10.

Table 10 Summary of Results of Pre-Treatment Subjective Post Sleep Questionnaires –Mean Over the Two Screening Nights (All Subjects, ITT Population)

Post Sleep Questionnaire	N	Mean	Standard Deviation
Sleep Onset Latency (SOL)	48	74.03	37.95
Total Sleep Time (TST)	48	325.02	52.78
Wake after Sleep Onset (WASO)	48	93.43	55.75
Number of Awakenings	48	3.76	1.47
Sleep Quality	48	2.74	0.50
LSEQ –Getting to Sleep Domain	48	48.88	7.63
LSEQ –Quality of Sleep Domain	48	49.76	7.86
LSEQ –Awakening from Sleep Domain	48	52.97	10.24
LSEQ –Behavior Following Wakefulness Domain	48	48.97	11.79
Stanford Sleepiness Scale	48	3.09	1.08

Data Source: Table 6.2

6.4.2.3. Baseline Cognitive Data

A summary of the pre-treatment cognitive data are presented in Table 11. Detailed listings are located in Table DS41 and Table DS44, respectively. A description of the Digit Symbol Substitution Test (DSST) and the HVLT-R are provided in Section 5.8.6.2.

Table 11 Summary of Pre-Treatment Cognitive Data (ITT Population)

Cognitive Data	N	Mean	Standard Deviation
DSST (mean of D1/D2)	48	74.71	17.26
HVLT-R Total Recall (mean of N1 plus D1/D2)	48	26.94	4.10
HVLT-R Delayed Recall (mean of N1 plus D1/D2)	48	9.15	2.15
HVLT-R Retention % (mean of N1 plus D1/D2)	48	87.92	15.46
HVLT-R Recognition Discrimination Index (mean of N1 plus D1/D2)	48	10.60	1.65

Data Source: Table 6.3

6.4.3. Previous Medications

No subject presented with conditions or medical history that the Investigator considered likely to affect the conduct or outcome of the study or safety of the subject.

A listing of prior medications is provided in Table DS4. None of these prior medications was considered by the Investigator as likely to affect the outcome of the study or safety of the subject.

6.5. Concomitant Medications

A listing of concomitant medications is provided in Table DS4. None of these medications was considered by the Investigator as likely to affect the outcome of the study or safety of the subject.

6.6. Treatment Compliance

Study medication was administered under the supervision of study personnel. The oral cavity of each subject was examined following dosing to assure that study medication was taken.

7. RESULTS OF EFFICACY AND COGNITIVE EVALUATIONS

This section presents the analyses of the efficacy data for the primary and secondary efficacy variables. These analyses were conducted using the ITT population. Where available, results for the Per Protocol (PP) population are also provided. Results of Cognitive assessments are also presented in this section. Spectral analyses and pharmacokinetic/pharmacodynamic (PK/PD) analyses are reported separately.

7.1. Primary Efficacy Results– Wake After Sleep Onset (WASO)

The protocol-defined primary efficacy endpoint was the wake time after sleep onset (WASO) derived from the polysomnographic (PSG) recording. Table 12 presents the summary of WASO PSG for the ITT population. WASO was significantly less versus placebo for both the 30mg and 90mg doses of GW679769 (p = 0.001 and p = 0.017, respectively). Both doses were associated with about a 10 minute less wake time after sleep onset versus placebo. Statistical significance between treatments was not demonstrated (GW679769 90mg vs. 30mg).

As shown in Table 8, the mean screening WASO was 69.02 +/- 35.88 minutes signifying some habituation to the sleep clinic when comparisons are made to values in Table 12 for the placebo group.

Table 12 Summary of Results of the Statistical Analysis of Post-Treatment WASO (Minutes) PSG Data (ITT Population)

Pbo[1] N = 47	GW679769 30mg[1] N = 45	GW679769 90mg[1] N = 45	Difference GW679769 30mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs 30mg [95% CI] p-value
42.92	30.38	33.56	-12.54 [-20.12, -4.96] p = 0.001	-9.36 [-16.96, -1.75] p = 0.017	3.19 [-4.50, 10.87] p = 0.413

Data Source: Table 7.1 and Table 7.3
1. LS Mean presented; Mean over the two nights.

Table 13 presents the analysis of the summary of WASO for the PP population. The results of the analysis of the PP population confirm statistical significance over placebo as seen in the ITT population for the GW679769 30mg treatment group (treatment difference -10.89; CI [-18.77, -3.01]; p-value 0.007). However, results of the comparison of GW679769 90mg vs. placebo and for GW679769 90mg vs. GW679769 30mg for the PP population were not statistically significant (0.060 and 0.431, respectively), although results for the 90mg – placebo comparison showed a trend towards significance with a p-value very close to the limit of significance (p = 0.060).

Table 13 Summary of Results of the Statistical Analysis of Post-Treatment WASO (Minutes) PSG Data (PP Population)

Pbo[1] N = 41	GW679769 30mg[1] N = 40	GW679769 90mg[1] N = 39	Difference GW679769 30mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs 30mg [95% CI] p-value
41.12	30.23	33.39	-10.89 [-18.77, -3.01] p = 0.007	-7.72 [-15.78, 0.33] p = 0.060	3.16 [-4.79, 11.12] p = 0.431

Data Source: Table 7.2 and Table 7.4
1. LS Mean presented; Mean over the two nights.

No signal of the presence of a first-order carry-over effect of a treatment by session interaction or of a treatment by center interaction was detected (See Attachment 6). No statistically significant night or night by treatment interaction effect was detected even if there was trend towards a reduction of the difference between active and placebo in the second night.

Analysis of residuals showed a departure from normality. For this reason the analysis was repeated on log-transformed WASO data confirming the results of the model on original data.

7.2. Secondary Efficacy Results

7.2.1. Other PSG Endpoints

7.2.1.1. Total Sleep Time (TST) and Latency to Persistent Sleep (LPS)

A summary of the analysis of Total Sleep Time (TST) and Latency to Persistent Sleep (LPS) as derived from PSG recordings for the ITT population are presented in Table 14.

TST and LPS were statistically different for both of the active treatments (GW679769 30mg and GW679769 90mg) compared to placebo (p-values <0.001 for both treatment groups compared to placebo), indicating a longer TST and a shorter LPS value associated with each treatment versus placebo. A statistically significant difference between the two doses of GW679769 was not observed for both endpoints (TST and LPS).

These results were confirmed both in the analyses on the Per-Protocol Population and in the analyses on log-transformed LPS values (there was no need to apply log transformation to TST values). Treatment effects were also highly consistent between the two nights.

Table 14 Objective Measures of Sleep Continuity –TST and LPS (Minutes) - (ITT Population)

Pbo[1] N = 47	GW679769 30mg[1] N = 45	GW679769 90mg[1] N = 45	Difference GW679769 30mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs 30mg [95% CI] p-value
Mean TST (min) Over the Two Nights					
411.28	435.27	431.76	24.00 [14.66, 33.34] p <0.001	20.49 [11.11, 29.87] p <0.001	-3.51 [-12.99, 5.97] p = 0.464
Mean LPS (min) Over the Two Nights					
28.50	17.17	17.83	-11.33 [-16.70, -5.96] p <0.001	-10.67 [-16.05, -5.28] p <0.001	0.67 [-4.78, 6.11] p = 0.809

Data Source: Table 7.5 and Table 7.6

1. LS Mean presented

7.2.1.2. Wake During Sleep (WDS), Wake After Sleep (WAS) and Number of Awakenings During Sleep

Table 15 presents the summary of the analysis of Wake During Sleep (WDS), Wake After Sleep (WAS) and the number of awakenings over the two nights as derived from PSG recordings.

The change in WDS was significantly less for the GW679769 30mg group vs placebo (p = 0.004). A trend toward significance was seen for the GW679769 90mg group vs placebo (p = 0.055). A statistically significant difference between the two doses of GW679769 was not observed for Wake During Sleep (p-value 0.457).

Statistically significant differences from placebo were not observed for both the GW679769 30mg and GW679769 90mg versus placebo comparisons (p-value 0.253 and 0.213, respectively) for Wake After Sleep. In addition, a statistically significant difference between the two doses of GW679769 was not observed (p-value 0.919).

A statistically significant difference was observed in the one minute awakenings for the GW679769 30mg comparison to placebo.

Table 15 Objective Measures of Sleep Continuity –Wake During Sleep (WDS), Wake After Sleep (WAS) and Number of Awakenings (ITT Population)

Pbo[1] N = 47	GW679769 30mg[1] N = 45	GW679769 90mg[1] N = 45	Difference GW679769 30mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs 30mg [95% CI] p-value
Mean WDS (min) Over the Two Nights					
37.04	26.52	30.04	-10.52 [-17.67, -3.68] p = 0.004	-7.00 [-14.17, 0.17] p = 0.055	3.52 [-3.72, 10.77] p = 0.336
Mean WAS (min) Over the Two Nights					
5.92	3.83	3.64	-2.09 [-5.71, 1.52] p = 0.253	-2.28 [-5.90, 1.34] p = 0.213	-0.19 [-3.85, 3.47] p = 0.919
Mean Number of One Minute Awakenings Over the Two Nights					
7.83	6.34	7.08	-1.49 [-2.51, -0.46] p = 0.005	-0.75 [-1.78, 0.28] p = 0.152	0.74 [-0.30, 1.78] p = 0.161

Data Source: Table 7.5 and Table 7.6
1. LS Mean presented

7.2.1.3. PSG Measures of Sleep Structure

The summary of results for the statistical analysis of the PSG measures of Sleep Structure is presented in Table 16. Measures of sleep architecture showed a statistically significant difference for both doses versus placebo in both Stage 2 and Slow Wave Sleep (SWS) with the former being increased at the expense of the latter. These effects were seen when the data are expressed as both the percent of time and the total time spent in Stage 2 and SWS. These effects were further supported by statistically significant differences in the percent of time and total time spent in both sleep stages between doses (GW679769 90mg vs. GW679769 30mg).

The percentage of time and total time spent in REM sleep was significantly greater than placebo with the 30mg dose of GW679769. A trend towards significance was observed for the greater time spent in REM sleep for the 90mg treatment group (p = 0.072). Significantly less REM latency versus placebo was also observed for the 90mg group.

Table 16 Objective PSG Measures of Sleep Architecture (ITT Population)

Sleep Architecture Measure[1]	Placebo N = 47	GW679769 30mg N = 45	GW679769 90mg N = 45
% Total Sleep Time in NREM Stage 1	6.20	6.54	5.84
% Total Sleep Time in NREM Stage 2	51.49	58.29[2]	61.19[2]
% Total Sleep Time in SWS	20.53	12.96[2]	10.72[2]
% Total Sleep Time in REM	21.74	23.03[5]	22.22
Total Time in NREM Stage 1 (min)	24.38	24.50	24.77
Total Time in NREM Stage 2 (min)	211.58	253.61[2]	264.87[2]
Total Time in SWS (min)	85.13	56.39[2]	46.90[2]
Total Time in REM (min)	90.32	100.86[3]	96.33
Latency to REM (min)	111.34	100.85	96.79[4]

Data Source: Table 7.7 and Table 7.8

1. Mean over the two nights, LS Mean presented
2. $p < 0.001$ active treatment vs. placebo
3. $p = 0.002$ active treatment vs. placebo
4. $p = 0.018$ active treatment vs. placebo
5. $p = 0.048$ active treatment vs. placebo

7.2.1.4. Spectral Analysis Data

The spectral analysis data will be reported separately.

7.2.2. Subjective Sleep Assessments

7.2.2.1. Post Sleep Questionnaires

A summary of the results of the statistical analysis of the Post Sleep Questionnaires are presented in Table 17. Total Sleep Time (TST) was significantly greater and Wake Time After Sleep Onset (WASO) was significantly less than placebo for the GW679769 30mg treatment group. In addition, significantly better sleep quality was observed for the GW679769 90mg treatment group versus placebo. All other comparisons were not statistically significant.

Table 17 Post-Sleep Questionnaire –ITT Population

Pbo[1] N = 47	GW679769 30mg[1] N = 45	GW679769 90mg[1] N = 45	Difference GW679769 30mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs Placebo 95% CI] p-value	Difference GW679769 90mg vs 30mg 95% CI] p-value
Sleep Onset Latency -Mean over the Two Nights					
43.45	36.89	42.76	-6.56 [-17.03, 3.91] p = 0.217	-0.69 [-11.20, 9.83] p = 0.897	5.87 [-4.76, 16.50] p = 0.275
Total Sleep Time (min) -Mean over the Two Nights					
366.63	386.57	380.58	19.93 [4.05, 35.82] p =0.015	13.95 [-2.03, 29.92] p = 0.086	-5.99 [-22.12, 10.15] p = 0.463
Wake after Sleep Onset (min) -Mean over the Two Nights					
68.71	52.46	62.97	-16.25 [-31.39, -1.11] p = 0.036	-5.74 [-20.92, 9.45] p = 0.455	10.51 [-4.84, 25.86] p = 0.177
Number of Awakenings -Mean over the Two Nights					
3.30	3.28	3.29	-0.02 [-0.58, 0.53] p = 0.935	-0.02 [-0.57, 0.54] p = 0.951	0.01 [-0.56, 0.57] p = 0.983
Sleep Quality (Numerical Score) - Mean over the Two Nights					
3.16	3.34	3.47	0.17 [-0.09, 0.43] p = 0.192	0.31 [0.05, 0.57] p = 0.021	0.14 [-0.13, 0.40] p = 0.305

Data Source: Table 7.9 and Table 7.10

1. LS Mean Presented

7.2.2.2. Subjective Sleep Scores - Leeds Sleep Evaluation Questionnaire (LSEQ) and Stanford Sleepiness Scale

A summary of the results of the statistical analysis of the LSEQ and Stanford Sleepiness Scale are presented in Table 18. Statistically significant differences between active treatments and placebo were observed for the Getting to Sleep domain for both doses of GW679769 and the Quality of Sleep domain of the LSEQ for the 30mg dose of GW679769. These effects indicate that subjects taking GW679769 on average felt that they got to sleep faster and had better quality sleep than subjects taking placebo.

No statistically significant differences versus placebo were observed for the Awakening from Sleep domain, or the Behavior Following Sleep domain of the LSEQ, or for the Stanford Sleepiness Scale for either dose of GW679769 or between doses.

Table 18 Leeds Sleep Evaluation Questionnaire (LSEQ) and Stanford Scale–ITT Population

	Pbo[1] N = 47	GW679769 30mg[1] N = 45	GW679769 90mg[1] N = 45	Difference GW679769 30mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs 30mg [95% CI] p-value
Leeds Sleep Evaluation Questionnaire						
Getting to Sleep	57.27	63.20	61.94	5.93 [1.65, 10.21] p = 0.007	4.67 [0.37, 8.97] p = 0.034	-1.26 [-5.60, 3.09] p = 0.567
Quality of Sleep	56.87	63.01	61.04	6.14 [0.86, 11.42] p = 0.023	4.17 [-1.14, 9.48] p = 0.122	-1.97 [-7.33, 3.39] p = 0.467
Awakenings from Sleep	55.31	56.44	57.21	1.13 [-2.85, 5.11] p = 0.574	1.90 [-2.10, 5.90] p = 0.348	0.77 [-3.27, 4.81] p = 0.705
Behavior Following Wakefulness	52.40	53.93	54.10	1.53 [-2.06, 5.12] p = 0.400	1.70 [-1.91, 5.32] p = 0.352	0.18 [-3.47, 4.82] p = 0.924
Stanford Sleepiness Scale						
	2.80	2.81	2.79	0.01 [-0.20, 0.23] p = 0.906	-0.01 [-0.23, 0.21] p = 0.937	-0.02 [-.0.24, 0.20] p = 0.846

Data Source: Table 7.9 and Table 7.10

1. LS Mean Presented

7.3. Daytime Cognitive Function

The summary of the results of the statistical analysis for the tests of cognitive functioning are provided in Table 19 and include the Digit Symbol Substitution Test (DSST) and the Hopkins Verbal Learning Test (HVLT).

Cognitive function as measured by these tests was similar to that measured during the screening PSG session (See Section 6.4.2.3).

No statistically significant differences were observed for the GW679769 30mg and 90mg treatment comparison to placebo for the DSST.

The Hopkins Verbal Learning Test showed no effect of treatment on total recall or recognition discrimination index versus placebo. However, verbal retention and delayed recall were greater in the GW679769 30mg and 90mg treatment groups than in the placebo group.

No difference was observed between doses of GW679769 on the DSST or any domain of the HVLT-R.

Table 19 Summary of Results of Daytime Cognitive Data (ITT Population)

Pbo[1] N = 45	GW679769 30mg[1] N = 45	GW679769 90mg[1] N = 45	Difference GW679769 30mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs Placebo [95% CI] p-value	Difference GW679769 90mg vs 30mg [95% CI] p-value
DSST- Mean Score for the Two Measures (D1 and D2)					
77.88	75.98	76.77	-1.90 [-4.91, 1.10] p = 0.221	-1.11 [-4.14, 1.92] p = 0.468	0.79 [-2.26, 3.85] p = 0.608
HVLT-R (Total Recall) – D2					
26.04	26.66	26.03	0.63 [-0.75, 2.00] p = 0.371	-0.01 [-1.38, 1.35] p = 0.985	-0.64 [-2.02, 0.75] p = 0.365
HVLT-R (Delayed Recall) – D2					
8.21	8.91	9.08	0.70 [0.10, 1.31] p = 0.023	0.87 [0.26, 1.47] p = 0.005	0.16 [-0.45, 0.78] p = 0.598
HVLT-R (Retention %) – D2					
81.24	88.50	91.47	7.26 [1.23, 13.29] p = 0.018	10.23 [4.23, 16.23] p <0.001	2.97 [-3.12, 9.06] p = 0.338
HVLT-R (Recognition Discrimination Index) –D2					
10.66	10.57	10.72	-0.08 [-0.67, 0.51] p = 0.781	0.06 [-0.53, 0.65] p = 0.839	0.14 [-0.45, 0.74] p = 0.634

Data Source: Table 7.11 and Table 7.12

1. LS Mean presented.

7.4. Efficacy Conclusion(s)

- This study showed an effect of GW679769 30mg and 90mg doses versus placebo on the main PSG endpoints, WASO, TST, and LPS. WASO, the primary endpoint of the study, was significantly less with both doses of GW679769. In addition, significant effects of both doses (i.e. greater TST and less LPS versus placebo), were demonstrated.
- Assessment of sleep architecture showed a greater duration of Stage 2 sleep and greater percentage of time spent in Stage 2 at the expense of Slow Wave Sleep with both doses versus placebo. There was no statistically significant difference in percentage of time or total time spent in Stage 1 Sleep and no reduction in duration of REM sleep.
- Statistically significant differences between active treatment and placebo were also observed for the Getting to Sleep domain of the LSEQ scale for both doses, the Quality of Sleep domain of the LSEQ scale at the 30mg dose, subjectively measured TST and WASO at the 30mg dose, and sleep quality at the 90mg dose.
- Cognitive tests performed on the morning following treatment showed no residual effect with either dose on attention, psychomotor or verbal memory tasks (DSST and HVLT).
- No consistent differences were detected on the main PSG or cognitive endpoints between the 30mg and the 90mg dose of GW679769.

8. SAFETY RESULTS

This section describes the safety data for this study. The safety data analyzed included adverse events, laboratory data, vital signs and ECG data.

8.1. Extent of Exposure

The extent of exposure was listed by subject, dose date and time (Table DS2).

Forty-eight subjects provided data from at least one blinded session: 43 completed the three treatment sessions as planned (47 subjects provided data after placebo, 45 subjects after GW679769 30mg and 45 subjects after 90mg).

8.2. Adverse Events

The methods used for coding and tabulating adverse events (AEs) were as follows: Adverse events occurring after the first dose of study medication during each PSG session and up to the time of first dose in the next treatment session (i.e. including the 12-Day washout period) were assigned to treatment in the first treatment session. Adverse events were assigned to treatment in the last treatment session if they occurred during or after the treatment session, up to 30 days following the last dose of study medication. If an event occurred more than 30 days following the last dose of study medication it was attributed to the last treatment session. Thus, the reporting period for adverse events after the last treatment session was longer that the first two treatment sessions.

Errata are described in each table when they occurred.

8.2.1. Treatment Emergent Adverse Events

Table 20 presents a summary of the treatment emergent adverse events by system organ class and preferred term by treatment group. Laboratory investigations reported by the investigator as an adverse event are also provided. A full description of laboratory values that met the sponsor's criteria for potential clinical concern as well as those reported as an AE are provided in Section 8.6.1.

A listing of all AEs by subject can be found in Table DS6 (key found in Table DS5) and are summarized in Table DS7, Table DS8 and Table DS9.

No event occurred at a rate greater than 8.5% and usually occurred at an incidence rate of 2-4%.

For subjects treated with placebo, treatment emergent adverse events were most likely to occur as laboratory investigations (abnormalities in hematology and serum chemistry), nervous system disorders (headache and dizziness), and gastrointestinal disorders (nausea and abdominal pain).

For subjects treated with 30mg of GW679769, treatment emergent adverse events were most likely to occur as nervous system disorders (headache and somnolence) and gastrointestinal disorders (nausea and diarrhea).

For subjects treated with 90mg of GW679769, treatment emergent adverse events were most likely to occur as laboratory investigations (abnormalities in hematology and one event of decreased serum glucose), gastrointestinal disorders (diarrhea and toothache), and respiratory, thoracic and mediastinal disorders (pharyngolaryngeal pain and throat irritation).

Table 20 Number (%) of Subjects with Treatment Emergent Adverse Events

	Treatment Group		
System Organ Class Preferred Term	Placebo N = 47[1] n (%)	GW679769 30mg N = 45 n (%)	GW679769 90mg N = 45 n (%)
Ear and Labyrinth Disorders			
Vertigo	0 (0)	1 (2.2)	0 (0)
Gastrointestinal Disorders			
Abdominal Pain	1 (2.1)	0 (0)	0 (0)
Diarrhea	0 (0)	1 (2.2)	1 (2.2)
Nausea[1]	2 (4.3)	2 (4.4)	0 (0)
Toothache	0 (0)	0 (0)	1 (2.2)
General Disorders and Administration Site Disorders			
Chills	0 (0)	1 (2.2)	0 (0)
Feeling Abnormal	1 (2.1)	0 (0)	0 (0)
Feeling Hot and Cold	0 (0)	1 (2.2)	0 (0)
Influenza like illness	0 (0)	0 (0)	1 (2.2)
Immune System Disorders			
Allergy to Arthropod Sting	0 (0)	1 (2.2)	0 (0)
Infections and Infestations			
Herpes Simplex	1 (2.1)	0 (0)	0 (0)
Sinusitis	0 (0)	0 (0)	1 (2.2)
Vaginitis bacterial	1 (2.1)	0 (0)	0 (0)
Injury, Poisoning and Procedural Complications			
Contusion	0 (0)	0 (0)	1 (2.2)
Investigations[3]			
Blood Bilirubin Increased	1 (2.1)	0 (0)	0 (0)
Blood Cholesterol Increased	1 (2.1)	0 (0)	0 (0)
Blood Glucose Decreased	0 (0)	0 (0)	1 (2.2)
Blood Triglycerides Increased	1 (2.1)	0 (0)	0 (0)
Drug Screen Positive[2]	2 (4.3)	0 (0)	0 (0)
Lymphocyte Count Increased	1 (2.1)	0 (0)	0 (0)
Neutrophil Count Decreased	1 (2.1)	0 (0)	2 (4.4)
Neutrophil Count Increased	0 (0)	0 (0)	1 (2.2)
Neutrophil Percentage Decreased	0 (0)	0 (0)	1 (2.2)
White Blood Cell Count Decreased	0 (0)	0 (0)	1 (2.2)
Metabolism and Nutrition Disorders			
Hypoglycemia	1 (2.1)	0 (0)	0 (0)
Musculoskeletal and Connective Tissue Disorders			
Back Pain	1 (2.1)	0 (0)	0 (0)

	Treatment Group		
System Organ Class Preferred Term	Placebo N = 47[1] n (%)	GW679769 30mg N = 45 n (%)	GW679769 90mg N = 45 n (%)
Nervous System Disorders			
Dizziness	1 (2.1)	0 (0)	0 (0)
Headache	4 (8.5)	3 (6.7)	0 (0)
Somnolence	0 (0)	1 (2.2)	0 (0)
Psychiatric Disorders			
Disorientation	1 (2.1)	0 (0)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders			
Pharyngolaryngeal Pain	0 (0)	0 (0)	1 (2.2)
Throat Irritation	0 (0)	0 (0)	1 (2.2)
Skin and Subcutaneous Tissue Disorders			
Eczema	1 (2.1)	0 (0)	0 (0)
Rash Macular	1 (2.1)	0 (0)	0 (0)
Rash	0 (0)	1 (2.2)	1 (2.2)
Vascular Disorders			
Flushing	0 (0)	0 (0)	1 (2.2)

Data Source: Table DS6, Table DS7, and Table DS8

1. Erratum: Data Source Table DS7 incorrectly reported one event occurring during the single-blind placebo treatment session: [redacted] This event was therefore, not considered treatment emergent.
2. [redacted]
3. A full description of laboratory values that met the sponsor's criteria for potential clinical concern as well as those reported as AEs are provided in Section 8.6.1.

8.2.1.1. Treatment Emergent Adverse Events by Frequency

Table 21 presents the number of subject sessions where adverse events were reported. Overall, 13/47 (27.7%) of subjects in the placebo group, 6/45 (13.3%) of subjects in the GW679769 30mg group and 7 /45 (15.6%) of subjects in the GW679769 90mg group reported one or more emergent adverse events during the treatment phase. The vast majority of adverse events occurred at a low rate (i.e. one subject per group or approximately 2%). Adverse events occurring at a greater rate (i.e. 2-4 subjects per treatment group or between approximately 4-9%) included headache, nausea, decreased neutrophil count and positive drug screen. The most common adverse events reported were headache and nausea. However, there was no clear association of adverse events with either dose of GW679769, compared to placebo.

Table 21 Number (%) of Subjects with Treatment Emergent Adverse Events

Adverse Event	Placebo N = 47[1] n (%)	GW679769 30mg N = 45 n (%)	GW679769 90mg N = 45 n (%)
Total Number of Subjects with AEs	13 (27.7)	6 (13.3)	7 (15.6)
Headache	4 (8.5)	3 (6.7)	0 (0)
Nausea[1]	2 (4.3)	2 (4.4)	0 (0)
Drug Screen Positive[2]	2 (4.3)	0 (0)	0 (0)
Abdominal Pain Upper	1 (2.1)	0 (0)	0 (0)
Back Pain	1 (2.1)	0 (0)	0 (0)
Blood Bilirubin Increased	1 (2.1)	0 (0)	0 (0)
Blood Cholesterol Increased	1 (2.1)	0 (0)	0 (0)
Blood Triglycerides Increased	1 (2.1)	0 (0)	0 (0)
Disorientation	1 (2.1)	0 (0)	0 (0)
Dizziness	1 (2.1)	0 (0)	0 (0)
Eczema	1 (2.1)	0 (0)	0 (0)
Feeling Abnormal	1 (2.1)	0 (0)	0 (0)
Herpes Simplex	1 (2.1)	0 (0)	0 (0)
Hypoglycemia	1 (2.1)	0 (0)	0 (0)
Lymphocyte Count Increased	1 (2.1)	0 (0)	0 (0)
Neutrophil Count Decreased	1 (2.1)	0 (0)	2 (4.4)
Rash macular	1 (2.1)	0 (0)	0 (0)
Vaginitis bacterial	1 (2.1)	0 (0)	0 (0)
Allergy to Arthropod Sting	0 (0)	1 (2.2)	0 (0)
Chills	0 (0)	1 (2.2)	0 (0)
Diarrhea	0 (0)	1 (2.2)	1 (2.2)
Feeling Hot and Cold	0 (0)	1 (2.2)	0 (0)
Rash	0 (0)	1 (2.2)	1 (2.2)
Somnolence	0 (0)	1 (2.2)	0 (0)
Vertigo	0 (0)	1 (2.2)	0 (0)
Blood Glucose Decreased	0 (0)	0 (0)	1 (2.2)
Contusion	0 (0)	0 (0)	1 (2.2)
Flushing	0 (0)	0 (0)	1 (2.2)
Influenza like illness	0 (0)	0 (0)	1 (2.2)
Neutrophil Count Increased	0 (0)	0 (0)	1 (2.2)
Neutrophil Percentage Decreased	0 (0)	0 (0)	1 (2.2)
Pharyngolaryngeal Pain	0 (0)	0 (0)	1 (2.2)
Sinusitis	0 (0)	0 (0)	1 (2.2)
Throat Irritation	0 (0)	0 (0)	1 (2.2)
Toothache	0 (0)	0 (0)	1 (2.2)
White Blood Cell Count Decreased	0 (0)	0 (0)	1 (2.2)

Data Source: Table DS8

1. Erratum: Data Source Table DS8 incorrectly reported one event occurring during the single-blind placebo treatment session: [redacted] This event was therefore, not considered treatment emergent in the above table. [redacted] Also, the total number of subjects in the placebo group has been changed above to accurately reflect the number of subjects receiving the double-blind placebo (i.e. 47). [redacted]
2. [redacted]

8.2.1.2. Treatment Emergent Adverse Events by Intensity

Table 22 presents the number of subjects with adverse events by intensity rating. In general, the majority of treatment emergent adverse events were rated by investigators as mild in intensity. Only one event of somnolence was judged to be severe by the investigator for the GW679769 30mg treatment group. No action was taken with respect to study medication and the event was listed as resolved.

Table DS6 provides a listing of all adverse events and intensity rating.

Table 22 Number (%) of Subjects with Adverse Events by Intensity Rating

Adverse Event Rating	Placebo N = 47[1] n (%)	GW679769 30mg N = 45 n (%)	GW679769 90mg N = 45 n (%)
Mild[1]	16 (34.0)	11 (24.4)	7 (15.6)
Moderate	7 (14.9)	0 (0)	8 (17.8)
Severe	0 (0)	1 (2.2)	0 (0)

Data Source: Table DS6 and Table DS7.

1. Erratum: Data Source Table DS7 incorrectly reported one event occurring during the single-blind placebo treatment session: [redacted]

8.2.1.3. Treatment Emergent Adverse Events Considered to be Probably Related or Suspected to be Related to Study Medication

The incidence of treatment emergent adverse events considered by investigators to be probably related or suspected to be related to study medication were 6/23 (26%) events in 13 subjects for the placebo treatment group, 8/14 events (57%) in 6 subjects for the GW679769 30mg treatment group, and 6/15 events (40.0%) in 7 subjects for the GW679769 90mg treatment group.

Table DS6 provides a listing of all adverse events and relationship.

Table 23 presents a summary of the number and nature of adverse events to be considered probably related or suspected to be related to study medication. The most common emergent adverse event considered probably related or suspected to be related to treatment with placebo was headache. Events considered probably related or suspected to be related occurred with similar frequency in the GW679769 30mg and 90mg treatment groups.

Table 23 Number of Subjects Experiencing Adverse Events Considered Probably Related or Suspected to be Related to Study Medication

Adverse Event	Placebo N Sessions = 47[1] n (%)	GW679769 30mg N Sessions = 45 n (%)	GW679769 90mg N Sessions = 45 n (%)
Total Number of Subjects with Adverse Events[1]	13 (27.7)	6 (13.3)	7 (15.6)
Abdominal Pain Upper	1 (2.1)	0 (0)	0 (0)
Disorientation	1 (2.1)	0 (0)	0 (0)
Feeling Abnormal	1 (2.1)	0 (0)	0 (0)
Headache	2 (4.3)	1 (2.2)	0 (0)
Nausea	1 (2.1)	1 (2.2)	0 (0)
Vertigo	0 (0)	1 (2.2)	0 (0)
Diarrhea	0 (0)	1 (2.2)	1 (2.2)
Rash	0 (0)	1 (2.2)	1 (2.2)
Somnolence	0 (0)	1 (2.2)	0 (0)
Pharyngolaryngeal Pain	0 (0)	0 (0)	1 (2.2)
Neutrophil Count Increased	0 (0)	0 (0)	1 (2.2)
Flushing	0 (0)	0 (0)	1 (2.2)
Contusion	0 (0)	0 (0)	1 (2.2)

Data Source: Table DS6, Table DS8, and Table DS9.

1. Erratum: Data Source Table DS8 incorrectly reported one event occurring during the single-blind placebo treatment session: [redacted] This event was therefore, not considered treatment emergent. [redacted] Likewise, DS9 contains all subjects reporting events during both the double-blind treatment session and the single-blind placebo treatment session. [redacted] These two subjects have been removed from the total count of subjects with adverse events for the placebo treatment group. As shown in this table, the total incidence of treatment emergent adverse events for the placebo treatment group is 13 subjects with 23 adverse events.

8.2.1.4. Adverse Events during the Follow-Up Phase

One event of a positive drug screening for benzodiazepines was reported during the follow-up phase (more than 30 days after dosing). [redacted] This subject did not complete all three treatment regimens.

8.3. Serious Adverse Events and Adverse Events Leading to Withdrawal

There were no deaths, serious non-fatal adverse events or adverse events leading to withdrawal reported during the conduct of this study.

8.3.1. Deaths

There were no deaths reported during the conduct of this study.

8.3.2. Non-Fatal Events

There were no non-fatal serious adverse events reported during the conduct of this study.

8.4. Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study

There were no adverse events leading to withdrawal reported during the conduct of this study.

8.5. Pregnancies

There were no pregnancies reported during the conduct of this study (Table DS32).

8.6. Clinical Laboratory Evaluations

Laboratory data including hematology, biochemistry and urinalysis were evaluated at screening, after treatment (i.e. following participation in all three double-blind treatment PSG sessions) and at the follow-up visit (14 +/- 2 days after the third session or Early Withdrawal). For recording purposes, the abnormality was attributed to the last treatment received. However, the exact relationship between dose and the abnormal lab value cannot be concluded due to the crossover design of the study.

Laboratory data are shown in Table DS17 (reference ranges in Table DS18) and values of potential clinical concern are summarized in Table DS16.

There was no consistent change in any mean laboratory values over the course of the study.

8.6.1. Abnormalities of Potential Clinical Concern

Overall nine subjects in the study had laboratory values that met the sponsor’s criteria for potential clinical concern during the study. All subjects with laboratory values of potential clinical concern after treatment that were not present at baseline are presented by treatment sequence in Table 24.

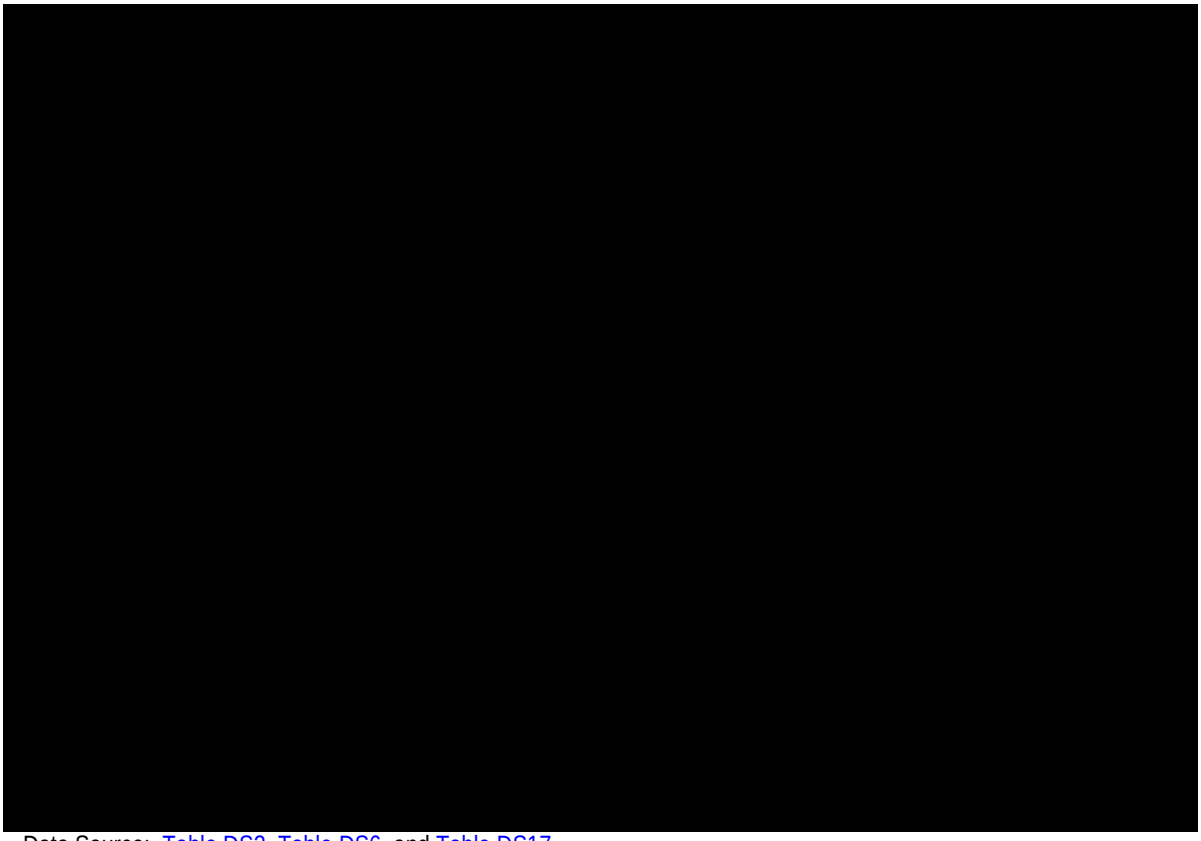
Table 24 Laboratory Values of Potential Clinical Concern

Data Source: Table DS2, Table DS16, and Table DS17

1. Laboratory values flagged as of potential clinical concern.
2. Laboratory values flagged as of potential clinical concern and noted by the investigator as an adverse event.
3. Reported as an adverse event of hypoglycemia.

Table 25 presents laboratory values that were not flagged as being of potential clinical concern, but were listed by the investigator as an adverse event.

Table 25 Laboratory Values not Flagged as of Potential Clinical Concern but Were Recorded by the Investigator as an Adverse Event



Data Source: Table DS2, Table DS6, and Table DS17
1. Laboratory value recorded as an adverse event.
2. [redacted]

8.7. Other Safety Evaluations

8.7.1. Vital Signs

Vital signs were evaluated at every treatment PSG session, pre-dose, one hour post-dose and 10 hours post-dose with GW679769 (30 or 90mg) or placebo. Evaluation of vital signs included sitting blood pressure, heart rate, and respirations.

Subjects with vital signs of potential clinical concern during treatment that were not present at the baseline visit are listed by treatment in Table 26.

Overall, six subjects had vital signs value(s) that met the sponsor's criteria for potential clinical concern (see Section 5.8.6.4.2) during the study. In all cases these values included changes in blood pressure and occurred in four subjects on placebo and one subject on GW679769 30mg and 90mg, respectively.

No significant changes in heart rate or respirations were identified. No value (systolic or diastolic blood pressure) that met the sponsor's pre-defined criteria for potential clinical concern was reported by the investigator as an adverse event.

Vital signs data (blood pressure, pulse, temperature and respiration rate) are shown in Table DS11 (reference ranges in Table DS12) and values of potential clinical concern are summarized in Table DS10.

Table 26 Vital Signs of Potential Clinical Concern

Data Source: Table DS10

1. Baseline is considered blood pressure recorded on the first night of each treatment PSG session prior to dosing

8.7.2. Electrocardiography

Serial 12-lead ECGs were performed at every visit pre-dose, 1 hour after dose, and 10 hours post-dose with GW679769 (30 or 90mg) or placebo.

Table 27 presents a summary of ECG values of potential clinical concern that occurred at any time during the study.

Four subjects had an ECG parameter(s) that met the sponsor's predefined criteria for potential clinical concern during the study (as an F3 flag). No PR interval, QRS, QTc or other ECG interval value was reported as an adverse event.

There was no consistent change in any ECG value over the course of the study.

ECG data are shown in Table DS14 (reference ranges in Table DS15) and values of potential clinical concern are summarized in Table DS13.

Table 27 ECG Values of Potential Clinical Concern

Data Source: Table DS13

8.7.3. Assessment of Morning Residual Effects

As described in Section 5.6.6.8, after each night, subjects were permitted to leave the sleep laboratory once they were able to perform the Romberg and heel-to-toe gait testing at a level of performance to indicate to the clinician that there were no residual effects of study medication. Residual effects that were present to the extent that the subject was unable to leave the sleep laboratory were to be recorded as adverse events. There were no residual motor effects recorded as an adverse event (Table DS46)

Results of daytime cognitive functioning are described in Section 7.3 (Daytime Cognitive Function).

8.7.4. Hepatic Safety Monitoring

Hepatic safety monitoring procedures are described in Section 5.6.6.9 (Hepatic Safety Monitoring). No liver function test (including ALT, AST, ALP, GGT, direct bilirubin or total bilirubin) met the criteria of being greater than or equal to twice the upper limit of the reference range (ULRR). These data are summarized in Table DS16, Table DS17, and Table DS18.

8.7.5. Peptic Ulcer Disease

The assessment of peptic ulcer symptoms and pepsinogen levels is described in Section 5.6.6.10 (Peptic Ulcer Disease). No peptic ulcer symptoms were reported as an adverse event. In addition, no pepsinogen level was reported to be of potential clinical concern. These data are summarized in Table DS16, Table DS17, and Table DS18.

8.8. Safety Conclusion(s)

- Treatment with GW679769 30mg and 90mg was generally well tolerated.
- There were no deaths, non-fatal Serious Adverse Events, or pregnancies during the conduct of this study.
- The most common adverse events were headache and nausea (4-8%). These events were only observed in the placebo and GW679769 30mg treatment group.

- Most events reported were mild in intensity. One event of somnolence was described as severe for the GW679769 30mg treatment group and was reported as resolved.
- No subject withdrew for an adverse event. Five subjects withdrew from the study due to protocol deviations (including non-compliance).
- There were no significant changes or consistent trends in clinical laboratory assessments (hematology, clinical chemistry, and urinalysis), vital signs (heart rate, respiration rate, systolic or diastolic blood pressure) or ECG values of potential clinical concern following any treatment.

9. PHARMACOKINETIC/PHARMACODYAMIC RESULTS

The pharmacokinetic data and the analysis of response relative to drug-blood concentrations are reported separately.

10. DISCUSSION AND CONCLUSIONS

10.1. Discussion

This was a randomized, double-blind, placebo-controlled, cross-over study in subjects with a primary diagnosis of primary insomnia, as defined by DSM-IV criteria (307.42), and symptoms for at least three months prior to the study. Potential subjects participated in a screening period consisting of a clinical screening visit and 2-night PSG recording in the sleep laboratory. Subjects that qualified for the study participated in three separate 2-night PSG sessions in which they were randomized to receive placebo or GW679769 (30mg or 90mg), one hour before bedtime, one treatment for each session in a balanced order. Each session was separated by a minimum of 12 days and occurred on the same day of the week (± 1 day).

This study showed an effect of GW679769 30mg and 90mg doses versus placebo on the main PSG endpoints, WASO, TST, and LPS. WASO, the primary endpoint of the study, was significantly less with both doses of GW679769. In addition, significant effects of both doses (i.e. greater TST and less LPS versus placebo), were demonstrated.

Assessment of sleep architecture showed a greater duration of Stage 2 sleep and greater percentage of time spent in Stage 2 at the expense of Slow Wave Sleep with both doses versus placebo. There was no statistically significant difference in percentage of time or total time spent in Stage 1 Sleep and no reduction in duration of REM sleep.

Statistically significant differences between active treatment and placebo were also observed for the Getting to Sleep domain of the LSEQ scale for both doses, the Quality of Sleep domain of the LSEQ scale at the 30mg dose, subjectively measured TST and WASO at the 30mg dose, and sleep quality at the 90mg dose.

Cognitive tests performed on the morning following treatment showed no residual effect with either dose on attention, psychomotor or verbal memory tasks (DSST and HVLT).

There were no consistent differences in effect on the main PSG or cognitive endpoints between the 30mg and the 90mg dose of GW679769.

Overall, treatment with GW679769 was generally well tolerated. There were no deaths, non-fatal Serious Adverse Events, or pregnancies during the conduct of this study. In addition, no subject withdrew for an adverse event during the conduct of the study. The most common adverse events were headache and nausea. Most adverse events reported were mild in intensity. One event of somnolence was described as severe for the GW679769 30mg treatment group and was reported as resolved. There were no significant changes or consistent trends in clinical laboratory assessments (hematology, clinical chemistry, or urinalysis), vital signs (heart rate, respiration rate, systolic or diastolic blood pressure) or ECG values of potential clinical concern following any treatment.

10.2. Conclusions

In summary, this study showed an effect of both doses of GW679769 over placebo on the main PSG endpoints, WASO, TST, and LPS. In addition, treatment with GW679769 (30mg and 90mg) in subjects with primary insomnia was generally well tolerated.

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STUDY POPULATION DATA SOURCE TABLES

Protocol: GW679769_903
Population: Intention To Treat

Table 6.1
Summary of pre-treatment PSG efficacy measures (ITT)

Parameter	All subjects (N= 48)
WASO (min) - first Screening night	
n	48
Mean	71.96
SD	39.590
Median	59.50
Min	24.0
Max	161.5
WASO (min) - second screening night	
n	48
Mean	66.07
SD	41.007
Median	53.00
Min	18.5
Max	200.0
WASO (min) - mean over the two Screening nights	
n	48
Mean	69.016
SD	35.8818
Median	58.125
Min	27.50
Max	180.50

Table 6.1
Summary of pre-treatment PSG efficacy measures (ITT)

Parameter	All subjects (N= 48)
TST (min) - first Screening night	
n	48
Mean	349.94
SD	46.763
Median	354.25
Min	239.5
Max	431.0
TST (min) - second screening night	
n	48
Mean	363.55
SD	48.220
Median	376.75
Min	231.0
Max	422.0
TST (min) - mean over the two Screening nights	
n	48
Mean	356.745
SD	42.6135
Median	366.625
Min	235.25
Max	422.25

Table 6.1
Summary of pre-treatment PSG efficacy measures (ITT)

Parameter	All subjects (N= 48)
LPS (min) - first Screening night	
n	48
Mean	64.31
SD	27.517
Median	60.25
Min	20.0
Max	149.0
LPS (min) - second screening night	
n	48
Mean	53.81
SD	26.867
Median	43.50
Min	20.5
Max	121.5
LPS (min) - mean over the two Screening nights	
n	48
Mean	59.063
SD	21.0423
Median	55.625
Min	24.50
Max	105.25

Table 6.1
Summary of pre-treatment PSG efficacy measures (ITT)

Parameter	All subjects (N= 48)
WDS (min) - first Screening night	
n	48
Mean	65.23
SD	37.120
Median	54.25
Min	22.5
Max	161.0
WDS (min) - second screening night	
n	48
Mean	55.93
SD	40.143
Median	41.50
Min	10.0
Max	199.5
WDS (min) - mean over the two Screening nights	
n	48
Mean	60.578
SD	33.8241
Median	50.625
Min	21.50
Max	180.25

Table 6.1
Summary of pre-treatment PSG efficacy measures (ITT)

Parameter	All subjects (N= 48)
WAS (min) - first Screening night	
n	48
Mean	6.73
SD	13.914
Median	0.00
Min	0.0
Max	62.0
WAS (min) - second screening night	
n	48
Mean	10.16
SD	21.151
Median	0.00
Min	0.0
Max	93.5
WAS (min) - mean over the two Screening nights	
n	48
Mean	8.443
SD	12.6552
Median	0.875
Min	0.00
Max	46.75

Table 6.1
Summary of pre-treatment PSG efficacy measures (ITT)

Parameter	All subjects (N= 48)
No of 1 min awakenings - first screening night	
n	48
Mean	10.92
SD	4.784
Median	10.50
Min	4.0
Max	24.0
No of 1 min awakenings - second screening night	
n	48
Mean	9.88
SD	4.325
Median	9.00
Min	4.0
Max	24.0
No of 1 min awakenings - mean over the two Screening nights	
n	48
Mean	10.396
SD	3.6173
Median	10.500
Min	4.50
Max	19.00

Table 6.1
Summary of pre-treatment PSG efficacy measures (ITT)

Parameter	All subjects (N= 48)
No of arousals per hour - first screening night	
n	48
Mean	12.26
SD	5.009
Median	11.40
Min	3.0
Max	23.3
No of arousals per hour - second screening night	
n	48
Mean	10.53
SD	5.558
Median	8.86
Min	4.6
Max	27.4
No of arousals per hour - mean over the two Screening nights	
n	48
Mean	11.394
SD	4.7402
Median	10.625
Min	4.65
Max	24.90

Table 6.1
Summary of pre-treatment PSG efficacy measures (ITT)

Parameter	All subjects (N= 48)
No of micro-arousals per hour - first screening night	
n	48
Mean	7.44
SD	5.413
Median	6.39
Min	0.8
Max	21.6
No of micro-arousals per hour - second screening night	
n	48
Mean	6.34
SD	5.681
Median	4.53
Min	0.0
Max	24.6
No of micro-arousals per hour - mean over the two Screening nights	
n	48
Mean	6.893
SD	5.1664
Median	5.956
Min	0.81
Max	23.03

Protocol: GW679769_903
Population: Intention To Treat

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
LSEQ GTS SCORE - first Screening night	
n	48
Mean	48.09
SD	10.478
Median	48.50
Min	19.0
Max	77.7
LSEQ GTS SCORE - second screening night	
n	48
Mean	49.67
SD	9.650
Median	50.00
Min	23.3
Max	75.7
LSEQ GTS SCORE - mean over the two Screening nights	
n	48
Mean	48.882
SD	7.6255
Median	49.500
Min	33.00
Max	67.83

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
LSEQ QOS SCORE - first Screening night	
n	48
Mean	50.48
SD	9.538
Median	50.00
Min	23.0
Max	80.5
LSEQ QOS SCORE - second screening night	
n	48
Mean	49.04
SD	12.202
Median	50.25
Min	13.0
Max	77.0
LSEQ QOS SCORE - mean over the two Screening nights	
n	48
Mean	49.760
SD	7.8603
Median	50.250
Min	32.75
Max	71.00

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
LSEQ AFS SCORE - first Screening night	
n	48
Mean	54.76
SD	10.946
Median	51.50
Min	36.0
Max	87.0
LSEQ AFS SCORE - second screening night	
n	47
Mean	50.41
SD	11.463
Median	49.50
Min	23.5
Max	87.0
LSEQ AFS SCORE - mean over the two Screening nights	
n	48
Mean	52.969
SD	10.2366
Median	50.750
Min	30.25
Max	87.00

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
LSEQ BFW SCORE - first Screening night	
n	48
Mean	49.13
SD	14.692
Median	48.67
Min	24.7
Max	91.7
LSEQ BFW SCORE - second screening night	
n	47
Mean	48.68
SD	13.958
Median	47.67
Min	25.7
Max	78.7
LSEQ BFW SCORE - mean over the two Screening nights	
n	48
Mean	48.972
SD	11.7850
Median	49.667
Min	28.17
Max	81.83

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
STANFORD SCALE - first Screening day	
n	46
Mean	3.0
SD	1.09
Median	3.0
Min	1
Max	6
STANFORD SCALE - second screening day	
n	48
Mean	3.2
SD	1.39
Median	3.0
Min	1
Max	6
STANFORD SCALE - mean over the two Screening days	
n	48
Mean	3.09
SD	1.080
Median	3.00
Min	1.0
Max	6.0

Protocol: GW679769_903
Population: Intention To Treat

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
SOL (sleep onset latency) - first Screening night	
n	48
Mean	77.9
SD	56.14
Median	60.0
Min	30
Max	380
SOL (sleep onset latency) - second screening night	
n	48
Mean	70.2
SD	40.07
Median	60.0
Min	20
Max	210
SOL (sleep onset latency) - mean over the two Screening nights	
n	48
Mean	74.03
SD	37.947
Median	60.00
Min	25.0
Max	202.5

Protocol: GW679769_903
Population: Intention To Treat

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
TST (min) - first Screening night	
n	48
Mean	323.2
SD	55.94
Median	330.0
Min	180
Max	480
TST (min) - second screening night	
n	48
Mean	326.8
SD	56.37
Median	330.0
Min	210
Max	420
TST (min) - mean over the two Screening nights	
n	48
Mean	325.02
SD	52.780
Median	330.00
Min	195.0
Max	450.0

Protocol: GW679769_903
Population: Intention To Treat

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
WASO (min) - first Screening night	
n	47
Mean	91.8
SD	60.59
Median	80.0
Min	15
Max	240
WASO (min) - second screening night	
n	45
Mean	92.8
SD	55.76
Median	90.0
Min	4
Max	240
WASO (min) - mean over the two Screening nights	
n	48
Mean	93.43
SD	55.754
Median	77.50
Min	24.5
Max	240.0

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
No awakenings - first screening night	
n	47
Mean	3.7
SD	1.62
Median	3.0
Min	1
Max	10
No awakenings - second screening night	
n	48
Mean	3.9
SD	1.64
Median	3.3
Min	1
Max	8
No awakenings - mean over the two Screening nights	
n	48
Mean	3.76
SD	1.471
Median	3.50
Min	1.3
Max	8.5

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)
Sleep Quality (numerical score) - first screening night	
n	47
Mean	2.8
SD	0.76
Median	3.0
Min	1
Max	4
Sleep Quality (numerical score) - second screening night	
n	48
Mean	2.7
SD	0.72
Median	3.0
Min	1
Max	4
Sleep Quality (numerical score) - mean over the two Screening nights	
n	48
Mean	2.74
SD	0.495
Median	3.00
Min	1.5
Max	3.5

Protocol: GW679769_903
Population: Intention To Treat

Table 6.2
Summary of results of pre-treatment subjective post sleep questionnaires (ITT)

Parameter	All subjects (N= 48)	
Sleep Quality (categrical score) - first screening night		
n	47	
Very poor	2	(4%)
Poor	12	(26%)
Average	25	(53%)
Good	8	(17%)
Very Good	0	
Sleep Quality (categorical score) - second screening night		
n	48	
Very poor	3	(6%)
Poor	14	(29%)
Average	27	(56%)
Good	4	(8%)
Very Good	0	

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter	All subjects (N= 48)
DSST SCORE following first Screening night	
n	48
Mean	71.6
SD	17.79
Median	72.5
Min	31
Max	114
DSST SCORE following second screening night	
n	48
Mean	77.8
SD	19.44
Median	76.5
Min	25
Max	130
DSST SCORE mean over the two measures	
n	48
Mean	74.71
SD	17.264
Median	74.50
Min	28.0
Max	113.5

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter	All subjects (N= 48)
HVLT-R Total Recall Night 1	
n	48
Mean	26.1
SD	5.20
Median	27.0
Min	15
Max	36
HVLT-R Total Recall Day 1 (following Night 1)	
n	40
Mean	30.1
SD	4.67
Median	30.0
Min	14
Max	36

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter	All subjects (N= 48)
HVLT-R Total Recall Day 2 (following Night 2)	
n	47
Mean	25.0
SD	5.05
Median	25.0
Min	14
Max	36
HVLT-R Total Recall mean over the three measures	
n	48
Mean	26.94
SD	4.100
Median	27.33
Min	15.3
Max	34.3

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter	All subjects (N= 48)
HVLT-R Delayed Recall Night 1	
n	48
Mean	9.0
SD	2.63
Median	10.0
Min	2
Max	12
HVLT-R Delayed Recall Day 1 (following Night 1)	
n	48
Mean	9.9
SD	2.40
Median	10.0
Min	0
Max	12

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter	All subjects (N= 48)
HVLT-R Delayed Recall Day 2 (following Night 2)	
n	45
Mean	8.6
SD	2.74
Median	9.0
Min	1
Max	12
HVLT-R Delayed Recall mean over the three measures	
n	48
Mean	9.15
SD	2.149
Median	9.33
Min	2.7
Max	12.0

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter	All subjects (N= 48)
HVLT-R Retention (%) Night 1	
n	48
Mean	86.408
SD	21.4335
Median	91.000
Min	23.00
Max	125.00
HVLT-R Retention (%) Day 1 (following Night 1)	
n	40
Mean	90.629
SD	18.9466
Median	100.000
Min	0.00
Max	111.00

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter	All subjects (N= 48)
HVLT-R Retention (%) Day 2 (following Night 2)	
n	45
Mean	87.347
SD	23.8307
Median	91.000
Min	13.30
Max	133.00
HVLT-R Retention (%) mean over the three measures	
n	48
Mean	87.9234
SD	15.46282
Median	90.9500
Min	35.713
Max	108.500

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter	All subjects (N= 48)
HVLT-R Recognition Discrimination Index Night 1	
n	45
Mean	10.8
SD	2.65
Median	12.0
Min	0
Max	12
HVLT-R Recognition Discrimination Index Day 1 (following Night 1)	
n	39
Mean	10.6
SD	3.16
Median	12.0
Min	0
Max	12

Protocol: GW679769_903
Population: Intention To Treat

Table 6.3
Summary of pre-treatment cognitive data (ITT)

Parameter		All subjects (N= 48)
HVLT-R Recognition Discrimination Index	Day 2 (following Night 2)	
n		44
Mean		10.5
SD		1.45
Median		11.0
Min		6
Max		12
HVLT-R Recognition Discrimination Index	mean over the three measures	
n		47
Mean		10.60
SD		1.653
Median		11.00
Min		5.3
Max		12.0

EFFICACY DATA SOURCE TABLES

Protocol: GW679769_903
Population: Intention To Treat

Table 7.1
Summary of post treatment WASO PSG data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
WASO (min) - first night			
n	46	45	45
Mean	44.88	29.99	30.50
SD	35.948	26.923	19.758
Median	36.25	22.00	25.00
Min	7.0	4.0	6.0
Max	164.0	149.0	87.0
WASO (min) - second night			
n	47	44	44
Mean	40.21	30.92	37.15
SD	32.835	22.134	29.965
Median	26.00	24.75	26.75
Min	5.5	5.0	6.5
Max	155.5	110.0	118.0
WASO (min) - mean over the two nights			
n	47	45	45
Mean	43.165	30.322	33.778
SD	27.3977	20.4406	22.6399
Median	41.000	25.000	30.750
Min	6.25	4.75	7.50
Max	103.00	96.75	87.50

Table 7.2
Summary of post treatment WASO PSG data (PP)

Parameter	Placebo (N= 41)	GW679769 30 mg (N= 40)	GW679769 90 mg (N= 39)
WASO (min) - first night			
n	40	40	39
Mean	45.55	30.95	30.63
SD	37.680	27.766	20.042
Median	36.50	21.50	25.00
Min	7.0	10.0	6.0
Max	164.0	149.0	87.0
WASO (min) - second night			
n	39	38	38
Mean	38.86	31.16	35.82
SD	33.295	22.608	28.753
Median	25.00	24.75	23.25
Min	5.5	5.0	6.5
Max	155.5	110.0	112.0
WASO (min) - mean over the two nights			
n	40	40	39
Mean	42.000	30.700	33.186
SD	27.2684	20.7318	21.9926
Median	38.125	24.500	28.500
Min	6.25	7.50	7.75
Max	100.00	96.75	81.25

Protocol: GW679769_903
Population: Intention To Treat

Table 7.3
Summary of Results of the Statistical Analysis of post treatment WASO PSG data (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
Mean WASO over the two nights					
GW679769 30 mg - placebo	30.38	42.92	-12.54	(-20.12 to -4.96)	0.001
GW679769 90 mg - placebo	33.56	42.92	-9.36	(-16.96 to -1.75)	0.017
GW679769 90 mg - GW679769 30 mg	33.56	30.38	3.19	(-4.50 to 10.87)	0.413

Protocol: GW679769_903
Population: Per-Protocol

Table 7.4
Summary of Results of the Statistical Analysis of post treatment WASO PSG data (PP)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
Mean WASO over the two nights					
GW679769 30 mg - placebo	30.23	41.12	-10.89	(-18.77 to -3.01)	0.007
GW679769 90 mg - placebo	33.39	41.12	-7.72	(-15.78 to 0.33)	0.060
GW679769 90 mg - GW679769 30 mg	33.39	30.23	3.16	(-4.79 to 11.12)	0.431

Protocol: GW679769_903
Population: Intention To Treat

Table 7.5
Summary of other post treatment PSG efficacy measures (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
TST (min) - first night			
n	46	45	45
Mean	409.97	432.23	432.89
SD	42.688	34.376	25.530
Median	418.00	443.00	441.00
Min	267.0	297.0	379.5
Max	466.5	466.5	468.0
TST (min) - second night			
n	47	44	44
Mean	413.79	438.24	430.52
SD	47.224	24.442	35.641
Median	425.00	441.00	440.75
Min	281.0	349.5	316.5
Max	471.5	471.5	468.0
TST (min) - mean over the two nights			
n	47	45	45
Mean	411.021	435.328	431.811
SD	33.7259	23.8895	28.1862
Median	417.500	440.500	439.750
Min	329.50	361.75	350.25
Max	468.75	469.00	465.00

Protocol: GW679769_903
Population: Intention To Treat

Table 7.5
Summary of other post treatment PSG efficacy measures (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LPS (min) - first night			
n	46	45	45
Mean	28.84	19.49	19.69
SD	18.680	15.240	12.513
Median	26.25	15.00	18.00
Min	0.0	0.0	3.5
Max	74.5	76.5	51.0
LPS (min) - second night			
n	47	44	45
Mean	27.67	14.63	15.51
SD	35.039	11.324	12.036
Median	13.50	13.25	13.00
Min	0.0	0.5	0.0
Max	169.0	47.0	56.0
LPS (min) - mean over the two nights			
n	47	45	45
Mean	28.463	17.089	17.600
SD	21.7884	10.1595	10.6387
Median	25.750	16.500	16.000
Min	3.25	0.25	3.50
Max	98.00	46.25	53.50

Protocol: GW679769_903
Population: Intention To Treat

Table 7.5
Summary of other post treatment PSG efficacy measures (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
WDS (min) - first night			
n	46	45	45
Mean	39.73	27.52	27.64
SD	34.558	25.525	17.093
Median	30.50	20.00	24.00
Min	7.0	4.0	6.0
Max	163.5	148.0	66.0
WDS (min) - second night			
n	47	44	44
Mean	33.70	25.77	32.94
SD	29.378	16.034	26.655
Median	21.00	23.00	23.25
Min	5.5	4.5	0.5
Max	124.5	72.0	105.5
WDS (min) - mean over the two nights			
n	47	45	45
Mean	37.298	26.511	30.200
SD	24.6585	17.4808	19.8876
Median	29.250	22.000	28.250
Min	6.25	4.75	4.50
Max	94.50	94.25	81.25

Table 7.5
Summary of other post treatment PSG efficacy measures (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
WAS (min) - first night			
n	46	45	45
Mean	5.15	2.47	2.86
SD	13.997	6.190	7.426
Median	0.00	0.00	0.00
Min	0.0	0.0	0.0
Max	69.5	32.5	45.5
WAS (min) - second night			
n	47	44	44
Mean	6.51	5.15	4.20
SD	12.869	15.148	9.113
Median	0.00	0.00	0.00
Min	0.0	0.0	0.0
Max	52.5	76.5	39.0
WAS (min) - mean over the two nights			
n	47	45	45
Mean	5.867	3.811	3.578
SD	10.9527	8.1436	7.3401
Median	0.750	0.500	0.250
Min	0.00	0.00	0.00
Max	61.00	38.25	39.75

Table 7.5
Summary of other post treatment PSG efficacy measures (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
No of 1 min awakenings - first night			
n	46	45	45
Mean	8.57	6.29	7.22
SD	4.564	4.159	3.982
Median	8.00	5.00	7.00
Min	2.0	0.0	1.0
Max	23.0	19.0	21.0
No of 1 min awakenings - second night			
n	47	44	44
Mean	7.06	6.25	6.89
SD	3.824	3.883	4.571
Median	6.00	6.00	6.00
Min	1.0	0.0	0.0
Max	15.0	18.0	23.0
No of 1 min awakenings - mean over the two nights			
n	47	45	45
Mean	7.809	6.256	7.056
SD	3.3615	3.6628	3.6106
Median	7.500	5.500	7.000
Min	2.00	0.00	1.50
Max	16.00	15.50	18.00

Protocol: GW679769_903
Population: Intention To Treat

Table 7.5
Summary of other post treatment PSG efficacy measures (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
No of arousals per hour - first night			
n	46	45	45
Mean	10.84	9.61	8.47
SD	5.196	3.563	3.846
Median	9.84	9.24	7.06
Min	3.7	4.1	2.8
Max	35.2	22.5	20.1
No of arousals per hour - second night			
n	47	44	44
Mean	10.63	9.16	8.99
SD	4.435	4.948	3.461
Median	10.05	8.14	8.46
Min	3.2	2.1	3.4
Max	22.3	24.1	17.8
No of arousals per hour - mean over the two nights			
n	47	45	45
Mean	10.774	9.405	8.780
SD	4.2324	3.8851	3.3004
Median	9.895	8.520	7.331
Min	3.45	4.10	3.80
Max	25.76	22.42	17.11

Table 7.5
Summary of other post treatment PSG efficacy measures (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
No of micro-arousals per hour - first night			
n	46	45	45
Mean	5.70	6.39	4.96
SD	5.313	5.968	4.288
Median	4.19	5.29	4.00
Min	0.0	0.1	0.1
Max	20.6	24.7	19.7
No of micro-arousals per hour - second night			
n	47	44	44
Mean	5.22	4.45	5.28
SD	4.512	3.449	4.405
Median	4.36	3.99	3.93
Min	0.3	0.1	0.0
Max	17.9	12.8	19.5
No of micro-arousals per hour - mean over the two nights			
n	47	45	45
Mean	5.473	5.498	5.102
SD	4.2251	4.0858	3.7561
Median	4.637	4.760	5.040
Min	0.24	0.72	0.22
Max	15.83	15.26	17.23

Protocol: GW679769_903
Population: Intention To Treat

Table 7.6
Summary of Results of the Statistical Analysis of other post treatment PSG efficacy measures (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
Mean TST (min) over the two nights					
GW679769 30 mg - placebo	435.27	411.28	24.00	(14.66 to 33.34)	<0.001
GW679769 90 mg - placebo	431.76	411.28	20.49	(11.11 to 29.87)	<0.001
GW679769 90 mg - GW679769 30 mg	431.76	435.27	-3.51	(-12.99 to 5.97)	0.464
Mean LPS (min) over the two nights					
GW679769 30 mg - placebo	17.17	28.50	-11.33	(-16.70 to -5.96)	<0.001
GW679769 90 mg - placebo	17.83	28.50	-10.67	(-16.05 to -5.28)	<0.001
GW679769 90 mg - GW679769 30 mg	17.83	17.17	0.67	(-4.78 to 6.11)	0.809

Table 7.6
Summary of Results of the Statistical Analysis of other post treatment PSG efficacy measures (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
Mean WDS (min) over the two nights					
GW679769 30 mg - placebo	26.52	37.04	-10.52	(-17.67 to -3.38)	0.004
GW679769 90 mg - placebo	30.04	37.04	-7.00	(-14.17 to 0.17)	0.055
GW679769 90 mg - GW679769 30 mg	30.04	26.52	3.52	(-3.72 to 10.77)	0.336
Mean WAS (min) over the two nights					
GW679769 30 mg - placebo	3.83	5.92	-2.09	(-5.71 to 1.52)	0.253
GW679769 90 mg - placebo	3.64	5.92	-2.28	(-5.90 to 1.34)	0.213
GW679769 90 mg - GW679769 30 mg	3.64	3.83	-0.19	(-3.85 to 3.47)	0.919

Protocol: GW679769_903
Population: Intention To Treat

Table 7.6
Summary of Results of the Statistical Analysis of other post treatment PSG efficacy measures (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
Mean number of 1 min awakenings over the two nights					
GW679769 30 mg - placebo	6.34	7.83	-1.49	(-2.51 to -0.46)	0.005
GW679769 90 mg - placebo	7.08	7.83	-0.75	(-1.78 to 0.28)	0.152
GW679769 90 mg - GW679769 30 mg	7.08	6.34	0.74	(-0.30 to 1.78)	0.161
Mean number of arousals per hour over the two nights					
GW679769 30 mg - placebo	9.44	10.82	-1.38	(-2.36 to -0.41)	0.006
GW679769 90 mg - placebo	8.96	10.82	-1.86	(-2.83 to -0.88)	<0.001
GW679769 90 mg - GW679769 30 mg	8.96	9.44	-0.47	(-1.46 to 0.52)	0.345

Protocol: GW679769_903
Population: Intention To Treat

Table 7.6
Summary of Results of the Statistical Analysis of other post treatment PSG efficacy measures (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
Mean number of micro-arousals per hour over the two nights					
GW679769 30 mg - placebo	5.65	5.52	0.13	(-0.86 to 1.12)	0.795
GW679769 90 mg - placebo	5.29	5.52	-0.22	(-1.22 to 0.77)	0.658
GW679769 90 mg - GW679769 30 mg	5.29	5.65	-0.35	(-1.35 to 0.65)	0.488

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
Stage 1 (min) - first night			
n	46	45	45
Mean	27.12	24.73	24.86
SD	21.814	15.713	16.136
Median	21.50	23.00	21.50
Min	3.5	3.0	3.0
Max	130.5	81.0	88.5
Stage 1 (min) - second night			
n	47	44	44
Mean	21.55	24.61	24.75
SD	11.962	15.301	17.395
Median	21.50	21.00	21.75
Min	5.5	2.5	3.0
Max	52.0	61.5	86.0
Stage 1 (min) - mean over the two nights			
n	47	45	45
Mean	24.170	24.528	24.889
SD	15.2335	14.2125	15.3707
Median	20.750	21.250	26.750
Min	5.50	4.75	3.75
Max	82.00	70.25	87.25

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
Stage 2 (min) - first night			
n	46	45	45
Mean	211.92	257.61	272.60
SD	38.134	37.196	38.651
Median	213.25	263.00	265.00
Min	123.0	190.0	210.5
Max	307.5	345.0	355.0
Stage 2 (min) - second night			
n	47	44	44
Mean	211.68	249.55	255.58
SD	46.074	40.506	39.197
Median	211.00	255.75	259.50
Min	115.0	135.5	187.5
Max	309.0	346.5	333.0
Stage 2 (min) - mean over the two nights			
n	47	45	45
Mean	211.282	253.767	264.194
SD	35.8892	33.9256	36.5180
Median	206.250	260.750	265.000
Min	133.75	166.00	199.00
Max	286.25	319.25	344.00

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
SWS (min) - first night			
n	46	45	45
Mean	85.09	51.69	40.79
SD	29.347	26.824	24.183
Median	88.00	50.00	42.00
Min	13.5	1.0	0.0
Max	143.0	111.0	97.0
SWS (min) - second night			
n	47	44	44
Mean	86.07	60.66	51.85
SD	39.558	29.211	25.440
Median	87.00	60.75	50.00
Min	8.5	0.0	10.5
Max	228.0	160.0	99.5
SWS (min) - mean over the two nights			
n	47	45	45
Mean	85.314	56.089	46.428
SD	27.6572	24.4622	22.9248
Median	82.500	54.000	42.250
Min	22.50	0.50	5.75
Max	163.50	114.75	94.75

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
REM (min) - first night			
n	46	45	45
Mean	85.84	98.20	94.64
SD	30.101	33.366	22.821
Median	86.00	97.50	91.50
Min	0.0	41.5	64.0
Max	147.0	222.5	165.5
REM (min) - second night			
n	47	44	44
Mean	94.48	103.42	98.34
SD	30.410	30.025	26.781
Median	94.00	104.00	102.25
Min	31.0	52.5	20.0
Max	207.5	236.5	167.5
REM (min) - mean over the two nights			
n	47	45	45
Mean	90.255	100.944	96.300
SD	26.2803	29.1542	22.3883
Median	83.750	97.750	97.250
Min	44.25	57.00	46.50
Max	177.25	229.50	166.50

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
Latency to REM (min) - first night			
n	46	45	45
Mean	124.42	104.09	105.16
SD	72.340	58.098	41.470
Median	106.50	86.00	89.00
Min	55.5	46.5	54.0
Max	485.0	328.5	218.0
Latecncy to REM (min) - second night			
n	47	44	44
Mean	98.73	98.17	88.55
SD	37.112	35.822	35.424
Median	87.00	86.00	82.75
Min	35.0	41.5	11.5
Max	233.5	183.0	215.0
Latency to REM (min) - mean over the two nights			
n	47	45	45
Mean	111.309	100.556	96.911
SD	41.8208	41.0934	30.0017
Median	99.000	91.500	87.250
Min	59.75	46.50	55.75
Max	286.25	255.75	172.00

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
Stage 1 (%) - first night			
n	46	45	45
Mean	7.07	5.83	5.79
SD	7.375	3.906	3.833
Median	5.30	5.38	4.94
Min	0.8	0.6	0.7
Max	48.9	19.4	20.9
Stage 1 (%) - second night			
n	47	44	44
Mean	5.42	7.40	5.95
SD	3.306	12.240	4.672
Median	5.12	4.81	5.10
Min	1.3	0.6	0.6
Max	15.2	83.2	24.6
Stage 1 (%) - mean over the two nights			
n	47	45	45
Mean	6.204	6.565	5.884
SD	4.5893	6.6983	3.9262
Median	4.972	4.912	6.117
Min	1.20	1.02	0.82
Max	28.16	44.42	22.73

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
Stage 2 (%) - first night			
n	46	45	45
Mean	51.81	59.62	62.85
SD	8.211	7.134	7.026
Median	52.27	59.65	61.96
Min	28.8	42.1	48.1
Max	71.2	77.3	77.0
Stage 2 (%) - second night			
n	47	44	44
Mean	51.20	56.99	59.23
SD	9.336	8.760	6.438
Median	51.34	58.82	58.45
Min	28.9	28.7	44.8
Max	68.3	76.2	73.5
Stage 2 (%) - mean over the two nights			
n	47	45	45
Mean	51.481	58.331	61.051
SD	7.6319	7.1778	6.2419
Median	51.394	59.687	60.227
Min	34.98	35.43	46.46
Max	64.92	72.73	75.26

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
SWS (%) - first night			
n	46	45	45
Mean	20.53	12.00	9.52
SD	6.513	6.204	5.702
Median	21.47	11.35	9.62
Min	5.1	0.2	0.0
Max	33.6	25.2	23.5
SWS (%) - second night			
n	47	44	44
Mean	20.67	13.82	12.10
SD	8.460	6.503	5.945
Median	20.49	14.19	12.73
Min	1.8	0.0	2.6
Max	48.7	34.4	23.3
SWS (%) - mean over the two nights			
n	47	45	45
Mean	20.574	12.887	10.830
SD	6.1250	5.5957	5.4116
Median	20.375	12.377	9.662
Min	5.65	0.11	1.38
Max	36.62	25.43	23.37

Table 7.7
Summary of post treatment PSG measures of sleep structure (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
REM (%) - first night			
n	46	45	45
Mean	20.59	22.55	21.84
SD	6.521	7.002	4.961
Median	19.35	21.53	21.90
Min	0.0	11.5	14.7
Max	34.1	47.7	36.5
REM (%) - second night			
n	47	44	44
Mean	22.72	23.50	22.72
SD	6.841	6.264	5.799
Median	22.76	23.37	22.59
Min	11.0	12.3	5.7
Max	52.2	50.2	38.9
REM (%) - mean over the two nights			
n	47	45	45
Mean	21.743	23.050	22.235
SD	5.8825	6.1130	4.8281
Median	21.043	21.988	21.900
Min	12.35	14.13	11.48
Max	43.17	48.93	37.70

Protocol: GW679769_903
Population: Intention To Treat

Table 7.8
Summary of Results of the Statistical Analysis of post treatment PSG measures of sleep structure (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
Stage 1 (min) - mean over the two nights					
GW679769 30 mg - placebo	24.50	24.38	0.12	(-3.07 to 3.32)	0.940
GW679769 90 mg - placebo	24.77	24.38	0.39	(-2.83 to 3.61)	0.809
GW679769 90 mg - GW679769 30 mg	24.77	24.50	0.27	(-2.98 to 3.52)	0.868
Stage 2 (min) - mean over the two nights					
GW679769 30 mg - placebo	253.61	211.58	42.02	(33.28 to 50.77)	<0.001
GW679769 90 mg - placebo	264.87	211.58	53.29	(44.49 to 62.09)	<0.001
GW679769 90 mg - GW679769 30 mg	264.87	253.61	11.27	(2.38 to 20.15)	0.014
SWS (min) - mean over the two nights					
GW679769 30 mg - placebo	56.39	85.13	-28.74	(-34.37 to-23.11)	<0.001
GW679769 90 mg - placebo	45.90	85.13	-39.23	(-44.90 to-33.56)	<0.001
GW679769 90 mg - GW679769 30 mg	45.90	56.39	-10.49	(-16.21 to -4.77)	<0.001

Table 7.8
Summary of Results of the Statistical Analysis of post treatment PSG measures of sleep structure (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
REM (min) - mean over the two nights					
GW679769 30 mg - placebo	100.86	90.32	10.54	(4.01 to 17.06)	0.002
GW679769 90 mg - placebo	96.33	90.32	6.01	(-0.55 to 12.57)	0.072
GW679769 90 mg - GW679769 30 mg	96.33	100.86	-4.52	(-11.15 to 2.10)	0.178
Latency to REM (min) - mean over the two nights					
GW679769 30 mg - placebo	100.85	111.34	-10.49	(-22.45 to 1.48)	0.085
GW679769 90 mg - placebo	96.79	111.34	-14.55	(-26.57 to -2.53)	0.018
GW679769 90 mg - GW679769 30 mg	96.79	100.85	-4.06	(-16.20 to 8.08)	0.508
Stage 1 (%) - mean over the two nights					
GW679769 30 mg - placebo	6.54	6.20	0.34	(-1.26 to 1.93)	0.676
GW679769 90 mg - placebo	5.84	6.20	-0.36	(-1.96 to 1.24)	0.654
GW679769 90 mg - GW679769 30 mg	5.84	6.54	-0.70	(-2.32 to 0.92)	0.393

Protocol: GW679769_903
Population: Intention To Treat

Table 7.8
Summary of Results of the Statistical Analysis of post treatment PSG measures of sleep structure (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
Stage 2 (%) - mean over the two nights					
GW679769 30 mg - placebo	58.29	51.49	6.79	(5.04 to 8.55)	<0.001
GW679769 90 mg - placebo	61.19	51.49	9.70	(7.93 to 11.46)	<0.001
GW679769 90 mg - GW679769 30 mg	61.19	58.29	2.90	(1.12 to 4.69)	0.002
SWS (%) - mean over the two nights					
GW679769 30 mg - placebo	12.96	20.53	-7.56	(-8.84 to -6.28)	<0.001
GW679769 90 mg - placebo	10.72	20.53	-9.80	(-11.09 to -8.52)	<0.001
GW679769 90 mg - GW679769 30 mg	10.72	12.96	-2.24	(-3.54 to -0.94)	<0.001
REM (%) - mean over the two nights					
GW679769 30 mg - placebo	23.03	21.74	1.29	(0.01 to 2.58)	0.048
GW679769 90 mg - placebo	22.22	21.74	0.47	(-0.82 to 1.77)	0.467
GW679769 90 mg - GW679769 30 mg	22.22	23.03	-0.82	(-2.12 to 0.48)	0.215

Protocol: GW679769_903
Population: Intention To Treat

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LSEQ GTS SCORE - first night			
n	46	44	44
Mean	55.43	59.95	63.22
SD	18.565	16.260	16.339
Median	58.17	58.33	60.50
Min	3.3	30.7	23.3
Max	92.7	96.0	96.3
LSEQ GTS SCORE - second night			
n	46	44	45
Mean	58.91	65.24	61.14
SD	17.710	16.163	16.921
Median	57.83	63.17	58.00
Min	14.0	33.3	25.3
Max	94.0	95.3	98.3
LSEQ GTS SCORE - mean over the two nights			
n	47	45	45
Mean	57.053	62.881	62.026
SD	13.7199	14.0890	13.1612
Median	56.667	58.333	59.167
Min	24.50	40.67	41.17
Max	92.50	93.00	96.17

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LSEQ QOS SCORE - first night			
n	47	45	44
Mean	53.70	59.73	60.19
SD	20.018	18.632	18.472
Median	54.50	53.50	57.50
Min	2.0	18.0	6.0
Max	95.5	96.0	95.5
LSEQ QOS SCORE - second night			
n	46	44	45
Mean	59.47	65.85	62.01
SD	19.892	16.988	19.534
Median	57.50	66.50	62.00
Min	8.0	33.5	16.5
Max	95.5	97.5	99.5
LSEQ QOS SCORE - mean over the two nights			
n	47	45	45
Mean	56.697	62.822	61.372
SD	16.2636	15.1680	16.7004
Median	58.250	60.750	59.250
Min	21.50	40.75	23.50
Max	95.50	96.00	97.50

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LSEQ AFS SCORE - first night			
n	47	45	44
Mean	52.49	54.24	56.36
SD	15.170	17.502	20.644
Median	51.50	51.00	54.25
Min	2.0	19.5	2.5
Max	95.0	93.5	95.0
LSEQ AFS SCORE - second night			
n	47	44	44
Mean	57.44	58.27	58.47
SD	15.916	17.702	19.031
Median	54.00	53.50	54.25
Min	16.5	17.0	10.5
Max	95.0	93.0	94.5
LSEQ AFS SCORE - mean over the two nights			
n	47	45	45
Mean	54.963	56.250	57.161
SD	13.7634	15.1601	17.8933
Median	52.500	52.750	55.000
Min	9.25	25.00	6.50
Max	95.00	92.75	94.75

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LSEQ BFW SCORE - first night			
n	47	45	44
Mean	51.65	49.91	53.27
SD	15.735	16.563	19.064
Median	51.33	49.00	51.00
Min	4.0	19.7	1.3
Max	88.3	92.0	90.3
LSEQ BFW SCORE - second night			
n	47	44	44
Mean	52.18	57.47	55.14
SD	15.126	15.976	17.694
Median	51.67	55.67	53.67
Min	21.0	29.0	14.3
Max	87.0	90.7	93.0
LSEQ BFW SCORE - mean over the two nights			
n	47	45	45
Mean	51.918	53.589	54.141
SD	11.8059	13.6923	16.8391
Median	50.667	51.333	53.833
Min	25.67	25.17	7.83
Max	87.67	90.00	91.67

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LSEQ GTS SCORE change vs placebo - first night			
n		43	42
Mean		5.83	7.20
SD		24.386	21.011
Median		5.67	3.00
Min		-30.0	-32.0
Max		87.3	62.3
LSEQ GTS SCORE change vs placebo - second night			
n		43	43
Mean		6.12	2.06
SD		17.999	20.975
Median		5.33	5.00
Min		-32.7	-52.7
Max		52.3	60.0
LSEQ GTS SCORE change vs placebo - mean over the two nights			
n		45	44
Mean		6.044	4.655
SD		16.8815	13.6952
Median		4.333	4.917
Min		-23.50	-24.00
Max		58.17	61.17

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LSEQ QOS SCORE change vs placebo - first night			
n		45	43
Mean		6.28	4.62
SD		28.504	22.523
Median		0.00	0.00
Min		-61.5	-44.5
Max		91.5	64.5
LSEQ QOS SCORE change vs placebo - second night			
n		43	43
Mean		6.47	0.98
SD		20.908	22.389
Median		2.00	4.00
Min		-28.5	-64.5
Max		73.5	60.5
LSEQ QOS SCORE change vs placebo - mean over the two nights			
n		45	44
Mean		6.194	3.244
SD		20.2945	17.3932
Median		1.750	1.250
Min		-39.25	-39.00
Max		56.50	43.25

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LSEQ AFS SCORE change vs placebo - first night			
n		45	43
Mean		1.48	2.30
SD		19.366	18.496
Median		1.00	1.00
Min		-49.5	-45.5
Max		51.5	50.5
LSEQ AFS SCORE change vs placebo - second night			
n		44	43
Mean		0.31	-0.12
SD		15.749	14.139
Median		-1.00	2.50
Min		-37.5	-31.0
Max		40.5	35.5
LSEQ AFS SCORE change vs placebo - mean over the two nights			
n		45	44
Mean		1.011	1.188
SD		13.8920	11.6912
Median		0.750	1.750
Min		-29.75	-23.50
Max		38.75	38.75

Protocol: GW679769_903
Population: Intention To Treat

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
LSEQ BFW SCORE change vs placebo - first night			
n		45	43
Mean		-1.70	1.08
SD		18.191	19.549
Median		-1.67	0.33
Min		-41.0	-55.0
Max		57.3	46.3
LSEQ BFW SCORE change vs placebo - second night			
n		44	43
Mean		5.16	1.53
SD		17.446	14.186
Median		3.83	1.00
Min		-47.7	-26.0
Max		47.7	30.0
LSEQ BFW SCORE change vs placebo - mean over the two nights			
n		45	44
Mean		1.515	1.402
SD		11.4380	13.3647
Median		-1.167	1.917
Min		-20.33	-32.33
Max		32.83	36.67

Protocol: GW679769_903
Population: Intention To Treat

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
STANFORD SCALE - first day			
n	47	45	44
Mean	3.0	3.0	2.9
SD	1.07	1.08	1.11
Median	3.0	3.0	3.0
Min	1	1	1
Max	7	6	6
STANFORD SCALE - second day			
n	47	44	45
Mean	2.6	2.7	2.7
SD	0.87	0.77	0.85
Median	3.0	3.0	3.0
Min	1	1	1
Max	6	5	6
STANFORD SCALE - mean over the two days			
n	47	45	45
Mean	2.81	2.83	2.78
SD	0.811	0.707	0.883
Median	3.00	3.00	3.00
Min	1.5	1.5	1.0
Max	6.0	4.5	6.0

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
SOL (sleep onset latency) - first night			
n	47	45	44
Mean	42.8	36.8	41.8
SD	32.20	23.16	46.00
Median	30.0	30.0	30.0
Min	0	5	0
Max	150	120	300
SOL (sleep onset latency) - second night			
n	45	44	45
Mean	45.0	36.8	43.1
SD	44.78	47.74	54.34
Median	30.0	30.0	30.0
Min	10	5	5
Max	240	330	370
SOL (sleep onset latency) - mean over the two nights			
n	47	45	45
Mean	43.35	36.72	42.20
SD	30.651	29.919	36.928
Median	37.50	30.00	30.00
Min	7.5	7.5	5.0
Max	165.0	202.5	190.0

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
TST (min) - first night			
n	47	45	44
Mean	356.6	374.4	375.5
SD	83.06	70.11	83.38
Median	360.0	390.0	390.0
Min	0	60	0
Max	480	460	480
TST (min) - second night			
n	44	44	45
Mean	370.8	395.9	386.9
SD	71.01	38.01	68.85
Median	385.0	397.5	410.0
Min	60	300	105
Max	460	460	480
TST (min) - mean over the two nights			
n	47	45	45
Mean	364.95	384.89	381.69
SD	60.173	46.181	59.973
Median	375.00	390.00	390.00
Min	165.0	210.0	217.5
Max	460.0	455.0	465.0

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
WASO (min) - first night			
n	46	44	42
Mean	72.0	57.2	71.3
SD	54.72	44.99	75.74
Median	55.0	45.0	60.0
Min	5	10	5
Max	240	180	480
WASO (min) - second night			
n	44	42	44
Mean	65.1	50.2	55.6
SD	47.48	31.04	43.38
Median	55.0	45.0	47.5
Min	5	5	3
Max	190	150	180
WASO (min) - mean over the two nights			
n	47	45	45
Mean	68.62	52.39	62.84
SD	45.420	34.476	49.377
Median	60.00	45.00	60.00
Min	10.0	10.0	4.0
Max	180.0	165.0	265.0

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
No awakenings - first night			
n	47	43	42
Mean	3.5	3.3	3.8
SD	2.29	2.24	3.12
Median	3.0	3.0	3.0
Min	1	1	1
Max	15	12	15
No awakenings - second night			
n	44	41	43
Mean	3.2	3.2	3.0
SD	2.03	2.12	1.89
Median	3.0	3.0	3.0
Min	1	1	1
Max	10	10	10
No awakenings - mean over the two nights			
n	47	44	45
Mean	3.32	3.19	3.31
SD	1.764	1.969	2.172
Median	3.00	2.50	3.00
Min	1.0	1.0	1.0
Max	9.0	10.0	12.5

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
Sleep Quality (numerical score) - first night			
n	47	45	45
Mean	3.1	3.3	3.5
SD	0.90	0.87	0.97
Median	3.0	3.0	4.0
Min	1	2	2
Max	5	5	5
Sleep Quality (numerical score) - second night			
n	46	44	45
Mean	3.2	3.4	3.4
SD	0.97	0.97	0.94
Median	3.0	3.0	4.0
Min	1	1	1
Max	5	5	5
Sleep Quality (numerical score) - mean over the two nights			
n	47	45	45
Mean	3.15	3.33	3.47
SD	0.744	0.754	0.710
Median	3.00	3.50	3.50
Min	1.5	1.5	2.0
Max	4.5	5.0	5.0

Table 7.9
Summary of Results of post treatment subjective post sleep questionnaires (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
Sleep Quality (categrical score) - first night			
n	47	45	45
Very poor	2 (4%)	0	0
Poor	8 (17%)	9 (20%)	8 (18%)
Average	21 (45%)	16 (36%)	12 (27%)
Good	14 (30%)	17 (38%)	18 (40%)
Very Good	2 (4%)	3 (7%)	7 (16%)
Sleep Quality (categorical score) - second night			
n	46	44	45
Very poor	3 (7%)	1 (2%)	1 (2%)
Poor	7 (15%)	7 (16%)	7 (16%)
Average	18 (39%)	15 (34%)	14 (31%)
Good	16 (35%)	16 (36%)	19 (42%)
Very Good	2 (4%)	5 (11%)	4 (9%)

Protocol: GW679769_903
Population: Intention To Treat

Table 7.10
Summary of Results of the Statistical Analysis of post treatment post sleep questionnaires (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
LSEQ GTS SCORE - mean over the two nights					
GW679769 30 mg - placebo	63.20	57.27	5.93	(1.65 to 10.21)	0.007
GW679769 90 mg - placebo	61.94	57.27	4.67	(0.37 to 8.97)	0.034
GW679769 90 mg - GW679769 30 mg	61.94	63.20	-1.26	(-5.60 to 3.09)	0.567
LSEQ QOS SCORE - mean over the two nights					
GW679769 30 mg - placebo	63.01	56.87	6.14	(0.86 to 11.42)	0.023
GW679769 90 mg - placebo	61.04	56.87	4.17	(-1.14 to 9.48)	0.122
GW679769 90 mg - GW679769 30 mg	61.04	63.01	-1.97	(-7.33 to 3.39)	0.467

Table 7.10
Summary of Results of the Statistical Analysis of post treatment post sleep questionnaires (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
LSEQ AFS SCORE - mean over the two nights					
GW679769 30 mg - placebo	56.44	55.31	1.13	(-2.85 to 5.11)	0.574
GW679769 90 mg - placebo	57.21	55.31	1.90	(-2.10 to 5.90)	0.348
GW679769 90 mg - GW679769 30 mg	57.21	56.44	0.77	(-3.27 to 4.81)	0.705
LSEQ BFW SCORE - mean over the two nights					
GW679769 30 mg - placebo	53.93	52.40	1.53	(-2.06 to 5.12)	0.400
GW679769 90 mg - placebo	54.10	52.40	1.70	(-1.91 to 5.32)	0.352
GW679769 90 mg - GW679769 30 mg	54.10	53.93	0.18	(-3.47 to 3.82)	0.924

Table 7.10
Summary of Results of the Statistical Analysis of post treatment post sleep questionnaires (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
STANFORD SCALE - mean over the two days					
GW679769 30 mg - placebo	2.81	2.80	0.01	(-0.20 to 0.23)	0.906
GW679769 90 mg - placebo	2.79	2.80	-0.01	(-0.23 to 0.21)	0.937
GW679769 90 mg - GW679769 30 mg	2.79	2.81	-0.02	(-0.24 to 0.20)	0.846
SOL (sleep onset latency) - mean over the two nights					
GW679769 30 mg - placebo	36.89	43.45	-6.56	(-17.03 to 3.91)	0.217
GW679769 90 mg - placebo	42.76	43.45	-0.69	(-11.20 to 9.83)	0.897
GW679769 90 mg - GW679769 30 mg	42.76	36.89	5.87	(-4.76 to 16.50)	0.275

Protocol: GW679769_903
Population: Intention To Treat

Table 7.10
Summary of Results of the Statistical Analysis of post treatment post sleep questionnaires (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
TST (min) - mean over the two nights					
GW679769 30 mg - placebo	386.57	366.63	19.93	(4.05 to 35.82)	0.015
GW679769 90 mg - placebo	380.58	366.63	13.95	(-2.03 to 29.92)	0.086
GW679769 90 mg - GW679769 30 mg	380.58	386.57	-5.99	(-22.12 to 10.15)	0.463
WASO (min) - mean over the two nights					
GW679769 30 mg - placebo	52.46	68.71	-16.25	(-31.39 to -1.11)	0.036
GW679769 90 mg - placebo	62.97	68.71	-5.74	(-20.92 to 9.45)	0.455
GW679769 90 mg - GW679769 30 mg	62.97	52.46	10.51	(-4.84 to 25.86)	0.177

Table 7.10
Summary of Results of the Statistical Analysis of post treatment post sleep questionnaires (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
No awakenings - mean over the two nights					
GW679769 30 mg - placebo	3.28	3.30	-0.02	(-0.58 to 0.53)	0.935
GW679769 90 mg - placebo	3.29	3.30	-0.02	(-0.57 to 0.54)	0.951
GW679769 90 mg - GW679769 30 mg	3.29	3.28	0.01	(-0.56 to 0.57)	0.983
Sleep Quality (numerical score) - mean over the two nights					
GW679769 30 mg - placebo	3.34	3.16	0.17	(-0.09 to 0.43)	0.192
GW679769 90 mg - placebo	3.47	3.16	0.31	(0.05 to 0.57)	0.021
GW679769 90 mg - GW679769 30 mg	3.47	3.34	0.14	(-0.13 to 0.40)	0.305

Protocol: GW679769_903
Population: Intention To Treat

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
DSST SCORE following first night			
n	47	45	45
Mean	74.6	76.9	74.3
SD	19.27	18.20	18.36
Median	74.0	80.0	73.0
Min	21	40	23
Max	120	124	108
DSST SCORE following second night			
n	47	44	45
Mean	81.9	75.2	77.2
SD	19.75	21.17	20.59
Median	81.0	73.0	76.0
Min	28	23	26
Max	125	115	131
DSST SCORE mean over the two measures			
n	47	45	45
Mean	78.29	76.26	75.77
SD	18.507	18.468	18.119
Median	78.50	78.00	73.50
Min	24.5	33.0	24.5
Max	113.5	119.5	112.0

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
HVLT-R Total Recall Night 1			
n	47	45	45
Mean	27.3	27.3	27.0
SD	4.87	5.20	4.33
Median	27.0	27.0	27.0
Min	16	16	18
Max	36	35	35
HVLT-R Total Recall Day 1 (following Night 1)			
n	38	38	38
Mean	31.4	31.4	30.6
SD	4.38	5.02	5.33
Median	32.5	33.0	32.5
Min	22	19	14
Max	36	36	36

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
HVLT-R Total Recall Day 2 (following Night 2)			
n	47	44	45
Mean	26.1	26.5	26.1
SD	5.08	5.19	5.89
Median	26.0	27.0	27.0
Min	15	15	12
Max	36	36	36
HVLT-R Total Recall mean over the three measures			
n	47	45	45
Mean	28.07	28.35	27.79
SD	3.938	4.361	4.301
Median	28.00	29.33	28.33
Min	20.3	17.3	15.0
Max	35.7	35.0	35.0

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
HVLT-R Delayed Recall Night 1			
n	47	45	45
Mean	9.8	9.7	9.6
SD	2.12	2.15	2.02
Median	10.0	10.0	10.0
Min	3	2	4
Max	12	12	12
HVLT-R Delayed Recall Day 1 (following Night 1)			
n	46	45	44
Mean	10.1	10.5	9.9
SD	2.07	1.90	2.33
Median	10.5	11.0	10.0
Min	3	5	4
Max	12	12	12

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
HVLT-R Delayed Recall Day 2 (following Night 2)			
n	47	44	45
Mean	8.2	8.9	9.1
SD	2.72	2.73	2.75
Median	9.0	9.5	10.0
Min	3	3	2
Max	12	12	12
HVLT-R Delayed Recall mean over the three measures			
n	47	45	45
Mean	9.39	9.69	9.52
SD	1.974	1.997	2.059
Median	9.67	10.00	10.00
Min	3.0	3.3	3.3
Max	12.0	12.0	12.0

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
HVLT-R Retention (%) Night 1			
n	47	45	45
Mean	92.576	95.012	92.873
SD	17.9900	15.7666	13.3985
Median	100.000	100.000	100.000
Min	20.00	55.00	50.00
Max	120.00	138.00	114.29
HVLT-R Retention (%) Day 1 (following Night 1)			
n	37	38	37
Mean	91.330	96.383	90.221
SD	15.2831	9.4232	15.2032
Median	100.000	100.000	92.000
Min	30.00	62.00	45.00
Max	113.00	116.70	111.10

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
HVLT-R Retention (%) Day 2 (following Night 2)			
n	47	44	45
Mean	81.133	88.206	91.420
SD	21.4995	21.3383	22.5448
Median	88.900	100.000	100.000
Min	20.00	42.90	28.00
Max	109.00	138.00	137.50
HVLT-R Retention (%) mean over the three measures			
n	47	45	45
Mean	87.9757	92.7305	91.1953
SD	14.55474	10.99007	12.92410
Median	93.3333	94.6667	94.7633
Min	38.667	53.333	42.667
Max	105.000	112.667	111.500

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
HVLT-R Recognition Discrimination Index Night 1			
n	46	44	45
Mean	10.9	11.2	11.0
SD	1.41	1.16	1.23
Median	11.0	11.5	11.0
Min	7	7	6
Max	12	12	12
HVLT-R Recognition Discrimination Index Day 1 (following Night 1)			
n	37	37	38
Mean	10.9	11.1	11.4
SD	2.20	1.99	1.22
Median	12.0	12.0	12.0
Min	0	2	6
Max	12	12	12

Table 7.11
Summary of post treatment cognitive data (ITT)

Parameter	Placebo (N= 47)	GW679769 30 mg (N= 45)	GW679769 90 mg (N= 45)
HVLT-R Recognition Discrimination Index Day 2 (following Night 2)			
n	46	43	44
Mean	10.7	10.6	10.8
SD	1.71	1.48	2.02
Median	11.0	11.0	11.0
Min	4	6	0
Max	12	12	12
HVLT-R Recognition Discrimination Index mean over the three measures			
n	46	45	45
Mean	10.86	10.94	11.03
SD	1.206	1.073	1.149
Median	11.33	11.00	11.33
Min	6.7	7.3	7.0
Max	12.0	12.0	12.0

Protocol: GW679769_903
Population: Intention To Treat

Table 7.12
Summary of Results of the Statistical Analysis of post treatment cognitive data (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
DSST SCORE - mean over the two measures following night 1 and 2					
GW679769 30 mg - placebo	75.98	77.88	-1.90	(-4.91 to 1.10)	0.211
GW679769 90 mg - placebo	76.77	77.88	-1.11	(-4.14 to 1.92)	0.468
GW679769 90 mg - GW679769 30 mg	76.77	75.98	0.79	(-2.26 to 3.85)	0.608

Table 7.12
Summary of Results of the Statistical Analysis of post treatment cognitive data (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
HVLT-R Total Recall Night 1					
GW679769 30 mg - placebo	27.45	27.19	0.26	(-1.10 to 1.62)	0.708
GW679769 90 mg - placebo	27.00	27.19	-0.18	(-1.55 to 1.18)	0.791
GW679769 90 mg - GW679769 30 mg	27.00	27.45	-0.44	(-1.82 to 0.94)	0.527
HVLT-R Total Recall Day 1 (following Night 1)					
GW679769 30 mg - placebo	31.71	31.71	-0.00	(-1.50 to 1.49)	0.997
GW679769 90 mg - placebo	30.85	31.71	-0.86	(-2.36 to 0.64)	0.259
GW679769 90 mg - GW679769 30 mg	30.85	31.71	-0.86	(-2.36 to 0.64)	0.260
HVLT-R Total Recall Day 2 (following Night 2)					
GW679769 30 mg - placebo	26.66	26.04	0.63	(-0.75 to 2.00)	0.371
GW679769 90 mg - placebo	26.03	26.04	-0.01	(-1.38 to 1.35)	0.985
GW679769 90 mg - GW679769 30 mg	26.03	26.66	-0.64	(-2.02 to 0.75)	0.365

Table 7.12
Summary of Results of the Statistical Analysis of post treatment cognitive data (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
HVLT-R Delayed Recall Night 1					
GW679769 30 mg - placebo	9.73	9.78	-0.05	(-0.66 to 0.55)	0.858
GW679769 90 mg - placebo	9.56	9.78	-0.22	(-0.82 to 0.39)	0.478
GW679769 90 mg - GW679769 30 mg	9.56	9.73	-0.16	(-0.77 to 0.45)	0.599
HVLT-R Delayed Recall Day 1 (following Night 1)					
GW679769 30 mg - placebo	10.51	10.12	0.38	(-0.22 to 0.99)	0.212
GW679769 90 mg - placebo	9.88	10.12	-0.24	(-0.85 to 0.37)	0.445
GW679769 90 mg - GW679769 30 mg	9.88	10.51	-0.62	(-1.24 to -0.01)	0.047
HVLT-R Delayed Recall Day 2 (following Night 2)					
GW679769 30 mg - placebo	8.91	8.21	0.70	(0.10 to 1.31)	0.023
GW679769 90 mg - placebo	9.08	8.21	0.87	(0.26 to 1.47)	0.005
GW679769 90 mg - GW679769 30 mg	9.08	8.91	0.16	(-0.45 to 0.78)	0.598

Table 7.12
Summary of Results of the Statistical Analysis of post treatment cognitive data (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
HVLT-R Retention (%) Night 1					
GW679769 30 mg - placebo	95.31	92.68	2.63	(-3.36 to 8.61)	0.389
GW679769 90 mg - placebo	92.92	92.68	0.24	(-5.76 to 6.24)	0.937
GW679769 90 mg - GW679769 30 mg	92.92	95.31	-2.38	(-8.45 to 3.68)	0.440
HVLT-R Retention (%) Day 1 (following Night 1)					
GW679769 30 mg - placebo	95.93	90.92	5.02	(-1.61 to 11.64)	0.137
GW679769 90 mg - placebo	89.58	90.92	-1.34	(-8.03 to 5.35)	0.694
GW679769 90 mg - GW679769 30 mg	89.58	95.93	-6.36	(-12.99 to 0.28)	0.060
HVLT-R Retention (%) Day 2 (following Night 2)					
GW679769 30 mg - placebo	88.50	81.24	7.26	(1.23 to 13.29)	0.018
GW679769 90 mg - placebo	91.47	81.24	10.23	(4.23 to 16.23)	<0.001
GW679769 90 mg - GW679769 30 mg	91.47	88.50	2.97	(-3.12 to 9.06)	0.338

Table 7.12
Summary of Results of the Statistical Analysis of post treatment cognitive data (ITT)

Treatment comparison	LSmean Test Treatment	LSmean Ref. Treatment	Diff.	95% CI	p-value
HVLT-R Recognition Discrimination Index Night 1					
GW679769 30 mg - placebo	11.16	10.90	0.26	(-0.33 to 0.84)	0.383
GW679769 90 mg - placebo	10.98	10.90	0.08	(-0.50 to 0.66)	0.789
GW679769 90 mg - GW679769 30 mg	10.98	11.16	-0.18	(-0.77 to 0.41)	0.547
HVLT-R Recognition Discrimination Index Day 1 (following Night 1)					
GW679769 30 mg - placebo	11.05	10.92	0.13	(-0.51 to 0.77)	0.689
GW679769 90 mg - placebo	11.33	10.92	0.40	(-0.24 to 1.04)	0.218
GW679769 90 mg - GW679769 30 mg	11.33	11.05	0.27	(-0.37 to 0.91)	0.407
HVLT-R Recognition Discrimination Index Day 2 (following Night 2)					
GW679769 30 mg - placebo	10.57	10.66	-0.08	(-0.67 to 0.51)	0.781
GW679769 90 mg - placebo	10.72	10.66	0.06	(-0.53 to 0.65)	0.839
GW679769 90 mg - GW679769 30 mg	10.72	10.57	0.14	(-0.45 to 0.74)	0.634

SAFETY DATA SOURCE TABLES

Table DS1

DEMOGRAPHY DETAILS OF STUDY GW679769/903

Sub no	Sex	Age (Yrs)	Height (cm)	Weight (kg)	Body Mass Index	Race

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Female 77%, Male 23%
White/Caucasian 56%, Black 40%, American Hispanic 2%,
East & South East Asian 2%

* = Withdrawn after dosing
a = Protocol deviation (including non-compliance)
. = No data available

Table DS2

DOSING DETAILS OF STUDY GW679769/903

Sub No	Dosing Date	Dosing Time	Actual dose

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

Table DS3

WITHDRAWAL DATA OF STUDY GW679769/903

Sub no	Date and time of withdrawal	Date and time of last study medication	Regimen	Coded withdrawal reason [Verbatim]

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. = No data available

[WTHDR007:LIS] [28SEP2005:10:10]

Table DS4

OTHER MEDICATION DATA OF STUDY GW679769/903 - Prior Medications

Sub No	Drug Name	Dose	Freq-uency	Route	Duration	Indication	Date Medication Stopped	Date and Time of First Dose of Study Drug

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Route : PO = Oral, TD = Transdermal, TO = Topical
Frequency : BID = Twice a day, OD = Every day, SD = Single dose, TID = Three times a day,
. = No data available

[OMED008:LIS] [28SEP2005:10:11]

Table DS5
SIGNS AND SYMPTOMS / ADVERSE EVENTS KEY OF STUDY GW679769/903

Field	Column Heading	Decode
Action	Action	DDL=Dose delayed DDR=Dose delayed & reduced DIR=Dose interrupted/restarted DOI=Dose increased DOR=Dose reduced DST=Drug stopped NON=None
Course	Course	CNT=Constant INT=Intermittent UNK=Unknown nnn=nnn episodes
Outcome	Outcome	D=Died O=Ongoing R=Resolved T=Corrective Therapy given UNK=Unknown W=Withdrawn
Outcome	Serious	1=Fatal 2=Life threatening 3=Disabling/incapacitating 4=Results in hospitalisation 5=Prolongs a hospital stay 6=Associated with an abnormality 7=Associated with cancer 8=Associated with overdose 9=Other A=Results in death B=Life threatening C=Requires hospitalisation or prolongation of existing hospitalisation D=Results in disability/incapacity E=Congenital anomaly/birth defect F=Other
Relation	Rel	PRO=Probable SUS=Suspected (reasonable possibility) UNL=Unlikely UNR=Not related
Severity	Sev	MIL=Mild MOD=Moderate SEV=Severe

Table DS6

SIGNS AND SYMPTOMS OF STUDY GW679769/903 - BASELINE

Sub no	Preferred Term [Verbatim]	Start date and time	Duration	Time from Onset to Dose	Sev	Course	Outcome

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

[ADEXL021:LIS] [05OCT2005:16:41]

Table DS7

TREATMENT EMERGENT ADVERSE EVENTS OF STUDY GW679769/903

Regimen=Placebo
Total Subject Sessions=95

Subject Sessions where Signs and Symptoms were reported		Intensity			
		MILD		MODERATE	
		N	%	N	%
System Organ Class	Preferred Term				
Gastrointestinal disorders	Abdominal pain upper	1	1.1	.	.
	Nausea	3	3.2	.	.
General disorders and administration site conditions	Feeling abnormal	1	1.1	.	.
Infections and infestations	Herpes simplex	.	.	1	1.1
	Vaginitis bacterial	.	.	1	1.1
Investigations	Blood bilirubin increased	1	1.1	.	.
	Blood cholesterol increased	1	1.1	.	.
	Blood triglycerides increased	1	1.1	.	.
	Drug screen positive	1	1.1	1	1.1
	Lymphocyte count increased	1	1.1	.	.
	Neutrophil count decreased	1	1.1	.	.
Metabolism and nutrition disorders	Hypoglycaemia	.	.	1	1.1
Musculoskeletal and connective tissue disorders	Back pain	.	.	1	1.1
Nervous system disorders	Dizziness	1	1.1	.	.
	Headache	2	2.1	2	2.1

(CONTINUED)

Table DS7

TREATMENT EMERGENT ADVERSE EVENTS OF STUDY GW679769/903

Regimen=Placebo
Total Subject Sessions=95

Subject Sessions where Signs and Symptoms were reported		Intensity			
		MILD		MODERATE	
		N	%	N	%
System Organ Class	Preferred Term				
Psychiatric disorders	Disorientation	1	1.1	.	.
Skin and subcutaneous tissue disorders	Eczema	1	1.1	.	.
	Rash macular	1	1.1	.	.

Table DS7

TREATMENT EMERGENT ADVERSE EVENTS OF STUDY GW679769/903

Regimen=GW679769 30 mg
Total Subject Sessions=45

Subject Sessions where Signs and Symptoms were reported		Intensity			
		MILD		SEVERE	
		N	%	N	%
System Organ Class	Preferred Term				
Ear and labyrinth disorders	Vertigo	1	2.2	.	.
Gastrointestinal disorders	Diarrhoea	1	2.2	.	.
	Nausea	2	4.4	.	.
General disorders and administration site conditions	Chills	1	2.2	.	.
	Feeling hot and cold	1	2.2	.	.
Immune system disorders	Allergy to arthropod sting	1	2.2	.	.
Nervous system disorders	Headache	3	6.7	.	.
	Somnolence	.	.	1	2.2
Skin and subcutaneous tissue disorders	Rash	1	2.2	.	.

Table DS7

TREATMENT EMERGENT ADVERSE EVENTS OF STUDY GW679769/903

Regimen=GW679769 90 mg
Total Subject Sessions=45

Subject Sessions where Signs and Symptoms were reported		Intensity			
		MILD		MODERATE	
		N	%	N	%
System Organ Class	Preferred Term				
Gastrointestinal disorders	Diarrhoea	.	.	1	2.2
	Toothache	.	.	1	2.2
General disorders and administration site conditions	Influenza like illness	.	.	1	2.2
Infections and infestations	Sinusitis	.	.	1	2.2
Injury, poisoning and procedural complications	Contusion	1	2.2	.	.
Investigations	Blood glucose decreased	1	2.2	.	.
	Neutrophil count decreased	2	4.4	.	.
	Neutrophil count increased	.	.	1	2.2
	Neutrophil percentage decreased	1	2.2	.	.
	White blood cell count decreased	1	2.2	.	.
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	.	.	1	2.2
	Throat irritation	.	.	1	2.2
Skin and subcutaneous tissue disorders	Rash	.	.	1	2.2
Vascular disorders	Flushing	1	2.2	.	.

Table DS8

TREATMENT EMERGENT ADVERSE EVENTS OF STUDY GW679769/903

Number of Subject Sessions where Adverse Event reported

Adverse Event	Regimen A	Regimen B	Regimen C
Headache	4	3	0
Nausea	3	2	0
Drug screen positive	2	0	0
Abdominal pain upper	1	0	0
Back pain	1	0	0
Blood bilirubin increased	1	0	0
Blood cholesterol increased	1	0	0
Blood triglycerides increased	1	0	0
Disorientation	1	0	0
Dizziness	1	0	0
Eczema	1	0	0
Feeling abnormal	1	0	0
Herpes simplex	1	0	0
Hypoglycaemia	1	0	0
Lymphocyte count increased	1	0	0
Neutrophil count decreased	1	0	2
Rash macular	1	0	0
Vaginitis bacterial	1	0	0
Allergy to arthropod sting	0	1	0
Chills	0	1	0
Diarrhoea	0	1	1
Feeling hot and cold	0	1	0
Rash	0	1	1
Somnolence	0	1	0
Vertigo	0	1	0
Blood glucose decreased	0	0	1
Contusion	0	0	1
Flushing	0	0	1
Influenza like illness	0	0	1
Neutrophil count increased	0	0	1
Neutrophil percentage decreased	0	0	1
Pharyngolaryngeal pain	0	0	1
Sinusitis	0	0	1

Regimen : A = Placebo
B = GW679769 30 mg
C = GW679769 90 mg
. = No data available

[ADEXS023:FRQ]

[05OCT2005:16:46]

Table DS8

TREATMENT EMERGENT ADVERSE EVENTS OF STUDY GW679769/903

Number of Subject Sessions where Adverse Event reported

Adverse Event	Regimen A	Regimen B	Regimen C
Throat irritation	0	0	1
Toothache	0	0	1
White blood cell count decreased	0	0	1
Number of Subjects with AEs	13	6	7
Number of Subjects Exposed	48	45	45

Regimen : A = Placebo
B = GW679769 30 mg
C = GW679769 90 mg
. = No data available

[ADEXS023:FRQ]

[05OCT2005:16:46]

Table DS9

ADVERSE EVENT TOTALS OF STUDY GW679769/903

	Regimen - Placebo	
Relationship	AEs	Subjects With AEs
Not related	11	8
Unlikely	8	5
Suspected (reasonable possibility)	6	2
Probable	0	0
Total	25	14

. = No data available

Table DS9

ADVERSE EVENT TOTALS OF STUDY GW679769/903

Regimen - GW679769 30 mg

Relationship	AEs	Subjects With AEs
Not related	2	2
Unlikely	4	2
Suspected (reasonable possibility)	6	2
Probable	2	1
Total	14	6

. = No data available

Table DS9

ADVERSE EVENT TOTALS OF STUDY GW679769/903

Regimen - GW679769 90 mg

Relationship	AEs	Subjects With AEs
Not related	4	2
Unlikely	5	4
Suspected (reasonable possibility)	5	3
Probable	1	1
Total	15	7

. = No data available

Table DS10

VITAL SIGNS VALUES OF POTENTIAL CLINICAL CONCERN OF STUDY GW679769/903

Placebo

Sub no	Relative time	Vital Signs parameter	Baseline value	Flagged value	Reason for flagging

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. = No data available

[VITFS013:LIS] [28SEP2005:10:21]

Table DS11

VITAL SIGNS DATA OF STUDY GW679769/903

Sitting
Placebo

Sub no	Sess no	SCR2PRE	SCR2+1H	SCR2+10H	SCR3PRE	SC3+1H	SC3+10H

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Flagging performed for Sitting Systolic BP, Diastolic BP, Pulse, Temperature
Key : L = Below Potential Clinical Concern threshold
H = Above Potential Clinical Concern threshold
. = No data available

Table DS12

VITAL SIGNS FLAGGING RANGES OF STUDY GW679769/903

Parameter	Position	Flagging reason
Diastolic BP	Sitting	>20mmHg decrease or >20mmHg increase from baseline
Pulse	Sitting	<35bpm or >120bpm
Systolic BP	Sitting	>30mmHg decrease or >30mmHg increase from baseline

. = No data available

Table DS13

ECG VALUES OF POTENTIAL CLINICAL CONCERN OF STUDY GW679769/903

Placebo

Sub no	Sess no	Relative time	ECG parameter	Baseline	Flagged value	Reason for flagging

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

[ECGFS016:LIS]

[28SEP2005:10:33]

Table DS14

ECG DATA OF STUDY GW679769/903

HR (bpm)
Placebo

Sub no	Sess no	SCR2PRE	SCR2+1H	SCR2+10H	SCR3PRE	SCR3PRE-	SC3+1H

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Key : H = Above Potential Clinical Concern range
. = No data available

Table DS15

ECG FLAGGING RANGES OF STUDY GW679769/903

Parameter	Flag	Flagging reason	Sex
PR interval	F3	> 219msec	
QRS interval	F3	> 119msec	
QTc interval	F3	> 470msec	Male
	F3	> 470msec	Female
	F3	> 480msec	Female

. = No data available

[ECGT018:REF] [28SEP2005:10:36]

Table DS16

LABORATORY VALUES OF POTENTIAL CLINICAL CONCERN OF STUDY GW679769/903

Placebo

Subject number	Relative time	Parameter type	Parameter	Value	Clinical Concern Threshold

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Key : H=High, L=Low
A=Above Potential Clinical Concern Threshold
B=Below Potential Clinical Concern Threshold
. = No data available

[LABFS019:LIS] [28SEP2005:10:38]

Table DS17

LABORATORY DATA OF STUDY GW679769/903

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Regimen C : GW679769 90 mg

Key : H=High, L=Low
A=Above Potential Clinical Concern Threshold
B=Below Potential Clinical Concern Threshold
. = No data available

Table DS18

LABORATORY DATA RANGES OF STUDY GW679769/903

Lab : Quest Diagnostics, 7600 Tyrone Avenue, Van Nuys, CA 91405 USA

Parameter	Description	Sex	F1 Age range	Reference Range and Units		Clinical Concern Thresholds and Units	
Hematology							
Hgb	Hemoglobin	Female	18-64 years	12.0-15.6	g/dL	10.5-16.1	g/dL
		Male	18-64 years	13.8-17.2	g/dL	12-18	g/dL
Hct%	Hematocrit (PCV)	Female	18-64 years	35.0-46.0	%	31-51	%
		Male	18-64 years	41.0-50.0	%	36-54	%
WBC	White cells	Female	18-99 years	3.8-10.8	10^9/L	2.8-13.8	10^9/L
		Male	18-99 years	3.8-10.8	10^9/L	2.8-13.8	10^9/L
RBC	Red cells	Female	18-64 years	3.9-5.2	10^12/L		
		Male	18-64 years	4.4-5.8	10^12/L		
MCV	Mean cell volume	Female	18-64 years	80-100	fL		
		Male	18-64 years	80-100	fL		
MCHC	Mean cell hemoglobin concentration	Female	18-99 years	32.0-36.0	%		
		Male	18-99 years	32.0-36.0	%		
Platelets	Platelets	Female	18-99 years	130000-400000	10^6/L	80000-500000	10^6/L
		Male	18-99 years	130000-400000	10^6/L	80000-500000	10^6/L
Neut	Neutrophils	Female	18-99 years	1.8-8	10^9/L		
		Male	18-99 years	1.8-8	10^9/L		
Neut%	Neutrophils %	Female	18-99 years	40.0-75.0	%		
		Male	18-99 years	40.0-75.0	%		

Subjects to whom this table is applicable:

[redacted]

. = No data available

[LABT020:REF] [28SEP2005:10:38]

Table DS18

LABORATORY DATA RANGES OF STUDY GW679769/903

Lab : Quest Diagnostics, 7600 Tyrone Avenue, Van Nuys, CA 91405 USA

Parameter	Description	Sex	F1 Age range	Reference Range and Units		Clinical Concern Thresholds and Units
Hematology (continued)						
Eosin	Eosinophils	Female	18-99 years	0.05-0.55	10^9/L	
		Male	18-99 years	0.05-0.55	10^9/L	
Eosin%	Eosinophils %	Female	18-99 years	0.0-7.0	%	
		Male	18-99 years	0.0-7.0	%	
Bas	Basophils	Female	18-99 years	0-0.2	10^9/L	
		Male	18-99 years	0-0.2	10^9/L	
Bas%	Basophils %	Female	18-99 years	0.0-2.0	%	
		Male	18-99 years	0.0-2.0	%	
Mon	Monocytes	Female	18-99 years	0.2-1.1	10^9/L	
		Male	18-99 years	0.2-1.1	10^9/L	
Mon%	Monocytes %	Female	18-99 years	0.0-12	%	
		Male	18-99 years	0.0-12	%	
Lym	Lymphocytes	Female	18-99 years	0.85-4.1	10^9/L	
		Male	18-99 years	0.85-4.1	10^9/L	
Lym%	Lymphocytes %	Female	18-99 years	16.0-46.0	%	
		Male	18-99 years	16.0-46.0	%	
Pepsino I	BC_PEPI	Female	18-99 years	40-140	ug/L	
		Male	18-99 years	40-140	ug/L	
Pepsino II	BC_PEPII	Female	18-99 years	0-22	ng/mL	
		Male	18-99 years	0-22	ng/mL	

Subjects to whom this table is applicable:

[redacted]

. = No data available

[LABT020:REF]

[28SEP2005:10:38]

Table DS18

LABORATORY DATA RANGES OF STUDY GW679769/903

Lab : Quest Diagnostics, 7600 Tyrone Avenue, Van Nuys, CA 91405 USA

Parameter	Description	Sex	F1 Age range	Reference Range and Units		Clinical Concern Thresholds and Units	
Biochemistry							
Na	Sodium	Female	18-99 years	135-146	mEq/L	130-151	mEq/L
		Male	18-99 years	135-146	mEq/L	130-151	mEq/L
K	Potassium	Female	18-99 years	3.5-5.3	mEq/L	3-5.8	mEq/L
		Male	18-99 years	3.5-5.3	mEq/L	3-5.8	mEq/L
Cl	Chloride	Female	18-99 years	95-108	mEq/L		
		Male	18-99 years	95-108	mEq/L		
Total CO2	Total carbon dioxide	Female	13-99 years	20-32	mEq/L		
		Male	13-99 years	20-32	mEq/L		
Ca total	Total calcium	Female	18-99 years	8.5-10.3	mg/dL	7.2-12	mg/dL
		Male	18-99 years	8.5-10.3	mg/dL	7.2-12	mg/dL
Phos	Inorganic phosphate	Female	18-64 years	2.5-4.5	mg/dL	1.7-5.5	mg/dL
		Male	18-64 years	2.5-4.5	mg/dL	1.7-5.5	mg/dL
Mg	Magnesium	Female	18-99 years	1.2-2.0	mEq/L		
		Male	18-99 years	1.2-2.0	mEq/L		
BUN	Blood urea nitrogen	Female	18-64 years	7-25	mg/dL	0-37.5	mg/dL
		Male	18-64 years	7-25	mg/dL	0-37.5	mg/dL
Creatinine	Creatinine	Female	18-99 years	0.5-1.4	mg/dL	0-1.8	mg/dL
		Male	18-99 years	0.5-1.4	mg/dL	0-1.8	mg/dL

Subjects to whom this table is applicable:

[redacted]

. = No data available

[LABT020:REF] [28SEP2005:10:38]

Table DS18

LABORATORY DATA RANGES OF STUDY GW679769/903

Lab : Quest Diagnostics, 7600 Tyrone Avenue, Van Nuys, CA 91405 USA

Parameter	Description	Sex	F1 Age range	Reference Range and Units		Clinical Concern Thresholds and Units	
Biochemistry (continued)							
Glucose	Glucose	Female	18-49 years	70-115	mg/dL	59-124	mg/dL
		Female	50-99 years	70-125	mg/dL	59-124	mg/dL
		Male	18-49 years	70-115	mg/dL	59-124	mg/dL
Uric acid	Uric acid	Female	18-99 years	2.5-7.5	mg/dL	0-10.9	mg/dL
		Male	18-99 years	4.0-8.5	mg/dL	0-10.9	mg/dL
GGT	Gamma glutamyltransferase	Female	18-64 years	0-45	IU/L	0-90	IU/L
		Male	18-64 years	0-65	IU/L	0-130	IU/L
AST	Aspartate aminotransferase (SGOT)	Female	18-64 years	0-42	IU/L	0-84	IU/L
		Male	18-64 years	0-42	IU/L	0-84	IU/L
ALT	Alanine aminotransferase (SGPT)	Female	18-99 years	0-48	IU/L	0-96	IU/L
		Male	18-99 years	0-48	IU/L	0-96	IU/L
AP	Alkaline phosphatase	Female	18-99 years	20-125	IU/L	0-187.5	IU/L
		Male	18-99 years	20-125	IU/L	0-187.5	IU/L
BiliT	Total bilirubin	Female	18-99 years	0.0-1.3	mg/dL	0-1.95	mg/dL
		Male	18-99 years	0.0-1.3	mg/dL	0-1.95	mg/dL
BiliD	Direct bilirubin	Female	18-99 years	0.0-0.4	mg/dL		
		Male	18-99 years	0.0-0.4	mg/dL		

Subjects to whom this table is applicable: [redacted]

. = No data available

Table DS18

LABORATORY DATA RANGES OF STUDY GW679769/903

Lab : Quest Diagnostics, 7600 Tyrone Avenue, Van Nuys, CA 91405 USA

Parameter	Description	Sex	F1 Age range	Reference Range and Units		Clinical Concern Thresholds and Units	
Biochemistry (continued)							
BiliInD	Indirect bilirubin	Female	18-99 years	0.0-1.3	mg/dL		
		Male	18-99 years	0.0-1.3	mg/dL		
Protein	Total proteins	Female	18-64 years	6.0-8.5	g/dL	5-9.5	g/dL
		Male	18-64 years	6.0-8.5	g/dL	5-9.5	g/dL
Albumin	Albumin	Female	18-99 years	3.2-5.0	g/dL	2.7-5.5	g/dL
		Male	18-99 years	3.2-5.0	g/dL	2.7-5.5	g/dL
Chol	Cholesterol	Female	18-99 years	0-199	mg/dL		
		Male	18-99 years	0-199	mg/dL		
Trig	Triglycerides	Female	18-99 years	0-199	mg/dL		
		Male	18-99 years	0-199	mg/dL		
TSH	Thyroid stimulating hormone	Female	18-99 years	0.4-5.5	uIU/mL		
		Male	18-99 years	0.4-5.5	uIU/mL		

Subjects to whom this table is applicable: [redacted]

. = No data available

Table DS18

LABORATORY DATA RANGES OF STUDY GW679769/903

Lab : Quest Diagnostics, 7600 Tyrone Avenue, Van Nuys, CA 91405 USA

Parameter	Description	Sex	F1 Age range	Reference Range and Units	Clinical Concern Thresholds and Units
Urinalysis					
SG	Specific gravity	Female	18-99 years	1.001-1.035	
		Male	18-99 years	1.001-1.035	
pH	pH	Female	18-99 years	4.6-8.0	
		Male	18-99 years	4.6-8.0	
Protein	Protein	Female	18-99 years	-	
		Male	18-99 years	-	
Glucose	Glucose	Female	18-99 years	-	
		Male	18-99 years	-	
Bilirubin	Urine bilirubin	Female	18-99 years	-	
		Male	18-99 years	-	
Ketones	Ketone	Female	18-99 years	-	
		Male	18-99 years	-	
Blood	Blood	Female	18-99 years	-	
		Male	18-99 years	-	
NO2	Nitrite	Female	18-99 years	-	
		Male	18-99 years	-	
RBC micros	Red blood cells - microscopy	Female	18-99 years	0-3	
		Male	18-99 years	0-3	

Subjects to whom this table is applicable:

[redacted]

. = No data available

Table DS18

LABORATORY DATA RANGES OF STUDY GW679769/903

Lab : Quest Diagnostics, 7600 Tyrone Avenue, Van Nuys, CA 91405 USA

Parameter	Description	Sex	F1 Age range	Reference Range and Units	Clinical Concern Thresholds and Units
Urinalysis (continued)					
WBC micros	White blood cells - microscopy	Female	18-99 years	0-10	
		Male	18-99 years	0-5	

Subjects to whom this table is applicable: [redacted]

. = No data available

[LABT020:REF] [28SEP2005:10:38]

Table DS31

PHARMACOKINETIC CONCENTRATION DATA OF STUDY GW679769/903

1
Sample type= Plasma
Placebo
Compound Analysed: GSK525060

Subject Number	Session	Date of Sample	Relative day	Actual clock time	Planned relative time (hrs to 2dp)	Time deviation	Actual time (hrs to 2 dp)	Concentration (ng/mL)

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

NA = Not analysed
NQ = Non quantifiable
NR = Non reportable
NS = No sample received
. = No data available

Table DS32

PREGNANCY FINDINGS AT FOLLOW-UP OF STUDY GW679769/903

Subject	Sex	Did the Subject become pregnant during the study	Did the female partner of a male subject become pregnant during the study

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. = No data available

[PREG025:LIS] [05OCT2005:16:54]

DS37

Pre-sleep questionnaire of study GW679769/903

Sub No	Date	Consumed alcohol last 24hrs (Y/N)?	If yes, When?	How much?	Time of evening meal	Consumed any caffeinated beverages today(Y/N)?	If yes what time?	Taken any naps today (Y/N)?	If yes how many?	How long? (min)	How do you feel during the day?	Describe ability to function during day?	Done any strenuous exercise this afternoon (Y/N)?

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. = No data available

DS38
Post-sleep questionnaire of study GW679769/903

Sub No	Date	How long do you think it look to fall asleep last night?	How long do you think you slept last night?	Did you wake up during the night(Y/N)?	If yes, how many times?	If yes, what is the total time you were awake?	How would you describe the quality of your sleep?
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.							

. = No data available

DS40
Leeds sleep evaluation questionnaire of study GW679769/903

Sub No	Date and time	VAS1	VAS2	VAS3	VAS4	VAS5	VAS6	VAS7	VAS8	VAS9	VAS10

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

KEY: How would you compare getting to sleep using the medication with getting to sleep normally?
VAS1- Harder/easier VAS2 - Slower/quicker VAS3 - Less/more drowsy
How would you compare the quality of sleep using the medication with non-medicated sleep?
VAS4- More restless/more restful VAS5 - More/fewer periods of wakefulness
How did your awakening after medication compare with your usual pattern of awakening?
VAS6- More difficult/easier VAS7 - Took longer/took shorter
How did you feel on waking? VAS8- Tired/alert How do you feel now? VAS9 - Tired/alert
How was your sense of balance and coordination on getting up? VAS10- More clumsy/less clumsy

DS41
Digit symbol substitution test (DSST) of study GW679769/903

Sub No	Date and time	DSST Score

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

DS42
Stanford sleepiness scale (SSS) of study GW679769/903

Sub No	Date and time	Scale rating

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

KEY: 1 = Feeling active, vital, alert or wide awake
2 = Functioning at high levels, but not at peak; able to concentrate
3 = Awake, but relaxed; responsive but not fully alert
4 = Somewhat foggy, let down
5 = Foggy; losing interesting remaining awake; slowed down
6 = Sleepy, woozy, fighting sleep; prefer to lie down
7 = No longer fighting sleep, sleep onset soon having dream-like thoughts
X = Asleep

DS43
PSG data of study GW679769/903

Sub No	Visit	Date and time	WASO (min)	TST (min)	LPS (min)	WDS (min)	WAS (min)	NWK (min)	AROUSAL

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

* PSG data obtained despite the occurrence of technical problems
. = No data available

DS44
Memory HVLT-R of study GW679769/903

Sub No	Visit	Date	Time	Form	Total recall	Delayed recall	Retention(%)	Recognition discrimination index

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

DS46
Romberg test, Heel-to-toe test of study GW679769/903

Sub No	Visit	Date	Time	Was the Romberg test successfully completed (Y/N)?

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

DS47
Psychiatric history of study GW679769/903

Sub No	Date	Duration of current episode? (weeks)

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

PAGE

DS48
Psychiatric history - update of study GW679769/903

Sub No	Visit	Date	Duration of current episode? (weeks)

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

PAGE

DS49
Sleep history of study GW679769/903

Sub No	Visit	Have you experienced previous sleeping problems (Y/N)?	Have you experienced previous sleeping problems (Y/N)?

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

PAGE

DS50
Sleep habit changes rewiew of study GW679769/903

Sub No	Visit	Have you experienced sleep habit changes (Y/N)?	If yes, please detail?

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

. = No data available

PAGE

Attachment 1: Definitions of Variables

A summary of general definitions for various polysomnographic (PSG) variables are included in the following table.

Variable	Abbreviation	Definition
Time in bed (minutes)	TIB	From lights off to lights on
Latency to persistent sleep (minutes)	LPS	Measured from lights off to the first epoch of 20 consecutive non-wake epochs (sleep onset). Calculation: number of epochs from lights off to the first of 20 consecutive non-wake epochs (sleep onset) divided by 2.
Total sleep time (minutes)	TST	Duration of REM plus non-REM (Stage 1, Stage 2, Stages 3/4) sleep from lights off to lights on. Calculation: number of REM plus non-REM (Stage 1, Stage 2, Stages 3/4) epochs from lights off to lights on divided by 2.
Wake after sleep onset (minutes)	WASO	Measured from persistent sleep onset to lights on. Calculation: number of wake epochs from persistent sleep onset to lights on divided by 2.
Number of awakenings		Number of periods of awakening from persistent sleep onset to lights on. Calculation: number of times after persistent sleep onset that there is a wake entry on the PSG recording of at least 1 minute duration (at least 2 consecutive wake epochs). Pairs of awakenings must be separated an epoch of non-REM sleep or REM sleep. NOTE: Two wake entries of at least one minute separated by stage 1 sleep is considered as a single awakening.
Sleep efficiency	SE	(total sleep time)/ (time in bed)x100 (%).
Apnea		At least 90% decrease in air flow lasting 10 seconds or longer.
Hypopnea		A 50-90% decrease in nasal or oral flow lasting 10 seconds or longer which is associated with an arousal, an awakening, or a greater than 3% decrease in oxygen saturation.
Apnea/Hypopnea Index	AHI	Number of apnea and hypopnea episodes divided by the TST expressed in hours.

Continued

Variable	Abbreviation	Definition
Periodic Leg Movement	PLM	A leg movement (LM) is defined as a burst of anterior tibialis muscle with a duration between onset and resolution of 0.5-5.0 seconds and with an amplitude of at least 25% of the leg movements recorded during calibration. The LM must be separated from a subsequent LM by at least 5 seconds and not more than 90 seconds. Movements are only counted if they are part of a series of 4 or more consecutive movements meeting these criteria. The LM must be associated with an arousal/awakening to be considered an event (LMA); and to score LMA, the arousal or awakening must follow the LM onset by not more than 3 seconds. Leg movements associated with "Wake" and respiratory events are not counted. (ASDA criteria; see Recording and scoring leg movements. Sleep 1993; 16:749-59) Note: For definition of arousal use ASDA criteria (EEG arousals scoring rules and examples. Sleep 1992;15:174-84).
Periodic Leg Movement Arousal Index	PLMAI	Number of Periodic Leg Movements associated with arousals or awakening divided by the TST expressed in hours.

Attachment 2: Sleep Staging

Wake: The EEG contains alpha activity and/or low voltage, mixed frequency activity.

Stage 1: Characterized by absence of alpha activity, low amplitude predominantly theta frequency range EEG activity, and slow-rolling eye-movements.

Stage 2: Onset requires the presence of either: 1) a K-complex defined as a negative sharp wave followed by a slower positive component that lasts more than 0.5 sec or 2) a Sleep Spindle defined as at least 0.5 sec of a centrally-predominant 12-14 Hz waveform. This occurs in the setting of a predominantly theta frequency background. Stage 2 is continued until either: an epoch of waking, SWS criteria are met, or a rapid eye-movement occurs signaling the onset of REM.

Stage SWS: At least 20% of the epoch is comprised of frontally-maximal waveforms that have a period of at least 0.5 sec with an amplitude of at least 75 microvolts.

Stage REM sleep: Onset defined by the presence of a rapid eye-movement defined as phasic lateral eye-movement of wave form period less than 1 sec with both rising and falling phases lasting for 50-200 msec. Electromyogram (EMG) is characterized by tonic suppression with phasic burst activity. EEG is relatively low voltage, mixed frequency with sawtooth waves (vertex maximal notched theta frequency waves). Once REM is identified, it continues until either: an epoch of waking, a spindle, or K complex.

Movement Time (MT): This is a scoring epoch, during which the polygraph record is obscured by movements of the subject. This score is assigned to epochs which immediately precede or follow sleep stages, but in which the EEG and EOG tracings are obscured in more than half the epochs by muscle tension and/or amplifier blocking artifacts associated with movements of the subject. When such an epoch is immediately preceded and followed by Wake, the epoch is scored Wake rather than MT. Discrete body movements and movement arousals

Division:	New Product Development	**Document Number:**	VM2004/00033/00
Document Type:	Reporting and Analysis Plan	**Study Identifier:**	GW679769/903
Site of Issue:	Verona		
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Title:

Reporting and Analysis Plan for Protocol GW679769/903: A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia.

Abstract: (For Internal Use Only)

This Reporting and Analysis Plan describes all planned analyses of study GW679769/903.

This is a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia. After meeting entry criteria, subjects will participate in 3 separate 2-night PSG sessions in which they will be randomized to receive placebo or GW679769 at 30 mg or 90 mg.

Authors: [redacted]

Compound Numbers/Keywords (if applicable): GW679769

Distribution:

[redacted] CPSP, Verona
[redacted] CPDS, Harlow
[redacted] CPK/M&S, Verona
[redacted] CPDM, Verona
[redacted] CPDM, Verona
[redacted] Discovery Medicine, RTP
[redacted] Study Team Leader, RTP

Approval Page

Study Identifier: GW679769/903

Study Title: A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia.

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[redacted] STL	Signature on file	

Approver(s):	**Signature:**	**Date:**
[redacted] Manager Statistics, CPSP	Signature on file	

Title:

Reporting and Analysis Plan for Protocol GW679769/903 : A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia.

VM2004/00033/00

Author(s):

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[redacted] CPK/M&S, Verona

Document/Version Number: Final

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Table of Contents

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area under the plasma concentration-time curve
AUC(0-τ)	Area under the plasma concentration-time curve over the dosing interval on multiple dosing
AUC(0-∞)	Area under the plasma concentration-time curve from time 0 (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the plasma concentration-time curve from zero (pre-dose) to the last quantifiable concentration
C_{max}	Maximum observed concentration
CIB or IB	Clinical investigator brochure or Investigator brochure
CPK	Clinical Pharmacokinetics
CPSP	Clinical Pharmacology Statistics and Programming
CRF	Case report form
HVLT-R	Hopkins Verbal Learning Test - Revised
DSM–IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSST	Digital Symbol Substitution Test
ECG	Electrocardiogram
EEG	Electroencephelogram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HR	Heart Rate
ITT	Intention to Treat
LOCF	Last observation carried forward
LPS	Latency to Persistent Sleep
LSEQ	Leeds Sleep Evaluation Questionnaire
MAOI	Monoamine oxidase inhibitor
MedRA	Medical Dictionary for Drug Regulatory Activities
MSDS	Material safety data sheet
Mg	Milligram
Min	Minute
mL	Milliliter
Ng	Nanograms
NK	Neurokinin
od	Once daily
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PP	per protocol
PSG	Polysomnographically
QC	Quality Control
REM	Rapid Eye Movement
RR	Respiratory Rate
SAE	Serious adverse event
SD	Standard deviation

SFA	Spindle Frequency Activity
SNP	Single Nucleotide Polymorphism
SOL	Sleep Onset Latency
SSS	Stanford Sleepiness Scale
SWS	Slow Wave Sleep
t1/2	Terminal phase half-life
T3U	T3 Uptake
t_{max}	First time of occurrence of Cmax
TST	Total Sleep Time
ULRR	Upper limit of the reference range
VAS	Visual Analog Scale
VC	Vigilance Control
WASO	Wake After Sleep Onset

1. INTRODUCTION

This protocol is based upon the study protocol for GW679769/903 [GSK Document Number :PM2004/00029/00] issued on 29 April 2004 and the following amendment

1. PM2004/00029/01 issued on October 2004.

The analyses required and here described will be reported in a Clinical Pharmacology Study Report.

Data listings, safety summaries, summary statistics and plots on plasma-concentration-time data will be produced by or under the direct auspices of New Technologies and Programming (NT&P, CPDS).

A qualified statistician within GSK CPSP will be responsible for analysing and reporting the other data.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

The primary objective is

- To evaluate the acute efficacy of on sleep continuity in adults with Primary Insomnia as determined objectively by polysomnography (PSG).

Secondary objectives are:

- To study the changes induced by GW679769 on various PSG sleep parameters.
- To investigate the effects of GW679769 on daytime cognitive functioning on the morning following dosing, including tests of alertness, memory, attention and fine motor control.
- To investigate the effects of GW679769 on subjective sleep quality using self reported Post-Sleep Questionnaires.
- To investigate the safety and the pharmacokinetic (PK) profile of GW679769 in subjects with primary insomnia after 2 consecutive days of oral administration.
- To investigate the potential effects on memory associated with REM sleep
- To investigate the relationship between plasma concentrations of GW679769 and all the sleep or cognitive parameters and to develop a PK/PD model.

2.2. Study Endpoint(s)

The primary endpoint is

- Wake time after sleep onset (WASO) derived from polysomnographic (PSG) recording.

Secondary endpoints are:

- Objective PSG measures of sleep continuity including: Total Sleep Time (TST), latency to persistent sleep (LPS), wake during sleep (WDS), wake after sleep (WAS), number of Arousals per hour of sleep, number of Micro-Arousals per hour of sleep and number of one minute awakenings.
- Objective PSG measures of sleep structure: Number of minutes or percentage of the night spent in stage 1/stage2/slow wave sleep/REM sleep, Latency to REM Sleep.
- Spectral analysis of EEG output: absolute and relative alpha//beta/delta/gamma/sigma/theta power in Non-REM for C3-A2.
- Subjective Post-Sleep Questionnaire: Leeds Sleep Evaluation Questionnaire (LSEQ), Stanford Sleepiness Scale (SSS), TST, WASO, SOL, number of awakenings, and sleep quality (SQ) to be applied on each morning following PSG recording.
- Daytime cognitive function data on the morning following dosing : Romberg test, DSST and HVLT-R (verbal memory tests)
- TST, SOL, SQ, WAS and number of awakenings measured with the Post-Sleep Questionnaire score collected on specified mornings at home during the 3-day period following each 2-night PSG sessions.
- Plasma concentration of GW679769 and its major metabolite (GSK 525060).

2.3. Statistical Hypotheses

The null hypothesis (HO) states there is no difference among the treatment groups in the efficacy end-points, while the alternative hypothesis (H1) assumes a difference between the treatment groups, in particular among the active treatments vs placebo.

3. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, cross-over study using a complete set of orthogonal Latin Squares. Potential subjects will participate in a screening period consisting of a clinical screening visit and 2-night PSG recording in the sleep laboratory. Subjects with primary insomnia that qualify will participate in 3 separate 2-night PSG sessions in which they will be randomized to receive placebo or GW679769 (30 mg or 90 mg), one treatment for each session in a balanced order. Each session will be separated by a minimum of 12 days and will occur on the same day of the week (± 1 day).

4. PLANNED ANALYSES

The final analyses will be performed upon the release of the database. The database will be released when all subjects have completed the study, all data have been entered and all queries have been resolved. At this stage random allocation details for each subject will be released ("unblinding").

4.1. Interim Analyses

An interim analysis is planned after half of the subjects (24 subjects) have been completed the 3 sessions of the study and after the data for those subjects are available. Subjects enrolled within the first 28 subjects and who did not complete the study (at the moment we know about the existence of 4 "drop-outs" subject) will be also included. So it is planned that the interim analyses will include the results of around 75-80 sessions.

The focus of this interim analysis will be the total sleep time (TST) which is a sensitive parameter even though the primary endpoint is wake time after sleep onset (WASO). Other primary parameters included in the interim analysis will be WASO and LPS. The other objective PSG measures of sleep continuity and sleep structure will be also described.

So the interim analysis will include Table 1, Table 5 (only sleep structure) Table 6, Table 7, Table 8, Table 9 (only TST, and LPS), Table 16 and Figure 2, Figure 4, Figure 6. The reference population for these tables and plots will be the "Interim Analysis population" described above and in Section 6.

A PK/PD analysis, as described in Section 14.3, will be carrid-out including ut not limited to TST, WASO and LPS.

To maintain the blind, only aggregate data will be released to GSK personnel and will not be communicated to any study site. The study team and the investigators will remain blinded throughout the entire study. The result of the interim analysis should not affect the conduct of the remainder of the study. Only in the rare chance that both doses of GW679769 are statistically significantly inferior to placebo will the study be stopped. The study will not be terminated after the interim analysis due to superior efficacy.

5. SAMPLE SIZE CONSIDERATIONS

The final sample size was based on the primary efficacy end-point "wake time after sleep onset (WASO)". In a previous study (NKD10014) a within subjects standard deviation of about 14 min was observed. So assuming a difference vs. placebo of at least 10 min, 43 subjects completing the study would provide a 90% power to detect a difference between active drugs and placebo.

A greater power is expected on the most important of the secondary endpoint (TST) where, in the previous study, a within subjects standard deviation of about 17 min was observed and where differences vs placebo of at least 20 min are expected.

6. ANALYSIS POPULATIONS

Safety Population: including all subjects dosed at least once

Intent-to-Treat Population (ITT): including all subjects dosed at least once, with efficacy or PD measures available for at least one night in the double-blind phase

Interim Analysis: including all subjects dosed at least once, with efficacy measures for at least one night in the double-blind phase included in the Interim Analysis.

PK Concentration Population: including all subjects for whom at least a pharmacokinetic sample was obtained and analyzed

7. TREATMENT COMPARISONS

The primary comparisons of interest are:

GW679769 90 mg vs placebo

GW679769 30 mg vs placebo

Another comparison of interest is

GW679769 90 mg vs GW679769 30 mg

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The following conventions will be generally applied to the analyses described in this RAP:

- all data will be reported according to the actual treatment the subject received

8.1. Multicentre Studies

In the primary analysis the potential presence of a centre by treatment interaction will be investigated .

8.2. Other Strata and Covariates

None

8.3. Examination of Subgroups

None

8.4. Multiple Comparisons and Multiplicity

No adjustment for multiple comparisons will be made due to the exploratory nature of the study.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

Subjects who withdraw from the study will be reported and the reason for withdrawal will be described

Appropriate mixed models will be used. This approach is suitable for mildly unbalanced data when cases are missing at random.

9.2. Derived and Transformed Data

For each session and subject, mean values over the two nights will be obtained for PSG and the other measures collected during the two nights. Mean values will be obtained even when PSG data are available for just one night. Such cases will be highlighted in the text and appropriate sensitive analyses may be considered.

Mean values over 3-day periods will be also obtained for sleep parameters measured with the post-sleep Questionnaire. Sleep quality answers will be classified in this way:

Very poor = 1, Poor = 2, Average=3, Good=4, Very Good=5.

Leeds Sleep Questionnaire (LSEQ)

The Leeds Sleep Evaluation Questionnaire (LSEQ) has been used to monitor subjectively perceived changes in sleep during psychopharmacological investigation involving a variety of psychoactive agents. The questionnaire contains ten self-rating 100-mm-line analogue questions pertaining to four consecutive aspects of sleep: getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS) and behaviour following wakefulness (BFW).

Scores on the four LSEQ subscales vary between 100 (the largest possible positive change experienced after drug administration) and 0 (the largest possible negative change experienced after drug administration). In this placebo-controlled study, drug effects will be assessed both in absolute terms and with reference to a placebo value, by subtracting scores obtained after placebo administration. In this latest case, scores vary from –100 to +100 with positive values showing a drug induced improvement.

GTS domain will be derived as mean value of the items # 1,2,3

QOS domain will be derived as mean value of the items # 4,5

AFS domain will be derived as mean value of the items # 6,7

BFW domain will be derived as mean value of the items # 8,9,10

The presence of missing data prevents the calculation of the corresponding domain score.

Digit Symbol Substitution Test (DSST)

It is a widely used measure of performance impairment. It is a typical test of association involved in substituting symbols for digits over a period of time. The number of correct signs substituted is taken as the score. Subjects will mark a geometric pattern associated with one of the digits displayed on a computer screen. Subjects will have 90 seconds to match as many geometric patterns as possible. The dependent measure will be the number of patterns the subject will be able to mark correctly (i.e., number of trials correct). For each test this measure will be reported on the CRF.

HVLT-R

The HVLT-R tasks include an analysis of total recall and an extra delayed recall at 9 hours in the morning following the first PSG night of each session.

Scores will be reported on the CRF.

9.3. Assessment Windows

The actual sampling times will be used in the pharmacokinetic analysis.

9.4. Values of Clinical Concern

Threshold ranges for ECG, vital signs and laboratory data will be discussed in the attached CPDS RAP.

10. STUDY POPULATION

10.1. Disposition of Subjects

All subjects who withdraw from the study will be listed (Table DS3)

10.2. Protocol Deviations

File notes of any major protocol deviations will be provided to the study team leader by study personnel and will be noted in the final study report.

10.3. Demographic and Baseline Characteristics

Demographic characteristics (age, gender, race, height, weight and body mass index) will be listed and summarised (Table DS1).

Any prior and concomitant medication recorded will be listed (Table DS4), Medical History will be described (Table DS19). Results of pre-sleep questionnaire will be listed in Table DS37.

PSG measures, results of subjective post –sleep questionnaires and sleep parameters measured by means of diary cards and cognitive test related to the screening period will be summarised in Table 1, Table 2, Table 3, Table 4, Table 5.

10.4. Treatment Compliance

A listing of the actual treatments will be produced (Table DS2).

11. EFFICACY ANALYSES

11.1. Primary Efficacy Analysis(es)

Individual WASO data will be plotted by treatment and night (Figure 1, with an horizontal axis reporting screening night 1, screening night 2, placebo night 1, placebo night 2, GW679769 30 mg night 1, GW679769 30 mg night 2, GW679769 90 mg night 1, GW679769 90 mg night 2), as well as mean values by treatment and night (Figure 2)

WASO measures will be analyzed using a mixed effect model with session and treatment as fixed effect and subject as random effect.

Additional analyses will be performed to investigate the carry-over effect (effect of the treatment received in the previous period), the treatment by period interaction and the centre effect and the treatment by centre interaction. For each of these analyses a specific additional term will be added to the original model. Tests of significance will be performed at the 5% level. Least squares mean values will be evaluated for each treatment. Estimates for treatment differences expressed in pair-wise basis will be calculated together with 95% corresponding confidence intervals. Error diagnostics from the residuals will be examined to ensure that the model does not depart from the assumptions underlying analysis of variance. If the assumptions are seriously violated, transformations of the data or nonparametric methods will be considered.

Summary statistics by treatment will be presented in Table 6, while the results of the statistical comparisons will be reported in Table 7.

11.2. Secondary Efficacy Analysis(es)

PSG individual data will be described in Table DS43. LSEQ and SSS data will be reported in Table DS40 and Table DS42.

Secondary efficacy measures will be analyzed using the same approach described for the primary analysis. This affects the analysis of the following parameters :

Objective efficacy PSG measures : Total Sleep Time (TST), Latency to Persistent Sleep (LPS), Wake during sleep (WDS), Wake after sleep (WAS), number of Arousals per hour of sleep, number of Micro-Arousals per hour of sleep and number of one minute awakenings.

Subjective post-sleep questionnaire (PSG nights) : LSEQ domains, SSS, TST, WASO, Sleep Onset Latency (SOL), number of awakenings and Sleep Quality (SQ)

Subjective post sleep questionnaire collected on specific mornings at home during the 3-day period following each 2-night PSG session: LSEQ domains, SSS, TST, SOL, SQ, WAS.

Individual data of Post-sleep questionnaires will be reported in Table DS38.

Summary statistics by treatment will be presented in Table 8, Table 10, Table 12 (for objective efficacy PSG measures, Subjective post-sleep questionnaire during PSG nights and subjective post sleep questionnaire on specific mornings at home ,respectively).

Results of the statistical comparisons will be described in Table 9, Table 11, Table 13.

Plots will be provided for TST and LPS derived by PSG measures (Figure 3, Figure 4, Figure 5, Figure 6).

12. SAFETY ANALYSES

12.1. Extent of Exposure

Dosing details will be provided in Table DS2.

12.2. Adverse Events

A list of the codes used will be provided in Table DS5. All adverse events will be summarised and listed by treatment period according to MedDra coding dictionary (Table DS6, Table DS7 and Table DS8). Total numbers of AE's by treatment and relationship with study drug will be tabulated in Table DS9.

12.3. Deaths and Serious Adverse Events

These will be included in the listing of AE's by treatment if appropriate.

12.4. Device Incidents and Near Incidents

Not applicable.

12.5. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

These will be included in the listing of AE's by treatment if appropriate.

12.6. Pregnancies (as applicable)

Pregnancy findings at follow-up will be tabulated in Table DS33.

12.7. Clinical Laboratory Evaluations

A list of laboratory values of potential clinical concern will be reported in Table DS16. A complete list of labs data, flagged as 'H', 'L' (High, Low), 'A','B' (above/below potential clinical concern threshold) will be presented in Table DS17. Finally normal ranges and potential clinical concerns ranges will be given in Table DS18.

12.8. Other Safety Measures

Vital signs (Table DS10, Table DS11, Table DS12) and ECG data (Table DS13, Table DS14, Table DS15) will be listed by subject and time. Summary statistics of vital signs and ECG by treatment group will be presented in Table DS34-Table DS35.

13. HEALTH OUTCOMES ANALYSES

Not applicable.

14. CLINICAL PHARMACOLOGY DATA ANALYSES

The derivation of PK parameters and Plots of Individual Plasma concentration-time data by treatment will be the responsibility of CPK/M&S using validated pharmacokinetic software (NONMEM Version V).

Listing (Table DS31) summary and plot (Table 20, Table 11 and Figure 8-Figure 15) of pharmacokinetic concentration data will be provided by NT&P.

Listings of PK Derived data will be the responsibility of CPSP Statistics, GSK.

14.1. Pharmacokinetic Analyses

SOP-CPK-0001 v01 (Standard Methods for the Non-Compartmental Analysis of Pharmacokinetic Data) and SOP-BMD-4002 v01 (Standard Statistical Methods for the Analysis of Pharmacokinetic Data) will be followed for the analysis and reporting of the pharmacokinetic data for this study, where appropriate.

Plasma concentration-time data of GW679769 and its major metabolite GSK525060 will be listed by treatment (Table DS31) and summarised using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time (Table 20, Table 21). Individual plasma concentration-time data (Figure 7) and mean and median values will be plotted (Figure 8-Figure 15).

Values below the low limit of quantification of the assay (LLQ) will be considered as zero in the determination of the summary statistics. If there are multiple LLQs then the minimum limit will be used when applying these rules.

If appropriate, pharmacokinetic parameters such as AUC(0-t), Cmax, and tmax will be estimated using a non-linear mixed effect model. Actual sampling times will be used to derive all the parameters.

Population PK analysis will be performed using NONMEM Version V software. This software implements the non-linear mixed effects model. A common structural model with population parameters obtained from HVs studies will be applied. Based on the estimated population parameters from HVs, as a prior, and the individual data, individual specific parameters may be generated.

Derived pharmacokinetic parameters will be listed by subject and treatment (Listing 1, Listing 2).

14.2. Pharmacodynamic Analyses

Results of DSST, HVLT-R and Romberg test will be reported in Table DS41, Table DS42, Table DS44 and Table DS45.

The following PD endpoints :

DSST, , HVLT-R total recall, HVLT-R extra delayed recall)

will be analyzed using a mixed effect model with session and treatment as fixed effect and subject as random effect.

Additional analyses will be performed to investigate the carry-over effect (effect of the treatment received in the previous period) and the treatment by period interaction. In both the cases additional terms will be added to the original model. Tests of significance will be performed at the 5% level. Least squares mean values will be evaluated for each treatment. Estimates for treatment differences expressed in pair-wise basis will be calculated together with 95% corresponding confidence intervals. Error diagnostics from the residuals will be examined to ensure that the models do not depart from the assumptions underlying analysis of variance. If the assumptions are seriously violated, transformations of the data or nonparametric methods will be considered.

Summary statistics by treatment will be presented in Table 14 while results of the statistical comparisons will be described in Table 15.

The same approach will be used to report PSG measures of sleep structure (Number of minutes or percentage of the night spent in stage 1/stage2/slow wave sleep/REM sleep,

Latency to REM Sleep) and parameters derived from Spectral Analysis (absolute and relative alpha//beta/delta/gamma/sigma/theta power in Non-REM for C3-A2).

Summary statistics by treatment will be presented in Table 16, Table 18 while results of the statistical comparisons will be described in Table 17, Table 19.

Additional exploratory analyses may be conducted on these data.

14.3. Pharmacokinetic/Pharmacodynamic Analyses

This analysis will be the responsibility of CPK/M&S, GSK,Verona.

The objectives of this analysis are :

- To explore and, as appropriate, model the relationship between exposure of GW679769 and the primary endpoint of efficacy (difference from placebo in the Wake After Sleep Onset (WASO)). Also the Total Sleep Time (TST) will be evaluated
- Exploratory PK/PD analysis may include secondary endpoints of efficacy including but not limited to latency to persistent sleep (LPS), wake during sleep (WDS), wake after sleep (WAS), and number of awakenings during sleep

A preliminary exploratory analysis will be conducted to investigate the link between GW679769 exposure and WASO and TST.

Population PK/PD modelling. To support the hypothesis that GW679769 levels are related to clinical response PK/PD data modelling will be performed. This analysis will consist in :

- Probabilistic model: to determine whether GW679769 exposure could be considered as a statistically significant predictor of the clinical response (represented by the binary outcome) using a logistic regression analysis. The clinical relevant response will be an increase of WASO from placebo of at least 10 min and TST from placebo at least 20 min (averaged on the two nights).
- Deterministic model. A mechanistic model will be used to describe the changes in WASO and TST values from the placebo response. Alternative models will be investigated (linear, exponential, sigmoidal,..) and the optimal one will be used to evaluate the clinical response. Averaged (two nights) and daily measurements (one night) of WASO and TST will be considered to establish the PK/PD relationship

In both steps, alternative models will be investigated. The criteria for selecting the NONMEM best PK/PD model include: (i) improved fitting of the diagnostic scatter plots (observed versus predicted concentration, residual/weighted residual versus predicted concentration or time), (ii) convergence of the minimisation, (iii) significant decrease in the objective function (Δ) evaluated using the log-likelihood ratio test and the Akaike information criteria.

For the interim analysis CPSP will send to CPKM&S a csv file with the following columns :

PID = patient identification number; SUBJECT= subject identification ; CENTRE= centre code; SESS= session (0= screening, 1=session 1, 2=session 2, 3=session 3); VISIT = visit number (2-3 for session 0, 4-5 for session 1, 6-7 for session 2, 8-9 for session 3), NIGHT = first or second night of the session, TMT=treatment code (A= placebo, B= GW679769 30 mg, C= GW679769 90 mg); GPARAM = (parameter id); VALUE = numeric value.

15. BIOMARKER DATA ANALYSIS

Not applicable

16. PHARMACOGENETIC DATA ANALYSES

If at any time it appears there is potential variability in GW679769 response or handling (e.g., pharmacokinetics, safety, and/or efficacy) in this clinical trial or in a series of clinical trials, the following objectives may be investigated (assuming sample number is adequate and the availability of genotyping assays):

- to investigate the relationship between polymorphisms in the selected candidate genes and the subjective variability observed in response to GW679769 as measured by clinical efficacy measures and physiological parameters associated with anxiety.
- Dependent on the clinical study data additional analysis may be performed to investigate the relationship between genetic polymorphisms and tolerability of GW679769 using adverse events.
- Relationship between genetic variants and efficacy of investigational product.

No specific table is defined at this stage.

17. VIRAL GENOTYPING/PHENOTYPING

Not applicable

18. REFERENCES

1. GlaxoSmithKline Document Number: PM2004/00029/00 Study ID GW679769/903
2. GlaxoSmithKline Document Number: PM2004/00029/01 Study ID GW679769/903
3. GlaxoSmithKline SOP number : SOP-CPK-0001 : Standard methods for the non-compartmental analysis of Pharmacokinetic data.
4. GlaxoSmithKline SOP number : SOP-BMD-4002 : Standard Statistical Methods for the Analysis of Pharmacokinetic Data.

19. ATTACHMENTS

19.1. Table of Contents for Data Display Specifications

Tables

Number	Description	Responsibility
1	Summary of pre-treatment PSG efficacy measures	CPSP
2	Summary of results of pre-treatment subjective post sleep questionnaires	CPSP
3	Summary of pre-treatment sleep parameters (diary cards)	CPSP
4	Summary of pre treatment cognitive data	CPSP
5	Summary of pre-treatment PSG measures of sleep structure and Spectral Analysis data	CPSP
6	Summary of post treatment WASO data (PSG)	CPSP
7	Summary of Results of the Statistical Analysis of post treatment WASO data (PSG)	CPSP
8	Summary of other post treatment PSG efficacy measures	CPSP
9	Summary of Results of the Statistical Analysis of other post treatment PSG efficacy measures	CPSP
10	Summary of results of post treatment subjective post sleep questionnaires	CPSP
11	Summary of Results of the Statistical Analysis of post treatment subjective post sleep questionnaires data	CPSP
12	Summary of post-treatment sleep parameters (diary cards)	CPSP
13	Summary of Results of the Statistical Analysis of post treatment sleep parameters (diary cards)	CPSP
14	Summary of post treatment cognitive data	CPSP
15	Summary of Results of the Statistical Analysis of post treatment cognitive data	CPSP
16	Summary of post treatment PSG measures of sleep structure	CPSP

Number	Description	Responsibility
17	Summary of Results of the Statistical Analysis of post treatment PSG measures of sleep structure	CPSP
18	Summary of post treatment Spectral Analysis data	CPSP
19	Summary of Results of the Statistical Analysis of post treatment Spectral Analysis data	CPSP
20	Summary of Plasma GW679769 Concentration-time data by treatment	NT&P
21	Summary of Plasma GSK525060 Concentration-time data by treatment	NT&P

Listing

Number	Description	Responsibility
1	Listing of Derived Plasma GW679769 Pharmacokinetic parameter	CPSP
2	Listing of Derived Plasma GW525060 Pharmacokinetic parameter	CPSP

Figures

Number	Description	Responsibility
1	Plots of WASO Individual data (PSG) by treatment and night	CPSP
2	Plots of Mean values of WASO (PSG) by treatment and night	CPSP
3	Plots of TST individual data (PSG) by treatment and night	CPSP
4	Plots of Mean values of TST (PSG) by treatment and night	CPSP
5	Plots of LPS individual data (PSG) by treatment and night	CPSP
6	Plots of Mean values of LPS (PSG) by treatment and night	CPSP
7	Plots of individual Plasma GW679769, GSK525060 Concentration-time data, by subject (linear and semi-log)	NT&P

Number	Description	Responsibility
8	Plots of treatment mean Plasma GW679769 Concentration-Time data	NT&P
9	Plots of treatment mean Plasma GW679769 Concentration-Time data (semi-logarithmic scale)	NT&P
10	Plots of treatment median Plasma GW679769 Concentration-Time data	NT&P
11	Plots of treatment median Plasma GW679769 Concentration-Time data (semi-logarithmic scale)	NT&P
12	Plots of treatment mean Plasma GSK525060 Concentration-Time data	NT&P
13	Plots of treatment mean Plasma GSK525060 Concentration-Time data (semi-logarithmic scale)	NT&P
14	Plots of treatment median Plasma GSK525060 Concentration-Time data	NT&P
15	Plots of treatment median Plasma GSK525060Concentration-Time data (semi-logarithmic scale)	NT&P

CPDS tables

Program Table Number	Program Titles
Table DS1	Demographic Data
Table DS2	Dosing Details
Table DS3	Withdrawal Data
Table DS4	Other Medications
Table DS5	Adverse Experience Key
Table DS6	Adverse Experience Listing
Table DS7	Adverse Experience by Body System
Table DS8	Adverse Experience by Frequency
Table DS9	Adverse Experience Totals

Program Table Number	**Program Titles**
Table DS10	Vital Signs - Potential Clinical Concern
Table DS11	Vital Signs Data
Table DS12	Vital Signs Flagging Ranges
Table DS13	ECG – Potential Clinical Concern
Table DS14	ECG Data
Table DS15	ECG Flagging Ranges
Table DS16	Laboratory Data – Potential Clinical Concern
Table DS17	Laboratory Data
Table DS18	Laboratory Data Ranges
Table DS19	Medical History
Table DS31	Plasma Pharmacokinetic Data
Table DS33	Pregnancy findings at follow-up
Table DS34	Summary Stats for ECG
Table DS35	Summary Stats for Vitals
Table DS37	Pre–Sleep Questionnaire
Table DS38	Post-Sleep Questionnaire
Table DS40	Leeds Sleep Evaluation Questionnaire
Table DS41	Digit-Symbol Substitution Test
Table DS42	Stanford Sleepiness Scale
Table DS43	PSG data
Table DS44	Memory HVLT-R
Table DS45	Romberg test

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ACRF

Project	Protocol	Volunteer Panel Number	Center Number	Subject Number	Page
679769	903				1

A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia.

CASE REPORT FORM
SCREENING

Investigator:

Study Location:

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: [redacted]

GlaxoSmithKline Responsible Physician: [redacted] **M.D.**

GlaxoSmithKline Clinical Monitor: [redacted]

Location:

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: [redacted]

Please scan this as Project 679769 Protocol 903

GENERAL INSTRUCTIONS

The plastic writing board in the back of the binder should be used to divide each set of pages before writing on them with a ball-point pen.
Print clearly in CAPITAL LETTERS using a black ball-point pen and press firmly so that all copies are legible. DO NOT print in areas designated for GlaxoSmithKline use only. Answer all questions on every page. If a test is not done write ND, if zero write 0.

IMPORTANT: **Errors should be crossed out with a single line and the alteration made as close to the original as possible. All alterations must be printed, initialed and dated. Do not use masking fluid.**

Please ensure that the subject consent form is signed.

Please ensure that all ECG traces and any other loose data are attached at the back of the book.

Please notify study monitor of all protocol deviations.

Record all concomitant medications and adverse events. Please notify GlaxoSmithKline within 24 hours of all 'serious' occurrences.

Please complete subject study conclusion form.

DATE - Use the following three - letter abbreviation for month:

January	=	**JAN**	**July**	=	**JUL**
February	=	**FEB**	**August**	=	**AUG**
March	=	**MAR**	**September**	=	**SEP**
April	=	**APR**	**October**	=	**OCT**
May	=	**MAY**	**November**	=	**NOV**
June	=	**JUN**	**December**	=	**DEC**

EXAMPLE: | 0 1 | J A N | 2 0 0 0 | (Day Month Year) = **1st January 2000**

TIME - Unless specified otherwise, use the 24 hour clock: **00:00 - 23:59**

EXAMPLE: | 1 5 | 3 0 | (24hr:min) = **3:30 p.m.**

GlaxoSmithKline

Project	Protocol	Subject Number	SCREENING (VISIT 1)	Visit Date Day Month Year	Page
679769	903				2

ELIGIBILITY CHECKLIST

Does the subject meet the following eligibility criteria?
Answer the following questions by marking the appropriate box.

Inclusion Criteria	Yes	No
1. Is the subject able to read and understand the informed consent form and provide written informed consent? Indicating the subject's understanding of the purpose of the study and willingness to comply with all study procedures described in the protocol, including all sleep-laboratory restrictions and procedures.	☐	☐
2. Is the subject 18 - 64 years (inclusive)?	☐	☐
3. Has the subject been diagnosed with primary insomnia? As defined by Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) criteria 307.42. A complaint of difficulty initiating or maintaining sleep or of non-restorative sleep, which lasts for at least 3 months along with clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance in sleep does not occur exclusively during the course of another sleep disorder or occur exclusively during the course of another mental disorder. Lastly, the disturbance is not due to the direct physiological effects of a substance or a general medical condition.	☐	☐
4. Does the subjects self-reported sleep history include at least three months of a usual TST of less than 6.5 hours, SOL of at least 30 minutes and at least 3 awakening per night in at least 3 nights per week?	☐	☐
5. Was the subjects two screening PSGs (on single-blinded placebo administration at each night):		
• TST between 240 and 420 minutes on both nights.	☐	☐
• Mean LPS of 30 minutes but not < 20 minutes on either night.	☐	☐
• Mean WASO of 30 min with neither night < 20 min	☐	☐
6. Has the subjects time in bed been between 6.5 and 9 hours for at least 5 nights per week over the preceding 3 months?	☐	☐
7. Is the subject's bedtime between 21.00 and 24.00 hours and does not vary by more than ± 1 hour?	☐	☐

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If the answer to any of the above is **NO** the subject must be excluded from the study.

GlaxoSmithKline

Project	Protocol	Subject Number	SCREENING (VISIT 1)	Visit Date Day Month Year	Page
679769	903				3

ELIGIBILITY CHECKLIST

Does the subject meet the following eligibility criteria?
Answer the following questions by marking the appropriate box.

Inclusion Criteria

	Yes	No	N/A
8. Is the women of childbrearing potential able to commit to consistent and correct use of an acceptable method of birth control? GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of a physician, are as follows: a Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal. For purposes of this study, postmenopausal is defined as one year without menses); or, b child-bearing potential, has a negative serum pregnancy test result at screen and a negative urine dipstick pregnancy test at baseline (prior to study drug administration), and agrees to one of the following: • Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject, • Oral contraceptives (either combined or progestogen only), • Double-barrier method of contraception consisting of spermicide with either condom or diaphragm; • IUD with a documented failure rate of less than 1% per year; or • Complete abstinence from intercourse for two weeks before exposure to the study drug, throughout the clinical trial, and for a period after the trial to account for elimination of the drug (minimum of three days, equivalent to five half lives).	☐	☐	☐
9. Does the subject agree to follow GSK guidelines for the consistent and correct use of an acceptable method of birth control should they become sexually active?	☐	☐	
10. Is the subject in good healt as determined by medical and psychiatric history, physical examination, ECG, and serum chemistry, hematology, serology, and urinalysis results?	☐	☐	
11. Does the subject have a medical history of peptic ulcer disease? Subjects with a known etiology must provide documentation from a gastroenterologist of the etiology of the PUD and that effective treatment was provided with full eradication of ulcers and symptoms. Also that all steps have been taken to minimize reoccurrence risk (i.e. if NSAID induced that subject is no longer taking NSAIDs, if cause was H. Pylori, then subject should have negative antibody or breath test).	☐	☐	

If the answer to any of the above is **NO** the subject must be excluded from the study.

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Project	Protocol	Subject Number	SCREENING (VISIT 1)	Visit Date (Day Month Year)	Page
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ELIGIBILITY CHECKLIST

Does the subject meet the following eligibility criteria?
Answer the following questions by marking the appropriate box.

Exclusion Criteria

	Yes	No	N/A
1. Does the subject have any clinically significant unstable medical or surgical condition (treated or untreated)?	☐	☐	
2. Does the subject have any history of a clinically significant abnormality of the neurological system (including cognitive disorders or significant head injury) or any history of seizure (including febrile seizure)?	☐	☐	
3. Does the subject have a history of depression, anxiety or other Axis I or II disorders?	☐	☐	
4. Does the subject have current or recent (within six months) documented gastrointestinal disease; a history of malabsorption, esophageal reflux, or irritable bowel syndrome; frequent (more than once a week) occurrence of heartburn, or any surgical intervention (e.g. cholecystectomy) which would be expected to influence the absorption of drugs?	☐	☐	
5. Does the subject have active PUD and/or history of PUD of an unknown etiology, except as indicated in inclusion criteria number 11?	☐	☐	
6. Does the subject have an unstable medical disorder; or a disorder that would interfere with the action, absorption, distribution, metabolism, or excretion of GW679769 or interfere with the accurate assessment of safety or efficacy?	☐	☐	
7. Did the subject have a clinically significant abnormality in hematology, blood chemistry, ECG, urinalysis, physical exam, vital signs or other protocol-specified screening test which are not resolved by the baseline visit?	☐	☐	
8. Does the subject have a history of clinically significant hepatic, cardiac (e.g. including myocardial infarction), renal, neurologic (e.g. including seizures), cerebrovascular, metabolic or pulmonary disease?	☐	☐	
9. Does the subject have a known seropositivity for human immunodeficiency virus (HIV), Hepatitis B, or Hepatitis C?	☐	☐	
10. Does the female subject have a positive serum HCG pregnancy test at screening visit, a positive urine pregnancy dipstick or serum pregnancy test at Baseline Visit (Randomization), or who are lactating or planning to become pregnant within the 3 months following the Screening Visit?	☐	☐	☐
11. Does the subject have any clinically significant psychiatric disorder other than primary insomnia as defined by DSM-IV-TR?	☐	☐	

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If the answer to any of the above is **YES** the subject must be excluded from the study.

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Project	Protocol	Subject Number	SCREENING (VISIT 1)	Visit Date Day Month Year	Page
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ELIGIBILITY CHECKLIST

Does the subject meet the following eligibility criteria?
Answer the following questions by marking the appropriate box.

Exclusion Criteria

	Yes	No
12. Does the subject have a history of alcohol, narcotic, benzodiazepine, or other substance abuse or dependence (with the exception of tobacco use) within the past 12 months as defined by DSM-IV-TR?	☐	☐
13. Does the subject show any symptoms/signs that are consistent with any primary sleep disorder other than primary insomnia?	☐	☐
14. Is the subject's body mass index of 34 or more?	☐	☐
15. Is the subject's apnea-hypopnea index of 10 or more/hour of sleep on screening PSG?	☐	☐
16. Is the subject's movement arousal index of 10 or more/hour of sleep on screening PSG?	☐	☐
17. Is the subject on nightshift or rotating-shift work within the last 2 work weeks or during the study period?	☐	☐
18. Does the subject plan to travel across more than 3 time zones during the study or in the 2 weeks prior to screening?	☐	☐
19. Does the subject consume on average per day 300mg of xanthine-containing beverages (eg, coffee, cola, tea, chocolate) over the preceding 1 month [NOTE: 12 oz soda = ~50 mg, 7 oz coffee or 2 oz espresso = ~100 mg, 7 oz tea = ~75 mg of caffeine]?	☐	☐
20. Has the subject smoked more than 1 pack of cigarettes per day on average over the preceding 1 month, or inability to stop smoking during the sleep?	☐	☐
21. Is the subject's typical consumption of alcohol in any one week more that 14 alcoholic units, or more than 5 alcoholic units in any single day, over the preceding 1 month [NOTE: 1 unit = 8 oz beer, 3 oz wine, or 1 oz hard liquor]?	☐	☐
22. Was the subject's LFTs elevated above the reference range at pre-study screening and remained elevated with a repeat LFT (to be discussed with the sponsor, if necessary)?	☐	☐
23. Is subject euthyroid as evidenced by normal TSH? Subjects maintained on thyroid medication must be euthyroid for a period of at least six months prior to the screening visit; with no dose changes.	☐	☐
24. Does the subject have a history or evidence of clinically significant renal impairment (serum creatinine > 1.4 mg/dL) not resolved by the baseline visit?	☐	☐

Continued over page

If the answer to any of the above is **YES** the subject must be excluded from the study.

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Project	Protocol	Subject Number	SCREENING (VISIT 1)	Visit Date (Day Month Year)	Page
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ELIGIBILITY CHECKLIST

Does the subject meet the following eligibility criteria?
Answer the following questions by marking the appropriate box.

Exclusion Criteria

	Yes	No	N/A
25. Does the subject have anemia and low Mean Corpuscular Volume (<80 fL) at the screening visit (to avoid entering subjects with iron deficiency anemia)?	☐	☐	
26. Has the subject used any psychotropic medications or other medications, including over-the-counter (OTC) and herbal products, that may affect sleep/wake function within 1 week or 5 half-lives (whichever is longer) prior to screening or need to use any of these medications at any time during the study?	☐	☐	
27. Has the subject (i.e. asthmatics) used systemic corticosteroids within 1 week or 5 half-lives (whichever is longer) prior to the screening visit?	☐	☐	☐
28. Has the subject discontinued all other (non-psychotropic) drugs metabolized via the P450 3A4 pathway from baseline visit through to completeion of Session 3?	☐	☐	
29. Has the subject had use of any investigational drug within 30 days or 5 half-lives of the study compund prior to the Screening Visit?	☐	☐	
30. Does the subject have a positive urine screen (i.e., amphetamines. barbiturates, benzodiazepines, cannabinoids, cocaine, or opiates)?	☐	☐	
31. Has the subject exhibited intolerance to NK1 antagonists?	☐	☐	
32. Does the subject have any serious medical disorder or condition that would in the Investigator's opinion, preclude the administration of study medication.	☐	☐	
33. Would the subject in the opinion of the investigator, be noncompliant with the visit schedule or study procedures?	☐	☐	

If the answer to any of the above is **YES** the subject must be excluded from the study.

Investigator's Signature:_____ Date: Day Month Year

GlaxoSmithKline

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DEMOGRAPHY

DEMOG

DATE OF BIRTH ☐☐ Day ☐☐ Month ☐☐☐☐ Year — DOB

GENDER
- ☐ Male
- ☐ Female

SEX.

RACE
- ☐ American Hispanic
- ☐ Arabic/North African
- ☐ Black
- ☐ East & South East Asia
- ☐ Japanese
- ☐ South Asia
- ☐ White/Caucasian
- ☐ Other _____ RACETEXT

RACE

VITALS

HEIGHT ☐☐☐ cm — XVPARAM = HT

WEIGHT ☐☐☐.☐ kg — XVPARAM = WT

BODY MASS INDEX* ☐☐☐.☐ kg/m² — XVPARAM = BMI

VALUET.

* Body Mass Index calculated using the following formula

$$\text{Body Mass Index} = \frac{\text{Weight (kg)}}{(\text{Height (cm)})^2} \times 10{,}000$$

GlaxoSmithKline

Project	Protocol	Subject Number	SCREENING (VISIT 1)	Visit Date Day Month Year	Page
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SIGNIFICANT MEDICAL/SURGICAL HISTORY

Is the subject suffering from or has he/she ever suffered from any **significant** medical or surgical condition?

☐ **No**

☐ **Yes**_____ *List below one diagnosis per line. (Please print clearly)*

Only in the absence of a diagnosis, record the signs and symptoms on separate lines.

Diagnosis	GSK Use	Year of first diagnosis	Past	Ongoing
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				

GlaxoSmithKline

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PSYCHIATRIC HISTORY

1. Duration of current episode ☐☐☐ Weeks (Minimum of 2 weeks)

2. Subtype of depression:
   DSM-IV-TR CODE 296.☐☐ (Use codes below for the last two digits)

   22 = Major depression, single episode: moderate
   23 = Major depression, single episode: severe without psychotic features
   32 = Major depression, recurrent: moderate
   33 = Major depression, recurrent: severe without psychotic features

3. Identify specifiers - check all that apply:

   ☐ None
   ☐ Melancholic features
   ☐ Atypical features
   ☐ Seasonal pattern

4. Has the subject ever received treatment for the symptoms of depression? ☐ Yes ☐ No

If **Yes**, describe the treatment _____

_____

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PHYSICAL EXAMINATION

DATE: Day Month Year TIME: 24hr:min

Was the physical examination?

☐ Normal

☐ Abnormal Record below:

GlaxoSmithKline

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SLEEP HISTORY

PSTAT

PSTATQ = 1513

Have you experienced previous sleeping problems? ☐ Yes ☐ No

ANYYN

If YES, please detail below:

ANSTXT

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SERUM PREGNANCY TEST (Females only)

Was a pregnancy test carried out? ☐ Yes ☐ No

If **'No'**, please specify reason _____

If **'YES'**, please indicate date and time of test and result:

Date and Time of pregnancy test: ☐☐ ☐☐ ☐☐☐☐ Day Month Year ☐☐ 24hr:min

Positive ☐ Negative ☐

If **'Positive'**, withdraw the subject from the study.

GlaxoSmithKline

Project	Protocol	Subject Number	SCREENING (VISIT 1)	Page
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SITTING VITAL SIGNS VITALS. POST = SI

STUDY TIME OBS	DATE DAT	ACTUAL TIME TIM	BP (mmHg) SYSTOLIC	BP (mmHg) DIASTOLIC	HR (bpm)	RESPIRATORY RATE (breaths/min)	ORAL TEMPERATURE (°C)
Screening	Day Month Year	24hr:min	SYS	DIA	PUL	RSP.	TMP.
Unscheduled	Day Month Year	24hr:min			VPARAM		
Unscheduled	Day Month Year	24hr:min					

VALUET.

12-LEAD ECG ECGRES ECGINT COMMENTS

STUDY TIME OBS	DATE DAT	ACTUAL TIME TIM	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
Screening	Day Month Year	24hr:min	HR	PR	QRS	QT	QTC	ANSYN ☐ Yes ☐ No	COMMENTS
Unsched	Day Month Year	24hr:min		EPARAM				☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	

VALUET.

GlaxoSmithKline

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LABORATORY COLLECTIONS

LAB

CLINICAL CHEMISTRY & HEMATOLOGY - Ensure a blood sample has been taken for clinical chemistry and haematology analysis

Exact date and time of blood sampling

DAT TIM

Day Month Year 24hr:min

Comments:

Are there **CLINICALLY SIGNIFICANT ABNORMAL** values?
If **YES**, please record diagnosis on Baseline Signs and Symptoms page. ☐ Yes ☐ No

URINALYSIS - Ensure a urine sample has been taken for urinalysis

Exact date and time of urine sampling

DAT TIM

Day Month Year 24hr:min

Comments:

Are there **CLINICALLY SIGNIFICANT ABNORMAL** values?
If **YES**, please record diagnosis on Baseline Signs and Symptoms page. ☐ Yes ☐ No

DRUG SCREENING (URINE)

Exact date and time of sampling

Day Month Year 24hr:min

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below. ☐ Yes ☐ No

Type of drug	Comment

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LABORATORY COLLECTIONS

HIV AND HEPATITIS B & C - Ensure a blood sample has been taken to provide serum for screening for HIV antibodies, Hepatitis B surface antigen, Hepatitis C antibody.

Exact date and time of blood sampling

Day Month Year 24hr:min

Comments:

ALCOHOL BREATH TEST

Exact date and time of test

Day Month Year 24hr:min

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 2, NIGHT 1)	Visit Date Day Month Year	Page
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SIGNIFICANT MEDICAL/SURGICAL HISTORY - UPDATE

Is the subject suffering from or has he/she ever suffered from any **significant** medical or surgical condition?

☐ **No**

☐ **Yes**_____ *List below one diagnosis per line. (Please print clearly)*

Only in the absence of a diagnosis, record the signs and symptoms on separate lines.

Diagnosis	GSK Use	Year of first diagnosis	Past	Ongoing
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				

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PSYCHIATRIC HISTORY - UPDATE

1. Duration of current episode ☐☐☐ Weeks (Minimum of 2 weeks)

2. Subtype of depression:
   DSM-IV-TR CODE 296.☐☐ (Use codes below for the last two digits)

   22 = Major depression, single episode: moderate
   23 = Major depression, single episode: severe without psychotic features
   32 = Major depression, recurrent: moderate
   33 = Major depression, recurrent: severe without psychotic features

3. identify specifiers - check all that apply:

   ☐ None
   ☐ Melancholic features
   ☐ Atypical features
   ☐ Seasonal pattern

4. Has the subject ever received treatment for the symptoms of depression? ☐ Yes ☐ No

If **Yes**, describe the treatment _____

_____

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SLEEP HISTORY

SEE PAGE 11

Have you experienced previous sleeping problems? ☐ Yes ☐ No

If YES, please detail below:

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PREGNANCY TEST (Females only)

Was a pregnancy test carried out? ☐ Yes ☐ No

If **'No'**, please specify reason _____

If **'YES'**, please indicate date and time of test and result:

Date and Time of pregnancy test: ☐☐ ☐☐ ☐☐☐☐ Day Month Year ☐☐ 24hr:min

Positive ☐ Negative ☐

If **'Positive'**, withdraw the subject from the study.

Please mark box for test type

Dipstick urine HCG ☐

Serum HCG ☐

Other ☐ → please specify _____

Laboratory name, if applicable _____
ensure result is included on laboratory report

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LABORATORY COLLECTIONS

DRUG SCREENING (URINE)

Exact date and time of sampling ☐☐ ☐☐ ☐☐☐☐ (Day Month Year) ☐☐:☐☐ (24hr:min)

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below. ☐ Yes ☐ No

Type of drug	Comment

ALCOHOL BREATH TEST

Exact date and time of test ☐☐ ☐☐ ☐☐☐☐ (Day Month Year) ☐☐:☐☐ (24hr:min)

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

GlaxoSmithKline

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SITTING VITAL SIGNS

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR	RESPIRATORY RATE	ORAL TEMPERATURE
			SYSTOLIC	DIASTOLIC	(bpm)	(breaths/min)	(°C)
30 mins pre-dose	Day Month Year	24hr:min					
+60 mins post-dose	Day Month Year	24hr:min					
+10 hrs post-dose	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 2)	Page
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12-LEAD ECG

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
30 mins pre-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+60 mins post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+10 hrs post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	

PRE-SLEEP QUESTIONNAIRE PSTAT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

MEMORY HVLT-R

DISEASE

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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DOSING DETAILS

DOSTIM

Date and time of dosing

Day Month Year (DAT)

24hr:min (TIM)

Dose checked and administered by: _____

Dose checked and witnessed by: _____

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 2, NIGHT 1)	Page
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NOCTURNAL PSG

Was a Nocturnal PSG completed? ☐ Yes ☐ No

If **'YES'**, please indicate date and time:

Date and Time Nocturnal PSG completed: Day Month Year 24hr:min

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 2, DAY 1)	Visit Date & Time Day	Month	Year	24hr:min	Page
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LEEDS SLEEP EVALUATION QUESTIONNAIRE

PSTAT

ANSI

119

120

121

122

123

124

125

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LEEDS SLEEP EVALUATION QUESTIONNAIRE (LSEQ) Continued

How did you feel on waking? PSTATQ = 1427

ANSNO 126 8. Tired ——— Alert ANSTXT

How do you feel now? PSTATQ = 1428.

126 9. Tired ——— Alert

How was your sense of balance and coordination upon getting up? PSTATQ = 1429

127 10. More clumsy than usual ——— Less clumsy than usual

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 2, DAY 1)	Page
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POST-SLEEP QUESTIONNAIRE

PSTAT

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DIGIT SYMBOL SUBSTITUTION TEST (DSST)

GENERAL (GPARAM=DSST)

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MEMORY HVLT-R

SEE PAGE 24

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

ROMBERG TEST, HEEL-TO-TOE TEST

PSTAT.

Date and Time: Day Month Year ANSDAT 24hr:min ANSTIM

Was the Romberg test and heel-to-toe test sucessfully completed? ☐ Yes ☐ No ANSYN.

PSTATQ = 1512

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 2, DAY 1)	Visit Date (Day Month Year)	Page
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STANFORD SLEEPINESS SCALE (SSS)

GENERAL

(GPARAM = DEGSLEEP
METHOD = SSS

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VALUET

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 3, NIGHT 2)	Visit Date Day Month Year	Page
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SIGNIFICANT MEDICAL/SURGICAL HISTORY - UPDATE

Is the subject suffering from or has he/she ever suffered from any **significant** medical or surgical condition?

☐ **No**

☐ **Yes**_____ *List below one diagnosis per line. (Please print clearly)*

Only in the absence of a diagnosis, record the signs and symptoms on separate lines.

Diagnosis	GSK Use	Year of first diagnosis	Past	Ongoing
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				
		Month Year	☐	☐
For GSK				

GlaxoSmithKline

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PSYCHIATRIC HISTORY - UPDATE

1. Duration of current episode ☐☐☐ Weeks (Minimum of 2 weeks)

2. Subtype of depression:
   DSM-IV-TR CODE 296.☐☐ (Use codes below for the last two digits)

   22 = Major depression, single episode: moderate
   23 = Major depression, single episode: severe without psychotic features
   32 = Major depression, recurrent: moderate
   33 = Major depression, recurrent: severe without psychotic features

3. Identify specifiers - check all that apply:

   ☐ None
   ☐ Melancholic features
   ☐ Atypical features
   ☐ Seasonal pattern

4. Has the subject ever received treatment for the symptoms of depression? ☐ Yes ☐ No

If **Yes**, describe the treatment _____

_____

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SLEEP HISTORY

SEE PAGE 11

Have you experienced previous sleeping problems? ☐ Yes ☐ No

If YES, please detail below:

LABORATORY COLLECTIONS

DRUG SCREENING (URINE)

Exact date and time of sampling

Day Month Year

24hr:min

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below.

☐ Yes ☐ No

Type of drug	Comment

ALCOHOL BREATH TEST

Exact date and time of test

Day Month Year

24hr:min

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

SITTING VITAL SIGNS

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR	RESPIRATORY RATE	ORAL TEMPERATURE
			SYSTOLIC	DIASTOLIC	(bpm)	(breaths/min)	(°C)
30 mins pre-dose	Day Month Year	24hr:min					
+60 mins post-dose	Day Month Year	24hr:min					
+10 hrs post-dose	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 3)	Page
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12-LEAD ECG

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
30 mins pre-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+60 mins post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+10 hrs post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	

GlaxoSmithKline

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PRE-SLEEP QUESTIONNAIRE

SEE PAGE 23

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DOSING DETAILS

SEE PAGE 25

Date and time of dosing	Day Month Year	24hr:min

Dose checked and administered by: _____

Dose checked and witnessed by: _____

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 3, NIGHT 2)	Page
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NOCTURNAL PSG

Was a Nocturnal PSG completed?	☐ Yes ☐ No
If **'YES'**, please indicate date and time:	
Date and Time Nocturnal PSG completed:	Day Month Year 24hr:min

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 3, DAY 2)	Visit Date & Time Day	Month	Year	24hr:min	Page
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LEEDS SLEEP EVALUATION QUESTIONNAIRE

SEE PAGE 27

GlaxoSmithKline

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LEEDS SLEEP EVALUATION QUESTIONNAIRE (LSEQ) Continued

See Page 28

How did you feel on waking?

8. Tired ——— Alert

How do you feel now?

9. Tired ——— Alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual ——— Less clumsy than usual

GlaxoSmithKline

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POST-SLEEP QUESTIONNAIRE

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DIGIT SYMBOL SUBSTITUTION TEST (DSST)

SEE PAGE 30

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MEMORY HVLT-R

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

ROMBERG TEST, HEEL-TO-TOE TEST

Date and Time: ☐☐ ☐☐ ☐☐ Day Month Year ☐☐ 24hr:min

Was the Romberg test and heel-to-toe test sucessfully completed? ☐ Yes ☐ No

GlaxoSmithKline

Project	Protocol	Subject Number	PSG SCREENING (VISIT 3, DAY 2)	Visit Date (Day Month Year)	Page
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STANFORD SLEEPINESS SCALE (SSS)

SEE PAGE 31

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PRIOR AND CONCOMITANT MEDICATION

ROUTE KEY:

IA	=	intra-articular
IAR	=	intra-arterial
ID	=	intra-dermal
IH	=	inhalation
IM	=	intra-muscular
IT	=	intra-thecal
IV	=	intra-venous
NA	=	nasal
PO	=	oral
PR	=	rectal
SC	=	subcutaneous
SL	=	sublingual
TD	=	transdermal
TO	=	topical
VA	=	vaginal

Other routes may be entered onto the form when appropriate, and will be coded prior to data entry.

Start Date - As a minimum the year must be stated.

If Medical History section is included indications on Prior Medication page must correlate utilizing the same terminology.

Indication on concomitant page must be recorded on the Adverse Events Page and expressed utilizing the same terminology.

If a medication was marked continuing at the initial visit (on the Prior and Concomitant Medication Page), but has since had a dosage change or has been stopped, it must be recorded on this form as a change with the start and end date.

GlaxoSmithKline

Project	Protocol	Subject Number	SCREENING	Page
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PCMED

PRIOR MEDICATION

Has the subject taken any medication within 30 days **PRIOR** to the first dose of study medication? ☐ Yes ☐ No ANYYN

If '**YES**', please record the medications below. (*DM Use)

DSPEC

*	Drug Name (Trade Name Preferred)	SINGLE Dose/Unit (e.g.500mg)	Frequency of this Dose (e.g.BID,PRN)	Route	Indication	Duration of Therapy (eg.6 years)	End Date	*	Continuing at end of study?
	DRUGNAME	SDOSE	FREQTXT	ROUTE	INDICAT	DURMED DURUNITS	STOPD Day Month Year		CONTYN ☐ Yes ☐ No
							Day Month Year		☐ Yes ☐ No
							Day Month Year		☐ Yes ☐ No
							Day Month Year		☐ Yes ☐ No

Mark box if medications continue on next page. ☐

BASELINE SIGNS AND SYMPTOMS

DEFINITIONS

INTENSITY (Maximum)

MILD	*An event which is easily tolerated*
MODERATE	*An event which is sufficiently discomforting to interfere with daily activity*
SEVERE	*An event which prevents normal everyday activities*

RELATIONSHIP TO INVESTIGATIONAL STUDY PROCEDURES

NOT RELATED	*The event is definitely not related to the study procedures*
UNLIKELY	*There are other more likely causes and the study procedures are not suspected as a cause*
SUSPECTED (REASONABLE POSSIBILITY)	*A direct cause and effect relationship between the study procedures and the event has not been demonstrated but there is a reasonable possibility that the study procedures were involved*
PROBABLE	*There probably is a direct cause and effect relationship between the event and the study procedures*

SERIOUS BASELINE EVENT

A serious baseline event is any untoward medical occurrence that, at any dose:

a) results in death.

b) is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) requires hospitalisation or prolongation of existing hospitalisation.

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) is a congenital anomaly/birth defect.

f) other.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

IF A SERIOUS BASELINE EVENT OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two events

PLEASE REMEMBER ALL QUESTIONS ON BASELINE SIGNS AND SYMPTOMS FORM SHOULD BE COMPLETED

GlaxoSmithKline

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BASELINE SIGNS AND SYMPTOMS ACE

Please note any SERIOUS events should not be recorded on this page, but on the Serious Adverse Event pages provided.

Record any Baseline events (using standard medical terminology) observed or elicited by the following direct question to subject: "How do you feel?"
Provide the diagnosis, NOT symptoms where possible. (One baseline event per column)
If no baseline events experienced, please mark box ☐ *and sign form below* ANYYN .

Baseline Sign/Symptom	AE	
GSK Use		
Onset Date and Time STARTD	Day Month Year STARTT 24hr:min	Day Month Year 24hr:min
End Date and Time *(If ongoing please leave blank)* STOPD	Day Month Year STOPT 24hr:min	Day Month Year 24hr:min
Outcome OUTCOME **If subject died, please inform GSK within 24 hours and complete Form D*	☐ Resolved ☐ Ongoing ☐ Died*	☐ Resolved ☐ Ongoing ☐ Died*
Event Course COURSE	☐ Intermittent → No. of episodes ☐ EPISODES. ☐ Constant	☐ Intermittent → No. of episodes ☐ ☐ Constant
Intensity (maximum) INTENSIT	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Relationship to study procedures performed prior to randomisation RELATN.	☐ Not related ☐ Unlikely ☐ Suspected ☐ Probable (reasonable possibility)	☐ Not related ☐ Unlikely ☐ Suspected ☐ Probable (reasonable possibility)
Corrective Therapy *If 'Yes', Please record on Prior Medication form.* TREATYN	☐ Yes ☐ No	☐ Yes ☐ No
Was subject withdrawn due to this event? WITHAE	☐ Yes ☐ No	☐ Yes ☐ No

Investigator's Signature:_____ Date: Day Month Year

REPORTING SERIOUS ADVERSE EVENT (SAE)

INSTRUCTIONS

SAEs MUST BE REPORTED TO GLAXOSMITHKLINE WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Event Course' blank and update it later

SIGN AND DATE THE SAE PAGE

PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE

- *Demography*
- *Significant Medical/Surgical History and Physical Examination*
- *Study Medication Record*
- *Concomitant Medication*
- *Form D (if applicable)*

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local GSK CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local GSK CRA/Medical monitor within 24 hours

GlaxoSmithKline

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SERIOUS ADVERSE EVENT (SAE)

ACE

Person Reporting SAE *(Please print clearly)* ____________________		**AEGIS Number**
Serious Adverse Event *(Please print clearly)*	AE	Specify reason(s) for considering this a serious AE. Mark all that apply.
GSK Use		[A] ☐ results in Death SERCOD.
Onset Date and Time STARTD	Day Month Year; 24hr:min STARTT	[B] ☐ life threatening
End Date and Time STOPD. *(If ongoing please leave blank)*	Day Month Year; 24hr:min STOPT	[C] ☐ requires hospitalisation or prolongation of existing hospitalization
Outcome **If subject died, please inform GSK within 24 hours and complete Form D* OUTCOME	☐ Resolved ☐ Ongoing ☐ Died*	[D] ☐ results in disability/incapacity; [E] ☐ congenital anomaly/birth defect
Event Course COURSE	☐ Intermittent ☐ Constant → No. of episodes ☐ EPISODES	[F] ☐ other (see definition)
Intensity *(maximum)* INTENSIT	☐ Mild ☐ Moderate ☐ Severe	*Please specify* __________
Action Taken with Respect to Investigational Drug ACTION	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No. **If study medication was interrupted, stopped or dose reduced:** Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No. If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug RELATN	☐ Not related ☐ Unlikely → ☐ Suspected (reasonable possibility) ☐ Probable	**Assessment** The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) *Please specify* ______________
Corrective Therapy TREATYN *If 'Yes', Please record on Concomitant Medication form*	☐ Yes ☐ No	☐ Another condition (eg, condition under study, intercurrent illness) *Please specify* ______________
Was subject withdrawn due to this AE ? WITHAE	☐ Yes ☐ No	☐ Another drug *Please specify* ______________

SERIOUS ADVERSE EVENT (SAE) (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Year			
	Day Month Year			
	Day Month Year			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site? ☐ No ☐ Yes

Randomisation/Study Medication Number: ☐☐☐☐☐

Investigator's Signature: _____
(confirming that the above data are accurate and complete)
Please PRINT Name: _____
Day Month Year

GSK Medical Monitor's Signature: _____

Please PRINT Name: _____
Day Month Year

GlaxoSmithKline

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INVESTIGATOR'S STATEMENT

Investigator's checklist:	**Tick when done**
- Check all Baseline Signs and Symptoms form is up to date and complete	☐
- Check that the Prior Medication form is up to date	☐
- Check that all appropriate pages are signed (thus indicating completion) and dated	☐
- Check that laboratory results are included	☐

I certify that the observations and findings are recorded correctly and completely in this CRF.

Investigator: _____ Date: ☐☐ ☐☐ ☐☐☐☐
Day Month Year

GlaxoSmithKline

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A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia.

CASE REPORT FORM

Investigator:

Study Location:

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: [redacted]

GlaxoSmithKline Responsible Physician: [redacted] **M.D.**

GlaxoSmithKline Clinical Monitor: [redacted]

Location:

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: [redacted]

GENERAL INSTRUCTIONS

The plastic writing board in the back of the binder should be used to divide each set of pages before writing on them with a ball-point pen.
Print clearly in CAPITAL LETTERS using a black ball-point pen and press firmly so that all copies are legible. DO NOT print in areas designated for GlaxoSmithKline use only. Answer all questions on every page. If a test is not done write ND, if zero write 0.

IMPORTANT: **Errors should be crossed out with a single line and the alteration made as close to the original as possible. All alterations must be printed, initialed and dated. Do not use masking fluid.**

Please ensure that the subject consent form is signed.

Please ensure that all ECG traces and any other loose data are attached at the back of the book.

Please notify study monitor of all protocol deviations.

Record all concomitant medications and adverse events. Please notify GlaxoSmithKline within 24 hours of all 'serious' occurrences.

Please complete subject study conclusion form.

DATE - Use the following three - letter abbreviation for month:

January	=	**JAN**	**July**	=	**JUL**
February	=	**FEB**	**August**	=	**AUG**
March	=	**MAR**	**September**	=	**SEP**
April	=	**APR**	**October**	=	**OCT**
May	=	**MAY**	**November**	=	**NOV**
June	=	**JUN**	**December**	=	**DEC**

EXAMPLE: | 0 1 | J A N | 2 0 0 0 | = **1st January 2000**
Day Month Year

TIME - Unless specified otherwise, use the 24 hour clock: **00:00 - 23:59**

EXAMPLE: | 1 5 | 3 0 | = **3:30 p.m.**
24hr:min

GlaxoSmithKline

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PHARMACOGENETIC RESEARCH

GENPRO.

Consent for Pharmacogenetic Research

Has informed consent been obtained for Pharmacogenetic Research?

☐ Yes ☐ No GPCNS.

If Yes, record the date informed consent obtained for Pharmacogenetic Research GPCNSDT

Day Month Year

If No, ✓ one reason:

[1] ☐ Subject declined GPCNSRS

[2] ☐ Subject not asked by Investigator

[z] ☐ Other, specify GPCNSOTH.

Blood Sample Collection

Has a blood sample been collected for Pharmacogenetic Research?

☐ No ☐ Yes GP SMPCOL

If YES, record the date the sample was taken: GPSMPDT.

Day Month Year

Withdrawal of Consent

Has this subject withdrawn consent for Pharmacogenetic Research?

☐ Yes ☐ No GPCNSWD

Blood Sample Destruction

Has a request been made for sample destruction?

☐ No ☐ Yes GPDSREQ

If Yes, ✓ one reason:

[1] ☐ Subject requested GPDSRS

[z] ☐ Other, specify GPDSOTH

GlaxoSmithKline

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SLEEP HABIT CHANGES REVIEW

PSTAT

Have you experienced any sleep habit changes? ☐ Yes ☐ No ANYYN

PSTATQ=1514

If YES, please detail below:

ANSTXT

GlaxoSmithKline

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PREGNANCY TEST (Females only)

Was a pregnancy test carried out? ☐ Yes ☐ No

If **'No'**, please specify reason _____

If **'YES'**, please indicate date and time of test and result:

Date and Time of pregnancy test: ☐☐ ☐☐ ☐☐☐☐ (Day Month Year) ☐☐ (24hr:min)

Positive ☐ Negative ☐

If **'Positive'**, withdraw the subject from the study.

Please mark box for test type

Dipstick urine HCG ☐

Serum HCG ☐

Other ☐ → please specify _____

Laboratory name, if applicable _____

ensure result is included on laboratory report

GlaxoSmithKline

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PK SAMPLING

PSTAT. (XPSTATG = 494)

Instructions: Please collect a 5ml blood sample for pharmacokinetics at the times shown below.

Time relative to start of dose PCBS	Date ANSDAT	Actual Time ANSTIM	Sample Taken	Comments
Pre-dose	Day Month Year	24hr:min	☐ Yes ☐ No	
+10 hours from dosing	Day Month Year	24hr:min	☐ Yes ☐ No	

GlaxoSmithKline

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LABORATORY COLLECTIONS

DRUG SCREENING (URINE)

Exact date and time of sampling

Day Month Year 24hr:min

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below.

☐ Yes ☐ No

Type of drug	Comment

ALCOHOL BREATH TEST

Exact date and time of test

Day Month Year 24hr:min

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

GlaxoSmithKline

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SITTING VITAL SIGNS

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR	RESPIRATORY RATE	ORAL TEMPERATURE
			SYSTOLIC	DIASTOLIC	(bpm)	(breaths/min)	(°C)
30 mins pre-dose	Day Month Year	24hr:min					
+60 mins post-dose	Day Month Year	24hr:min					
+10 hrs post-dose	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

GlaxoSmithKline

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12-LEAD ECG

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
+30 mins pre-dose	☐☐ ☐☐ ☐☐☐☐ Day Month Year	☐☐ 24hr:min						☐ Yes ☐ No	
+60 mins post-dose	☐☐ ☐☐ ☐☐☐☐ Day Month Year	☐☐ 24hr:min						☐ Yes ☐ No	
+10 hrs post-dose	☐☐ ☐☐ ☐☐☐☐ Day Month Year	☐☐ 24hr:min						☐ Yes ☐ No	
Unsched	☐☐ ☐☐ ☐☐☐☐ Day Month Year	☐☐ 24hr:min						☐ Yes ☐ No	
Unsched	☐☐ ☐☐ ☐☐☐☐ Day Month Year	☐☐ 24hr:min						☐ Yes ☐ No	

PRE-SLEEP QUESTIONNAIRE

SEE PAGE 27

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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MEMORY HVLT-R

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GlaxoSmithKline

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DOSING DETAILS

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Date and time of dosing

Day Month Year 24hr:min

Dose checked and administered by: _____

Dose checked and witnessed by: _____

GlaxoSmithKline

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NOCTURNAL PSG

Was a Nocturnal PSG completed? ☐ Yes ☐ No

If **'YES'**, please indicate date and time:

Date and Time Nocturnal PSG completed: Day Month Year 24hr:min

GlaxoSmithKline

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PHYSICAL EXAMINATION

DATE Day Month Year TIME 24hr:min

Has there been any change from the last examination (screening)?

☐ No

☐ Yes

Record below. Any **clinically relevant worsening** since the last exam must be recorded on the Adverse Events page.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 4, DAY 1	Visit Date & Time				Page
				Day	Month	Year	24hr:min	
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LEEDS SLEEP EVALUATION QUESTIONNAIRE

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This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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LEEDS SLEEP EVALUATION QUESTIONNAIRE (LSEQ) Continued

See Page 28

How did you feel on waking?

8. Tired ——— Alert

How do you feel now?

9. Tired ——— Alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual ——— Less clumsy than usual

GlaxoSmithKline

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POST-SLEEP QUESTIONNAIRE

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DIGIT SYMBOL SUBSTITUTION TEST (DSST)

GENERAL (GPARAM = DSST)

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

MEMORY HVLT-R

SEE PAGE 24

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

ROMBERG TEST, HEEL-TO-TOE TEST

SEE PAGE 30

Date and Time: ☐☐ ☐☐ ☐☐☐☐ Day Month Year ☐☐:☐☐ 24hr:min

Was the Romberg test and heel-to-toe test sucessfully completed? ☐ Yes ☐ No

GlaxoSmithKline

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STANFORD SLEEPINESS SCALE (SSS)

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GlaxoSmithKline

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PK SAMPLING

SEE PAGE 54

Instructions: Please collect a 5ml blood sample for pharmacokinetics at the times shown below.

Time relative to start of dose	Date	Actual Time	Sample Taken	Comments
Pre-dose	Day Month Year	24hr:min	☐ Yes ☐ No	
+10 hours from dosing	Day Month Year	24hr:min	☐ Yes ☐ No	

GlaxoSmithKline

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SLEEP HABIT CHANGES REVIEW

SEE PAGE 52

Have you experienced any sleep habit changes? ☐ Yes ☐ No

If YES, please detail below:

GlaxoSmithKline

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LABORATORY COLLECTIONS

DRUG SCREENING (URINE)

Exact date and time of sampling

Day Month Year 24hr:min

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below.

☐ Yes ☐ No

Type of drug	Comment

ALCOHOL BREATH TEST

Exact date and time of test

Day Month Year 24hr:min

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

GlaxoSmithKline

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SITTING VITAL SIGNS

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STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR	RESPIRATORY RATE	ORAL TEMPERATURE
			SYSTOLIC	DIASTOLIC	(bpm)	(breaths/min)	(°C)
30 mins pre-dose	Day Month Year	24hr:min					
+60 mins post-dose	Day Month Year	24hr:min					
+10 hrs post-dose	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

GlaxoSmithKline

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12-LEAD ECG

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
+30 mins pre-dose	☐☐ Day ☐☐ Month ☐☐☐☐ Year	☐☐ 24hr:min						☐ Yes ☐ No	
+60 mins post-dose	☐☐ Day ☐☐ Month ☐☐☐☐ Year	☐☐ 24hr:min						☐ Yes ☐ No	
+10 hrs post-dose	☐☐ Day ☐☐ Month ☐☐☐☐ Year	☐☐ 24hr:min						☐ Yes ☐ No	
Unsched	☐☐ Day ☐☐ Month ☐☐☐☐ Year	☐☐ 24hr:min						☐ Yes ☐ No	
Unsched	☐☐ Day ☐☐ Month ☐☐☐☐ Year	☐☐ 24hr:min						☐ Yes ☐ No	

GlaxoSmithKline

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PRE-SLEEP QUESTIONNAIRE

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DOSING DETAILS

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Date and time of dosing

Day Month Year 24hr:min

Dose checked and administered by: _____

Dose checked and witnessed by: _____

GlaxoSmithKline

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NOCTURNAL PSG

Was a Nocturnal PSG completed? ☐ Yes ☐ No

If **'YES'**, please indicate date and time:

Date and Time Nocturnal PSG completed: Day Month Year 24hr:min

GlaxoSmithKline

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PHYSICAL EXAMINATION

DATE Day Month Year TIME 24hr:min

Has there been any change from the last examination (Visit 4)?

☐ No

☐ Yes

Record below. Any **clinically relevant worsening** since the last exam must be recorded on the Adverse Events page.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 5, DAY 2	Visit Date & Time				Page
				Day	Month	Year	24hr:min	
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LEEDS SLEEP EVALUATION QUESTIONNAIRE

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GlaxoSmithKline

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LEEDS SLEEP EVALUATION QUESTIONNAIRE (LSEQ) Continued

SEE PAGE 28

How did you feel on waking?

8. Tired ——— Alert

How do you feel now?

9. Tired ——— Alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual ——— Less clumsy than usual

GlaxoSmithKline

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POST-SLEEP QUESTIONNAIRE

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DIGIT SYMBOL SUBSTITUTION TEST (DSST)

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MEMORY HVLT-R

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

ROMBERG TEST, HEEL-TO-TOE TEST

Date and Time: Day Month Year 24hr:min

Was the Romberg test and heel-to-toe test sucessfully completed? ☐ Yes ☐ No

GlaxoSmithKline

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			VISIT 5, DAY 2	Day	Month	Year	
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STANFORD SLEEPINESS SCALE (SSS)

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This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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PREGNANCY TEST (Females only)

Was a pregnancy test carried out? ☐ Yes ☐ No

If **'No'**, please specify reason _____

If **'YES'**, please indicate date and time of test and result:

Date and Time of pregnancy test: ☐☐ ☐☐ ☐☐☐☐ (Day Month Year) ☐☐:☐☐ (24hr:min)

Positive ☐ Negative ☐

If **'Positive'**, withdraw the subject from the study.

Please mark box for test type

Dipstick urine HCG ☐

Serum HCG ☐

Other ☐ → please specify _____

Laboratory name, if applicable _____

ensure result is included on laboratory report

GlaxoSmithKline

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PK SAMPLING

SEE PAGE 54

Instructions: Please collect a 5ml blood sample for pharmacokinetics at the times shown below.

Time relative to start of dose	Date	Actual Time	Sample Taken	Comments
Pre-dose	Day Month Year	24hr:min	☐ Yes ☐ No	
+10 hours from dosing	Day Month Year	24hr:min	☐ Yes ☐ No	

GlaxoSmithKline

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SLEEP HABIT CHANGES REVIEW

SEE PAGE 52

Have you experienced any sleep habit changes? ☐ Yes ☐ No

If YES, please detail below:

GlaxoSmithKline

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LABORATORY COLLECTIONS

DRUG SCREENING (URINE)

Exact date and time of sampling

Day Month Year 24hr:min

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below. ☐ Yes ☐ No

Type of drug	Comment

ALCOHOL BREATH TEST

Exact date and time of test

Day Month Year 24hr:min

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

GlaxoSmithKline

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SITTING VITAL SIGNS

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STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR (bpm)	RESPIRATORY RATE (breaths/min)	ORAL TEMPERATURE (°C)
			SYSTOLIC	DIASTOLIC			
30 mins pre-dose	Day Month Year	24hr:min					
+60 mins post-dose	Day Month Year	24hr:min					
+10 hrs post-dose	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

GlaxoSmithKline

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12-LEAD ECG

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
+30 mins pre-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+60 mins post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+10 hrs post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	

GlaxoSmithKline

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PRE-SLEEP QUESTIONNAIRE

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GlaxoSmithKline

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MEMORY HVLT-R

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GlaxoSmithKline

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DOSING DETAILS

SEE PAGE 25

Date and time of dosing

Day Month Year 24hr:min

Dose checked and administered by: _____

Dose checked and witnessed by: _____

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 6, NIGHT 1	Page
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NOCTURNAL PSG

Was a Nocturnal PSG completed? ☐ Yes ☐ No

If **'YES'**, please indicate date and time:

Date and Time Nocturnal PSG completed: Day Month Year 24hr:min

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 6, DAY 1	Page
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PHYSICAL EXAMINATION

DATE Day Month Year TIME 24hr:min

Has there been any change from the last examination (Visit 5)?

☐ No

☐ Yes

Record below. Any **clinically relevant worsening** since the last exam must be recorded on the Adverse Events page.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 6, DAY 1	Visit Date & Time				Page
				Day	Month	Year	24hr:min	
679769	903							93

LEEDS SLEEP EVALUATION QUESTIONNAIRE

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GlaxoSmithKline

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LEEDS SLEEP EVALUATION QUESTIONNAIRE (LSEQ) Continued

SEE PAGE 28

How did you feel on waking?

8. Tired ——— Alert

How do you feel now?

9. Tired ——— Alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual ——— Less clumsy than usual

GlaxoSmithKline

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POST-SLEEP QUESTIONNAIRE

SEE PAGE 29

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GlaxoSmithKline

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DIGIT SYMBOL SUBSTITUTION TEST (DSST)

SEE PAGE 30

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

MEMORY HVLT-R

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

ROMBERG TEST, HEEL-TO-TOE TEST

Date and Time: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year ☐☐ 24hr:min

Was the Romberg test and heel-to-toe test sucessfully completed? ☐ Yes ☐ No

GlaxoSmithKline

Project	Protocol	Subject Number		Visit Date			Page
				Day	Month	Year	
679769	903		VISIT 6, DAY 1				97

STANFORD SLEEPINESS SCALE (SSS)

SEE PAGE 31

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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PK SAMPLING

SEE PAGE 54

Instructions: Please collect a 5ml blood sample for pharmacokinetics at the times shown below.

Time relative to start of dose	Date	Actual Time	Sample Taken	Comments
Pre-dose	Day Month Year	24hr:min	☐ Yes ☐ No	
+10 hours from dosing	Day Month Year	24hr:min	☐ Yes ☐ No	

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, NIGHT 2	Page
679769	903			99

SLEEP HABIT CHANGES REVIEW

SEE PAGE 52

Have you experienced any sleep habit changes? ☐ Yes ☐ No

If YES, please detail below:

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, NIGHT 2	Page
679769	903			100

LABORATORY COLLECTIONS

DRUG SCREENING (URINE)

Exact date and time of sampling

Day Month Year 24hr:min

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below.

☐ Yes ☐ No

Type of drug	Comment

ALCOHOL BREATH TEST

Exact date and time of test

Day Month Year 24hr:min

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7	Page
679769	903			101

SITTING VITAL SIGNS

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR	RESPIRATORY RATE	ORAL TEMPERATURE
			SYSTOLIC	DIASTOLIC	(bpm)	(breaths/min)	(°C)
30 mins pre-dose	Day Month Year	24hr:min					
+60 mins post-dose	Day Month Year	24hr:min					
+10 hrs post-dose	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

GlaxoSmithKline

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12-LEAD ECG

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
+30 mins pre-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+60 mins post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+10 hrs post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, NIGHT 2	Page
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PRE-SLEEP QUESTIONNAIRE

SEE PAGE 23

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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DOSING DETAILS

SEE PAGE 25

Date and time of dosing

Day Month Year 24hr:min

Dose checked and administered by: _____

Dose checked and witnessed by: _____

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, NIGHT 2	Page
679769	903			105

NOCTURNAL PSG

Was a Nocturnal PSG completed? ☐ Yes ☐ No

If **'YES'**, please indicate date and time:

Date and Time Nocturnal PSG completed: Day Month Year 24hr:min

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, DAY 2	Page
679769	903			106

PHYSICAL EXAMINATION

DATE Day Month Year TIME 24hr:min

Has there been any change from the last examination (Visit 6)?

☐ No

☐ Yes

Record below. Any **clinically relevant worsening** since the last exam must be recorded on the Adverse Events page.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, DAY 2	Visit Date & Time (Day / Month / Year / 24hr:min)	Page
679769	903				107

LEEDS SLEEP EVALUATION QUESTIONNAIRE

SEE PAGE 27

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, DAY 2	Page
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LEEDS SLEEP EVALUATION QUESTIONNAIRE (LSEQ) Continued SEE ~~PAGE~~ 28

How did you feel on waking?

8. Tired ——————————— Alert

How do you feel now?

9. Tired ——————————— Alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual ——————————— Less clumsy than usual

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, DAY 2	Page
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POST-SLEEP QUESTIONNAIRE

SEE PAGE 29

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, DAY 2	Page
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DIGIT SYMBOL SUBSTITUTION TEST (DSST)

SEE PAGE 30

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

MEMORY HVLT-R

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

ROMBERG TEST, HEEL-TO-TOE TEST

Date and Time: Day Month Year 24hr:min

Was the Romberg test and heel-to-toe test sucessfully completed? ☐ Yes ☐ No

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 7, DAY 2	Visit Date (Day / Month / Year)	Page
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STANFORD SLEEPINESS SCALE (SSS)

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GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8, NIGHT 1	Page
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SLEEP HABIT CHANGES REVIEW

SEE PAGE 52

Have you experienced any sleep habit changes? ☐ Yes ☐ No

If YES, please detail below:

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8 PRE-DOSE	Page
679769	903			113

PREGNANCY TEST (Females only)

Was a pregnancy test carried out? ☐ Yes ☒ No

If **'No'**, please specify reason _____

If **'YES'**, please indicate date and time of test and result:

Date and Time of pregnancy test: ☐☐ ☐☐ ☐☐☐☐ (Day Month Year) ☐☐ (24hr:min)

Positive ☐ Negative ☐

If **'Positive'**, withdraw the subject from the study.

Please mark box for test type

Dipstick urine HCG ☐

Serum HCG ☐

Other ☐ → please specify _____

Laboratory name, if applicable _____

ensure result is included on laboratory report

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8	Page
679769	903			114

PK SAMPLING

SEE PAGE 54

Instructions: Please collect a 5ml blood sample for pharmacokinetics at the times shown below.

Time relative to start of dose	Date	Actual Time	Sample Taken	Comments
Pre-dose	Day Month Year	24hr:min	☐ Yes ☐ No	
+10 hours from dosing	Day Month Year	24hr:min	☐ Yes ☐ No	

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8, NIGHT 1	Page
679769	903			115

LABORATORY COLLECTIONS

DRUG SCREENING (URINE)

Exact date and time of sampling

Day Month Year 24hr:min

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below. ☐ Yes ☐ No

Type of drug	Comment

ALCOHOL BREATH TEST

Exact date and time of test

Day Month Year 24hr:min

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

GlaxoSmithKline

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SITTING VITAL SIGNS

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR	RESPIRATORY RATE	ORAL TEMPERATURE
			SYSTOLIC	DIASTOLIC	(bpm)	(breaths/min)	(°C)
30 mins pre-dose	Day Month Year	24hr:min					
+60 mins post-dose	Day Month Year	24hr:min					
+10 hrs post-dose	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8	Page
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12-LEAD ECG

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
+30 mins pre-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+60 mins post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+10 hrs post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	

GlaxoSmithKline

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PRE-SLEEP QUESTIONNAIRE

SEE PAGE 23

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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MEMORY HVLT-R

SEE PAGE 24

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GlaxoSmithKline

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DOSING DETAILS

SEE PAGE 25

Date and time of dosing

Day Month Year 24hr:min

Dose checked and administered by: _____

Dose checked and witnessed by: _____

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8, NIGHT 1	Page
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NOCTURNAL PSG

Was a Nocturnal PSG completed? ☐ Yes ☐ No

If **'YES'**, please indicate date and time:

Date and Time Nocturnal PSG completed: ☐☐ Day ☐☐ Month ☐☐☐☐ Year ☐☐ 24hr:min

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8, DAY 1	Page
679769	903			122

PHYSICAL EXAMINATION

DATE Day Month Year TIME 24hr:min

Has there been any change from the last examination (visit 7)?

☐ No

☐ Yes

Record below. Any **clinically relevant worsening** since the last exam must be recorded on the Adverse Events page.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8, DAY 1	Visit Date & Time				Page
				Day	Month	Year	24hr:min	
679769	903							123

LEEDS SLEEP EVALUATION QUESTIONNAIRE

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[redacted]

GlaxoSmithKline

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LEEDS SLEEP EVALUATION QUESTIONNAIRE (LSEQ) Continued

See page 28

How did you feel on waking?

8. Tired ——— Alert

How do you feel now?

9. Tired ——— Alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual ——— Less clumsy than usual

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8, DAY 1	Page
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POST-SLEEP QUESTIONNAIRE

SEE PAGE 29

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 8, DAY 1	Page
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DIGIT SYMBOL SUBSTITUTION TEST (DSST)

SEE PAGE 30

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

MEMORY HVLT-R

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

ROMBERG TEST, HEEL-TO-TOE TEST

Date and Time: Day Month Year 24hr:min

Was the Romberg test and heel-to-toe test sucessfully completed? ☐ Yes ☐ No

GlaxoSmithKline

Project	Protocol	Subject Number		Visit Date			Page
679769	903		VISIT 8, DAY 1	Day	Month	Year	127

STANFORD SLEEPINESS SCALE (SSS)

SEE PAGE 31

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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PK SAMPLING

SEE PAGE 54

Instructions: Please collect a 5ml blood sample for pharmacokinetics at the times shown below.

Time relative to start of dose	Date	Actual Time	Sample Taken	Comments
Pre-dose	Day Month Year	24hr:min	☐ Yes ☐ No	
+10 hours from dosing	Day Month Year	24hr:min	☐ Yes ☐ No	

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9, NIGHT 2	Page
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SLEEP HABIT CHANGES REVIEW

SEE PAGE 52

Have you experienced any sleep habit changes? ☐ Yes ☐ No

If YES, please detail below:

GlaxoSmithKline

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LABORATORY COLLECTIONS

DRUG SCREENING (URINE)

Exact date and time of sampling Day Month Year 24hr:min

Were there any contra-indicated drugs detected?
If YES, please record all the relevant contra-indicated drugs below. ☐ Yes ☐ No

Type of drug	Comment

ALCOHOL BREATH TEST

Exact date and time of test Day Month Year 24hr:min

Positive ☐ Negative ☐

If positive please withdraw the subject from the study.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9	Page
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SITTING VITAL SIGNS

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR	RESPIRATORY RATE	ORAL TEMPERATURE
			SYSTOLIC	DIASTOLIC	(bpm)	(breaths/min)	(°C)
30 mins pre-dose	Day Month Year	24hr:min					
+60 mins post-dose	Day Month Year	24hr:min					
+10 hrs post-dose	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

GlaxoSmithKline

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12-LEAD ECG

SEE PAGE 13

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
+30 mins pre-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+60 mins post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
+10 hrs post-dose	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9, NIGHT 2	Page
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PRE-SLEEP QUESTIONNAIRE

SEE PAGE 23

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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DOSING DETAILS

SEE PAGE 25

Date and time of dosing

Day Month Year 24hr:min

Dose checked and administered by: _____

Dose checked and witnessed by: _____

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9, NIGHT 2	Page
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NOCTURNAL PSG

Was a Nocturnal PSG completed? ☐ Yes ☐ No

If **'YES'**, please indicate date and time:

Date and Time Nocturnal PSG completed: Day Month Year 24hr:min

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9, DAY 2	Page
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PREGNANCY TEST (Females only)

Was a pregnancy test carried out? ☐ Yes ☐ No

If **'No'**, please specify reason _____

If **'YES'**, please indicate date and time of test and result:

Date and Time of pregnancy test: ☐☐ ☐☐☐ ☐☐☐☐ (Day Month Year) ☐☐ (24hr:min)

Positive ☐ Negative ☐

If **'Positive'**, withdraw the subject from the study.

Please mark box for test type

Dipstick urine HCG ☐

Serum HCG ☐

Other ☐ → please specify _____

Laboratory name, if applicable _____

ensure result is included on laboratory report

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9, DAY 2	Page
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PHYSICAL EXAMINATION

DATE Day Month Year TIME 24hr:min

Has there been any change from the last examination (visit 7)?

☐ No

☐ Yes

Record below. Any **clinically relevant worsening** since the last exam must be recorded on the Adverse Events page.

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9, DAY 2	Page
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LABORATORY COLLECTIONS

SEE PAGE 14

CLINICAL CHEMISTRY & HEMATOLOGY - Ensure a blood sample has been taken for clinical chemistry and haematology analysis

Exact date and time of blood sampling

Day Month Year 24hr:min

Comments:

Are there **CLINICALLY SIGNIFICANT ABNORMAL** values?
If **YES**, please record diagnosis on the Adverse Events page. ☐ Yes ☐ No

URINALYSIS - Ensure a urine sample has been taken for urinalysis

Exact date and time of urine sampling

Day Month Year 24hr:min

Comments:

Are there **CLINICALLY SIGNIFICANT ABNORMAL** values?
If **YES**, please record diagnosis on the Adverse Events page. ☐ Yes ☐ No

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9, DAY 2	Visit Date & Time (Day / Month / Year / 24hr:min)	Page
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LEEDS SLEEP EVALUATION QUESTIONNAIRE

SEE PAGE 27

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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LEEDS SLEEP EVALUATION QUESTIONNAIRE (LSEQ) Continued SEE PAGE 28

How did you feel on waking?

8. Tired ——— Alert

How do you feel now?

9. Tired ——— Alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual ——— Less clumsy than usual

GlaxoSmithKline

Project	Protocol	Subject Number	VISIT 9, DAY 2	Page
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POST-SLEEP QUESTIONNAIRE

SEE PAGE 29

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

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DIGIT SYMBOL SUBSTITUTION TEST (DSST)

SEE PAGE 30

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

MEMORY HVLT-R

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

ROMBERG TEST, HEEL-TO-TOE TEST

Date and Time: ☐☐ ☐☐ ☐☐ Day Month Year ☐☐ 24hr:min

Was the Romberg test and heel-to-toe test sucessfully completed? ☐ Yes ☐ No

GlaxoSmithKline

Project	Protocol	Subject Number		Visit Date			Page
			VISIT 9, DAY 2	Day	Month	Year	
679769	903						143

STANFORD SLEEPINESS SCALE (SSS)

SEE PAGE 31

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION

DATE: Day Month Year TIME: 24hr:min

Was the physical examination?

☐ Normal

☐ Abnormal Record below:

GlaxoSmithKline

Project	Protocol	Subject Number	EARLY WITHDRAWAL/FOLLOW-UP	Page
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SEE PAGE 13

SITTING VITAL SIGNS

STUDY TIME	DATE	ACTUAL TIME	BP (mmHg)		HR (bpm)	RESPIRATORY RATE (breaths/min)	ORAL TEMPERATURE (°C)
			SYSTOLIC	DIASTOLIC			
Early Withdrawal/ Follow-up	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					
Unscheduled	Day Month Year	24hr:min					

12-LEAD ECG

STUDY TIME	DATE	ACTUAL TIME	HEART RATE (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTC (msec)	ECG NORMAL?	COMMENTS
Early Withdrawal/ Follow-up	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	
Unsched	Day Month Year	24hr:min						☐ Yes ☐ No	

GlaxoSmithKline

Project	Protocol	Subject Number	EARLY WITHDRAWAL/FOLLOW-UP	Page
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LABORATORY COLLECTIONS

SEE PAGE 14

CLINICAL CHEMISTRY & HAEMATOLOGY - Ensure a blood sample has been taken for clinical chemistry and haematology analysis

Exact date and time of blood sampling Day Month Year 24hr:min

Comments:

Are there **CLINICALLY SIGNIFICANT ABNORMAL** values?
If **YES**, please record diagnosis on the Adverse Events page. ☐ Yes ☐ No

URINALYSIS - Ensure a urine sample has been taken for urinalysis

Exact date and time of urine sampling Day Month Year 24hr:min

Comments:

Are there **CLINICALLY SIGNIFICANT ABNORMAL** values?
If **YES**, please record diagnosis on the Adverse Events page. ☐ Yes ☐ No

GlaxoSmithKline

Project	Protocol	Subject Number	EARLY WITHDRAWAL/FOLLOW-UP	Page
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SERUM PREGNANCY TEST (Females only)

Was a pregnancy test carried out? ☐ Yes ☒ No

If **'No'**, please specify reason _____

If **'YES'**, please indicate date and time of test and result:

Date and Time of pregnancy test: ☐☐ ☐☐ ☐☐☐☐ (Day Month Year) ☐☐ (24hr:min)

Positive ☐ Negative ☐

If **'Positive'**, withdraw the subject from the study.

POST-SLEEP QUESTIONNAIRE

SEE PAGE 29

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

GlaxoSmithKline

Project	Protocol	Subject Number	STUDY CONCLUSION	Page
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PREGNANCY INFORMATION

PSTAT.

Did the subject become pregnant during the study? (mark one box below)

[X] ☐ Not applicable (not of childbearing potential or male)

[N] ☐ No

PSTATQ = 534

[Y] ☐ Yes → If 'Yes' record details on Pregnancy Notification Form.

Did the female partner of a male subject become pregnant during the study? (mark one box below)

[X] ☐ Not applicable (subject is female, female partner not of childbearing potential or female partner)

[N] ☐ No

PSTATQ = 535.

[Y] ☐ Yes → If 'Yes' record details on Pregnancy Notification Form.

STUDY CONCLUSION

PATEND.

Did the subject complete the study as planned?

☐ Yes

ENDYN

☐ No → If **'NO'**, mark the one most appropriate category

[1] ☐ Adverse Event (complete Adverse Event Form)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Deviation from Protocol (including non-compliance)

[4] ☐ Lost to Follow-Up

} DISCODE

[5] ☐ Other, Please specify _____

Comments on reason for withdrawal:

ENDTXT

Date of Withdrawal: ☐☐ ☐☐ ☐☐☐☐ (Day Month Year) ENDDATE

Time of Withdrawal: ☐☐:☐☐ (24hr:min) ENDTIME

Date of Final Dose: ☐☐ ☐☐ ☐☐☐☐ (Day Month Year) LDOSD.

Time of Final Dose: ☐☐:☐☐ (24hr:min) LDOST

PRIOR AND CONCOMITANT MEDICATION

ROUTE KEY:

IA	=	intra-articular
IAR	=	intra-arterial
ID	=	intra-dermal
IH	=	inhalation
IM	=	intra-muscular
IT	=	intra-thecal
IV	=	intra-venous
NA	=	nasal
PO	=	oral
PR	=	rectal
SC	=	subcutaneous
SL	=	sublingual
TD	=	transdermal
TO	=	topical
VA	=	vaginal

Other routes may be entered onto the form when appropriate, and will be coded prior to data entry.

Start Date - As a minimum the year must be stated.

If Medical History section is included indications on Prior Medication page must correlate utilizing the same terminology.

Indication on concomitant page must be recorded on the Adverse Events Page and expressed utilizing the same terminology.

If a medication was marked continuing at the initial visit (on the Prior and Concomitant Medication Page), but has since had a dosage change or has been stopped, it must be recorded on this form as a change with the start and end date.

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CONCOMITANT MEDICATION

PCMED

Are there any concomitant medication **CHANGES** since the start of the study? ☐ Yes ☐ No ANYYN

If '**YES**', please record all medications used below. Where appropriate, medical conditions should be recorded on the Adverse Events Form, utilizing the same terminology. If a medication has had a dosage change it must be recorded with the start and stop date. (*DM Use)

*	Drug Name (Trade Name Preferred)	SINGLE Dose/Unit (eg.500mg)	Frequency of this Dose (e.g.BID,PRN)	Route	Indication	Start Date/Time (DSPEC)	*	End Date/Time (DSPEC)	*	Continuing at end of Study? CONTYN
	DRUGNAME	SDOSE	FREQTXT	ROUTE	INDICAT	START D Day Month Year 24hr:min START T		STOP D Day Month Year 24hr:min STOP T.		☐ Yes ☐ No
						Day Month Year 24hr:min		Day Month Year 24hr:min		☐ Yes ☐ No
						Day Month Year 24hr:min		Day Month Year 24hr:min		☐ Yes ☐ No
						Day Month Year 24hr:min		Day Month Year 24hr:min		☐ Yes ☐ No

Mark box if medications continue on next page. ☐

ADVERSE EVENTS (Non-serious)

DEFINITIONS

INTENSITY (maximum)	
MILD	Adverse Event which is easily tolerated.
MODERATE	Adverse Event sufficiently discomforting to interfere with daily activity.
SEVERE	Adverse Event which prevents normal everyday activities.

RELATIONSHIP TO INVESTIGATIONAL DRUG	
NOT RELATED	The adverse event is definitely not related to the test drug.
UNLIKELY	There are more likely causes and the drug is not suspected as a cause.
SUSPECTED (REASONABLE POSSIBILITY)	A direct cause and effect relationship between the drug and the adverse event has not been demonstrated but there is a reasonable possibility that the event was caused by the drug.
PROBABLE	There is probably a direct cause and effect relationship between the adverse event and the study drug.

SERIOUS ADVERSE EXPERIENCE (SAE)

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death.

b) is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) requires hospitalisation or prolongation of existing hospitalisation.

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) is a congenital anomaly/birth defect.

f) other.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two events

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EVENTS FORM SHOULD BE COMPLETED

GlaxoSmithKline

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ADVERSE EVENT

ACE

Please note any **SERIOUS** events should **not** be recorded on this page, but on the **Serious Adverse Event** pages provided.

Record any Adverse event (using standard medical terminology) observed or elicited by the following direct question to the subject: "*Do you feel different in any way since starting the treatment or since the last visit?*" Provide the diagnosis **not** symptoms where possible. (One adverse event per column)

If no adverse events, please mark box ☐ and sign form below ANYN

Adverse Event	AE	
GSK Use		
Onset Date/Time START D	Day Month Year START T 24hr:min	Day Month Year 24hr:min
End Date/Time (If ongoing, please leave blank) STOP D	Day Month Year STOP T 24hr:min	Day Month Year 24hr:min
Outcome OUTCOME	☐ Resolved ☐ Ongoing	☐ Resolved ☐ Ongoing
Event Course COURSE	☐ Intermittent ☐ Constant → No. of episodes ☐ EPISODES	☐ Intermittent ☐ Constant → No. of episodes ☐
Intensity (maximum) INTENSIT	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug ACTION	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug RELATN	☐ Not related ☐ Unlikely ☐ Suspected ☐ Probable (reasonable possibility)	☐ Not related ☐ Unlikely ☐ Suspected ☐ Probable (reasonable possibility)
Corrective Therapy. If "Yes", Please record on Concomitant Medication form TREATYN	☐ Yes ☐ No	☐ Yes ☐ No
Was subject withdrawn due to this AE? WITHAE	☐ Yes ☐ No	☐ Yes ☐ No

Mark box if Adverse Event continue on next page. ☐

Investigator's Signature: _____ Date: Day Month Year

GlaxoSmithKline

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ADVERSE EVENT

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Please note any **SERIOUS** events should **not** be recorded on this page, but on the **Serious Adverse Event** pages provided.

Record any Adverse event (using standard medical terminology) observed or elicited by the following direct question to the subject: "*Do you feel different in any way since starting the treatment or since the last visit?*" Provide the diagnosis **not** symptoms where possible. (One adverse event per column)

If no adverse events, please mark box ☐ and sign form below

Adverse Event		
GSK Use		
Onset Date/Time	Day Month Year 24hr:min	Day Month Year 24hr:min
End Date/Time (If ongoing, please leave blank)	Day Month Year 24hr:min	Day Month Year 24hr:min
Outcome	☐ Resolved ☐ Ongoing	☐ Resolved ☐ Ongoing
Event Course	☐ Intermittent ☐ Constant → No. of episodes ☐	☐ Intermittent ☐ Constant → No. of episodes ☐
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected ☐ Probable (reasonable possibility)	☐ Not related ☐ Unlikely ☐ Suspected ☐ Probable (reasonable possibility)
Corrective Therapy. If "Yes", Please record on Concomitant Medication form	☐ Yes ☐ No	☐ Yes ☐ No
Was subject withdrawn due to this AE?	☐ Yes ☐ No	☐ Yes ☐ No

Mark box if Adverse Event continue on next page. ☐

Investigator's Signature: _____ Date: Day Month Year

GlaxoSmithKline

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ADVERSE EVENT

SEE PAGE 151

Please note any **SERIOUS** events should **not** be recorded on this page, but on the **Serious Adverse Event** pages provided.

Record any Adverse event (using standard medical terminology) observed or elicited by the following direct question to the subject: "*Do you feel different in any way since starting the treatment or since the last visit?*" Provide the diagnosis **not** symptoms where possible. (One adverse event per column)

If no adverse events, please mark box ☐ and sign form below

Adverse Event		
GSK Use		
Onset Date/Time	Day Month Year 24hr:min	Day Month Year 24hr:min
End Date/Time (If ongoing, please leave blank)	Day Month Year 24hr:min	Day Month Year 24hr:min
Outcome	☐ Resolved ☐ Ongoing	☐ Resolved ☐ Ongoing
Event Course	☐ Intermittent →No. of episodes ☐ ☐ Constant	☐ Intermittent →No. of episodes ☐ ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy. If "Yes", Please record on Concomitant Medication form	☐ Yes ☐ No	☐ Yes ☐ No
Was subject withdrawn due to this AE?	☐ Yes ☐ No	☐ Yes ☐ No

Mark box if Adverse Event continue on next page. ☐

Investigator's Signature: _____ Date: Day Month Year

REPORTING SERIOUS ADVERSE EVENT (SAE)

INSTRUCTIONS

SAEs MUST BE REPORTED TO GLAXOSMITHKLINE WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Event Course' blank and update it later

SIGN AND DATE THE SAE PAGE

PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE

- *Demography*
- *Significant Medical/Surgical History and Physical Examination*
- *Study Medication Record*
- *Concomitant Medication*
- *Form D (if applicable)*

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local GSK CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local GSK CRA/Medical monitor within 24 hours

GlaxoSmithKline

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SERIOUS ADVERSE EVENT (SAE)

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Person Reporting SAE *(Please print clearly)*		**AEGIS Number**
Serious Adverse Event *(Please print clearly)*		Specify reason(s) for considering this a serious AE. Mark all that apply.
GSK Use		[A] ☐ results in Death
Onset Date and Time	Day Month Year 24hr:min	[B] ☐ life threatening
End Date and Time *(If ongoing please leave blank)*	Day Month Year 24hr:min	[C] ☐ requires hospitalisation or prolongation of existing hospitalization
Outcome **If subject died, please inform GSK within 24 hours and complete Form D*	☐ Resolved ☐ Ongoing ☐ Died*	[D] ☐ results in disability/incapacity [E] ☐ congenital anomaly/birth defect
Event Course	☐ Intermittent → No. of episodes ☐ ☐ Constant	[F] ☐ other (see definition)
Intensity *(maximum)*	☐ Mild ☐ Moderate ☐ Severe	*Please specify* __________
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No **If study medication was interrupted, stopped or dose reduced:** Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely → (Assessment) ☐ Suspected (reasonable possibility) ☐ Probable	**Assessment** The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) *Please specify* ______________
Corrective Therapy *If 'Yes', Please record on Concomitant Medication form*	☐ Yes ☐ No	☐ Another condition (eg, condition under study, intercurrent illness) *Please specify* ______________
Was subject withdrawn due to this AE ?	☐ Yes ☐ No	☐ Another drug *Please specify* ______________

SERIOUS ADVERSE EVENT (SAE) (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Month Year			
	Day Month Year			
	Day Month Year			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site? ☐ No ☐ Yes

Randomisation/Study Medication Number: ☐☐☐☐☐

Investigator's Signature: _____
(confirming that the above data are accurate and complete)
Please PRINT Name: _____
Day Month Year

GSK Medical Monitor's Signature: _____

Please PRINT Name: _____
Day Month Year

GlaxoSmithKline

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FORM D

Certified Cause of Death: _____

Date of Death ☐☐ ☐☐ ☐☐☐☐ Day Month Year

Complete Adverse Event Form.

Was an autopsy done?

☐ No

☐ Yes ⟶ please summarize findings (include diagnosis):

_____

_____

_____

_____

_____

Physician's Signature: _____

☐☐ ☐☐ ☐☐☐☐ Day Month Year

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INVESTIGATOR COMMENT LOG

Instructions: Use this form to document any other relevant information that is not noted elsewhere in the CRF.

Date of comment	CRF page number if applicable	Comment

GlaxoSmithKline

Project	Protocol	Subject Number	FOLLOW-UP	Page
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INVESTIGATOR'S STATEMENT

Investigator's checklist:	**Tick when done**
- Check all Adverse Event forms are up to date and complete	☐
- Check that the Concomitant Medication form is up to date	☐
- Check that all appropriate pages are signed (thus indicating completion) and dated	☐
- Check that laboratory results are included	☐

I certify that the observations and findings are recorded correctly and completely in this CRF.

Investigator: _____ Date: ☐☐ / ☐☐ / ☐☐☐☐
Day Month Year

Division:	Worldwide Development	**Document Number:**	VM2004/00033/01
Document Type:	Reporting and Analysis Plan Amendment	**Study Identifier:**	GW679769/903
Site of Issue:	Verona		
Classification:	Level 2	**Issue Date:**	08 AUG 05

Title:

Reporting and Analysis Plan for Protocol GW679769/903: A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia.

Abstract: (For Internal Use Only)

This Reporting and Analysis Plan describes all planned analyses of study GW679769/903.

This is a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia. After meeting entry criteria, subjects will participate in 3 separate 2-night PSG sessions in which they will be randomized to receive placebo or GW679769 at 30 mg or 90 mg.

Authors: [redacted]

Compound Numbers/Keywords (if applicable): GW679769

Distribution:

[redacted] CPSP, Verona
[redacted] CPDS, Harlow
[redacted] CPK/M&S, Verona
[redacted] CPDM, Verona
[redacted] CPDM, Verona
[redacted] Discovery Medicine, RTP
[redacted] Study Team Leader, RTP

Approval Page

Study Identifier: GW679769/903

Study Title: A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia.

Document/Version Number: VM2004/00033/01

Date of Issue: 08 AUG 05

Approver(s):	**Signature:**	**Date:**
[redacted] STL	Signature on file	

Approver(s):	**Signature:**	**Date:**
[redacted] Manager Statistics, CPSP	Signature on file	

Title:

Reporting and Analysis Plan for Protocol GW679769/903 : A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia.

VM2004/00033/01

Author(s):

[redacted] CPSP, Verona
[redacted] CPDS, Harlow
[redacted] CPK/M&S, Verona

Document/Version Number: VM2004/00033/01

Date of Issue: 08 AUG 05

Table of Contents

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area under the plasma concentration-time curve
AUC(0-τ)	Area under the plasma concentration-time curve over the dosing interval on multiple dosing
AUC(0-∞)	Area under the plasma concentration-time curve from time 0 (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the plasma concentration-time curve from zero (pre-dose) to the last quantifiable concentration
C_{max}	Maximum observed concentration
CIB or IB	Clinical investigator brochure or Investigator brochure
CPK	Clinical Pharmacokinetics
CPSP	Clinical Pharmacology Statistics and Programming
CRF	Case report form
HVLT-R	Hopkins Verbal Learning Test - Revised
DSM–IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSST	Digital Symbol Substitution Test
ECG	Electrocardiogram
EEG	Electroencephelogram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HR	Heart Rate
ITT	Intention to Treat
LOCF	Last observation carried forward
LPS	Latency to Persistent Sleep
LSEQ	Leeds Sleep Evaluation Questionnaire
MAOI	Monoamine oxidase inhibitor
MedRA	Medical Dictionary for Drug Regulatory Activities
MSDS	Material safety data sheet
Mg	Milligram
Min	Minute
mL	Milliliter
Ng	Nanograms
NK	Neurokinin
od	Once daily
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PP	per protocol
PSG	Polysomnographically
QC	Quality Control
REM	Rapid Eye Movement
RR	Respiratory Rate
SAE	Serious adverse event
SD	Standard deviation

SFA	Spindle Frequency Activity
SNP	Single Nucleotide Polymorphism
SOL	Sleep Onset Latency
SSS	Stanford Sleepiness Scale
SWS	Slow Wave Sleep
t1/2	Terminal phase half-life
T3U	T3 Uptake
t_{max}	First time of occurrence of Cmax
TST	Total Sleep Time
ULRR	Upper limit of the reference range
VAS	Visual Analog Scale
VC	Vigilance Control
WASO	Wake After Sleep Onset

1. INTRODUCTION

This amendment covers the following points:

- Handling of technical problems during PSG recordings
- Assessment of protocol violators and examination of subgroups
- deviations from the assumptions underlying analysis of variance (normal distribution of the residuals)
- "first night effect"
- HVLT-R analysis
- Additional graphical analyses

2. HANDLING OF TECHNICAL PROBLEMS

During the first part of the study some technical problems related to PSG data were noted as listed in the table below:

Sub.	Visit	Problem	Likely Effects on the Data

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

To handle the above listed problems and any other similar problem might happen in the second part of the study the following general rules will be applied:

When more than 10 minutes of PSG data are lost all the data regarding that night will be removed from the analyses.

When the minutes lost are not greater than 10 and if it is possible to guess the status of the subject (for instance we can assume that during the first and the last minutes of the period of observation the subjects is not sleeping) the sleep parameters will be adjusted

accordingly, otherwise all the data regarding that night will be removed from the analyses.

No action will be taken when EOG or EMG data are not recorded.

All the data will be listed and data with technical problems will be highlighted.

Additional analysis will be carried-out where all the nights with some technical problems will be removed from the analysis.

However, before the unblinding, a list with a description of all the technical problems pointed out (see previous tables) will be sent to a GSK team (to be defined). Cases will be analysed in order to define the management of each individual instance.

3. ASSESSMENT OF PROTOCOL VIOLATORS AND EXAMINATION OF SUBGROUPS

The respect of the inclusion criteria # 5 (listed below) will be checked.

On two screening PSGs (on single-blinded placebo administration at each night):

- *TST between 240 and 420 minutes on both nights.*
- *Mean LPS of 30 minutes or more, but not < 20 minutes on either night.*
- *Mean WASO of 30 minutes or more, with neither night < 20 minutes.*

A list of the subjects who does not meet these criteria will be included (Listing 3).

If this affects more than 10% of the study population a per-protocol population will be defined. Additional analyses on WASO, TST and LPS will be carried out in this population and removing any night with technical problems in PSG recordings.

Additional analyses on WASO, TST and LPS will be carried out also separately for subjects included and not included in the Interim Analysis.

4. DEVIATIONS FROM THE ASSUMPTION UNDERLYING ANALYSIS OF VARIANCE

During the Interim Analysis were noted some deviations from the assumptions underlying analysis of variance (normal distribution of the residual) for at least two keys parameters (WASO and LPS).

Therefore a log (as first attempt) or a rank transformation (if the assumptions will be still seriously violated) of WASO and LPS values will be applied. Results of the statistical comparisons will be reported in table 7.1 and Table 9.1

5. FIRST NIGHT EFFECT

The presence of a first night effect will be investigated:

- by means of the already planned plots by treatment and night (plots 1-6)
- and fitting the following model on WASO, TST, LPS single night values :

PROC MIXED data=... ;

class subject session treatment night ;

*model value= treatment session night treatment*night / ddfm=satterth ;*

*random subject subject*session ;*

6. HVLT-R ANALYSIS

Some additional information regarding this test are now available.

For each test, 4 scores will be derived and reported on the CRFs:

Total Recall, Delayed Recall, Retention and Recognition Discrimination Index.

Raw scores will be considered in the analyses.

Summary statistics by treatment and time point (Night 1, Day 1 and Day 2) will be presented in Table 14.

For each of the 4 scores the following model will be fitted:

PROC MIXED data=... ;

class subject session treatment rep ;

*model value= treatment session rep treatment*rep / ddfm=satterth ;*

*random subject subject*session ;*

where rep represents the 3 time points (Night 1, Day 1 and Day 2).

Treatment comparisons will be performed separately at each time point.

Additional analyses will be performed to investigate the carry-over effect (effect of the treatment received in the previous period) and the treatment by period interaction. In both the cases additional terms will be added to the original model. Tests of significance will be performed at the 5% level. Least squares mean values will be evaluated for each treatment. Estimates for treatment differences expressed in pair-wise basis will be calculated together with 95% corresponding confidence intervals. Error diagnostics from the residuals will be examined to ensure that the models do not depart from the

assumptions underlying analysis of variance. If the assumptions are seriously violated, transformations of the data or nonparametric methods will be considered.

Results of the statistical comparisons will be described in Table 15.

7. ADDITIONAL GRAPHICAL ANALYSES

The following additional plots will be provided:

Plot number 6.1: a bar graph where for each treatment group will be reported the LSmean percentage of the night spent in stage 1, stage2, SWS and REM

Plot numbers 6.2-6.4 : plots summarising the 95% C.I for treatment comparisons for WASO, TST, LPS (6.2) , WDS, WAS, Stage 1, Stage 2, SWS, REM, REM Latency (6.3), stage 1(%), stage 2 (%), SWS (%), REM (%) (6.4)

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

ANOVA MODEL : psg_m
Main Model

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

ANOVA MODEL : psg_m
Previous treatment ?

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

ANOVA MODEL : psg_m
Treatment by period interaction

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

ANOVA MODEL : psg_m
Centre and Centre by treatment Interaction

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Title:

A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia

Document Number: PM2004/00029/01
Study Identifier: GW679769/903
GSK Compound Number: GW679769
Issue Date: 26 Oct 2004
Protocol Amendment Number: 01

Author(s): [redacted]

Revision Chronology:

PM2004/00029/00	2004-Apr-29	Original
PM2004/00029/00	2004-Oct-26	Amendment No. 1: To clarify study procedures to be performed and the times of their completion; to re-define the "visit window" between Visits 3 and 4; and to refine Appendix 1, "Time and Events Table," so as to reflect the clarified study procedures and to improve this table's utility.

SPONSOR INFORMATION PAGE

Title:	A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep , PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subject with primary insomnia.
Study Identifier:	GW679769/903

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Sponsor Signatory:	Signature:	Date:
[redacted] Ph.D. Vice President, Discovery Medicine Psychiatry CEDD	[redacted]	26 OCT 2004
Sponsor Signatory:	**Signature:**	**Date:**
[redacted] MD Senior Research Physician Discovery Medicine Psychiatry CEDD		

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Sponsor Signatory:	**Signature:**	**Date:**
[redacted] MD Senior Research Physician Discovery Medicine Psychiatry CEDD	[redacted]	26/Oct/04

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INVESTIGATOR AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol amendment and with any other study conduct procedures provided by GlaxoSmithKline (GSK).
- Not to implement this protocol amendment without agreement from the sponsor and prior submission to and written approval from (where required) the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Note to implement any other changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described herein, and any other information provided by the sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), and approved product label (if the product is marketed in this country and the label is not already provided as an equivalent to an IB).
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK investigational product(s) and of their study-related duties and functions as described herein.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the Sponsor or the investigational product, and more generally about his/her financial ties with the Sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

  Hence I:

  - Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children);
  - Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
  - Agree that GSK may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Investigator Name: _____

_____ _____
Investigator Signature Date

The following co-signature is required only when the investigator is not a physician.

Physician Name: _____

_____ _____
Physician Signature Date

Table of Contents

ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvate transaminase)
AST (SGOT)	Aspartate amino-transferase (serum glutamic oxaloacetic transaminase)
ANCOVA	Analysis of Covariance
AUC	Area under the plasma concentration-time curve
AUC(0-τ)	Area under the plasma concentration-time curve over the dosing interval on multiple dosing
AUC(0-∞)	Area under the plasma concentration-time curve from time 0 (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the plasma concentration-time curve from zero (pre-dose) to the last quantifiable concentration
BP	Blood Pressure
BUN	Blood urea nitrogen
C_{max}	Maximum observed concentration
CIB or IB	Clinical investigator brochure or Investigator brochure
CK	Creatine phosphokinase
CL/F	Apparent plasma clearance
CL_R	Renal clearance
C_{mean}	
CNS	Central nervous system
CPK	Clinical Pharmacokinetics
CPSP	Clinical Pharmacology Statistics and Programming
CRF	Case report form
CTM	Clinical trial material
HVLT-R	Hopkins Verbal Learning Test - Revised
DNA	Deoxyribonucleic Acid
DSM–IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSST	Digital Symbol Substitution Test
ECG	Electrocardiogram
EEG	Electroencephelogram
EISR	Expedited Investigator Safety Report
fT_3	Free triiodothyronine
fT_4	Free thyroxine
FTI	Free thyroxine index
FTIH	First time in humans
FDA	Food and Drug Administration
GGT	Gamma glutamyltransferase
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HR	Heart Rate
Hb	Hemoglobin
H	Hour

IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intra–uterine device
kg	Kilogram
HDL	High density lipids
LDL	Low density lipids
LFT	Liver function test
LOCF	Last observation carried forward
LPS	Latency to Persistent Sleep
MAOI	Monoamine oxidase inhibitor
MedRA	Medical Dictionary for Drug Regulatory Activities
MSDS	Material safety data sheet
mg	Milligram
min	Minute
mL	Milliliter
ng	nanograms
NK	Neurokinin
NOAEL	No observable adverse effect level
NREM	non-REM
OC	Observed case
od	Once daily
OTC	Over the counter
PCV	Packed cell volume/hematocrit
PET	Positron emission tomography
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PP	per protocol
PSG	Polysomnographically
QC	Quality Control
R	Resting
REM	Rapid Eye Movement
RR	Respiratory Rate
SAE	Serious adverse event
SD	Standard deviation
SFA	Spindle Frequency Activity
SNP	Single Nucleotide Polymorphism
SOL	Sleep Onset Latency
SP	Substance P
SSRI	Selective serotonin reuptake inhibitor
SWS	Slow Wave Sleep
t1/2	Terminal phase half-life
T3U	T3 Uptake
t_{max}	First time of occurrence of Cmax
TSH	Thyroid stimulating hormone
TST	Total Sleep Time

ULRR	Upper limit of the reference range
VAS	Visual Analog Scale
VC	Vigilance Control
WASO	Wake After Sleep Onset

PROTOCOL SUMMARY

Rationale

Primary or persistent insomnia is associated with a wide array of individual and societal issues. The cost of insomnia in terms of lost productivity and accidents is estimated at 77-92 billion dollars per year. [Stroller, 1994] Primary insomnia is also an important unmet medical need. In fact, the majority of individuals with insomnia remain untreated. [Ancoli-Israel, 1999] This condition is only partially controlled using zolpidem, zoplicone and zalepon, non-benzodiazepinic GABA-A1 preferential agonists. [Nowell, 1997; Holbrook, 2000] These treatments are effective by decreasing sleep latency and improving total sleep time and can be prescribed both "as needed" [Walsh, 2002] or as daily dosing for few weeks. [Holbrook, 2000] However, data on long term efficacy of pharmacotherapy are limited, sleep maintenance is rarely improved, and there is no evidence of sustained improvement when the medication is withdrawn. [Holbrook, 2000; Smith, 2002] Furthermore, pharmacotherapy with benzodiazepines or GABA agonist with half-life above 5 hours (e.g., zoplicone) are associated with residual effects (i.e., cognitive impairment) the morning following bedtime administration. [Roth, 1985; Vermeeren, 2002] Residual effects generally consist of memory and divided attention impairments, the latter being correlated with deficits in operating machinery (e.g. driving a car). Generally, very short half-life benzodiazepines and GABA-A1 agonist (e.g., zalepon) do not show these residual effects at clinically used dose. In addition, GABA A1 has shown low abuse liability compared with the addictive properties of benzodiazepines.[Nowell, 1997] The development of a novel therapy for primary insomnia delivering efficacy in both short and long-term treatment scenarios with no residual effects or abuse liability is highly desirable.

During the past few years, emerging data suggests that substance P and neurokinin receptors can be involved in the control of arousal and sleep. Substance P is known to be released by several brain structures,[Carrasco, 2003] and is liberated as a result of exposure toenvironmental stressors. It is also known to reduce the total sleep time in preclinical species and humans.[Hetta, 2002] In particular, substance P (acting through NK1 receptor) is active on locus coeruleus and raphe nuclei, both structures involved in REM sleep regulation.[Sakai, 1991; Ma, 2002; Kohlmeier, 2002] The awakening effects of an infusion of substance P were recently studied in healthy volunteers, showing a decreased total sleep time and an increased sleep onset latency.[Lieb, 2002] NK1 antagonists, like benzodiazepines, also show anxiolytic-like effects in several preclinical models.[File, 1997; Rupniak, 1994; van der Hart, 2002] In humans, repeated administration of an NK1 antagonist, GW 205171, has been associated with anxiolytic effects in patients suffering from Social Anxiety Disorders [GSK Document Number VM2001/00013/00 Study ID NKD10013], and has shown antidepressant effects in patients with recurrent depression.[Kramer, 1998] Improvement on the measures associated with insomnia was reported in the latter studies, suggesting possible efficacy of NK1 antagonists in sleep disorders.[Holsboer, 2003]

The theory that NK1 antagonists may be of potential benefit for primary insomnia and act through a novel mechanism, different from benzodiazepines or related GABA-A receptor modulators is supported by data from a recent study using an investigational NK1

antagonist (GW597599). When administered at 15 mg and 25 mg, GW597599 produced transient pharmaco-EEG consisting of increases in delta and theta waves and decreases in alpha and beta rhythms modifications primarily in the first 2 hours after dosing in resting conditions when compared with placebo. Overall, the EEG pattern transiently produced by GW597599 was interpreted as reduced vigilance. At both doses, GW597599 improved sleep continuity, the sleep efficiency index and the Total Sleep Time. The sleep onset time and the time spent in non-REM sleep were found unchanged. However, the sleep architecture was altered, with stage 2 non-REM sleep being augmented at the expense of slow wave sleep (SWS). In particular, time spent in SWS stage 3 and 4 was significantly decreased. These effects were mostly observed during the first third of the night. On the contrary, time in REM sleep was increased up to 20%, REM latency was shortened and REM activity and density were increased. These sleep EEG alterations did not seem to be dose-dependent but somewhat related to the exposure of GW597599. In fact, exposure higher than 30 ng/ml/h, measured as Cmean, associated with more marked effects relative to lower exposure. In addition, the treatment did not affect the quality of sleep as reported on the Post-Sleep Questionnaire at any dose. Finally, non-REM sleep spectral analyses revealed that power in the spindle frequency activity (SFA) and in the adjacent alpha and beta 1 bands were increased while slow wave activity decreased after GW597599. These effects reached significance for SFA with the two doses of GW597599, and for alpha and beta 1 only with the 15mg dose. These changes are closely linked to the SWS-stage 2 modifications, since spindles are the hallmarks of stage 2 sleep while slow waves are those of SWS

The NK1 antagonist-enhancing properties on REM sleep may also have positive effects on daytime cognitive functions upon awakening the following morning. Research dating back as far as the 1970's indicate that REM sleep may have a role in memory consolidation. In particular, there is evidence that REM sleep is essential to remember and integrate information with an emotional valence.[Empson, 1970; Wagner, 2001; Siegel, 2001] In addition, a study assessing the effects of donezepil (a procholinergic drug that enhances REM sleep time) on memory showed improvement on tests of verbal learning (CVLT) in healthy elderly persons.[Schredl, 2001] Moreover, a recent article suggests that high SFA are associated with better information retention and recall.[Gais, 2002] In the present study, the HVLT-R (Hopkins verbal learning test - revised) will be used to evaluate if the potential SFA or REM-enhancing properties of NK1 antagonists are confirmed using GW679769 and will result in positive effects on memory.

The aim of the present experiment is to assess the short-term efficacy of one NK1 antagonists for use in the treatment of primary insomnia. The NK1 antagonist GW679769 is being proposed for use in this protocol based on the reasoning that GW679769 will deliver similar hypnotic affects to GW597599 if those effects are mediated by NK1 receptors. Furthermore, GW679769 shows a rapid brain penetrability and allows full brain NK1 receptor occupancy when used in the range of 60-90 mg.

Objective(s)

Primary

- To evaluate the acute efficacy of on sleep continuity in adults with Primary Insomnia as determined objectively by polysomnography (PSG).

Secondary

- To study the changes induced by GW679769 on various PSG sleep parameters.
- To investigate the effects of GW679769 on daytime cognitive functioning on the morning following dosing, including tests of alertness, memory, attention and fine motor control.
- To investigate the effects of GW679769 on subjective sleep quality using self reported Post-Sleep Questionnaires.
- To investigate the safety and the pharmacokinetic (PK) profile of GW679769 in subjects with primary insomnia after 2 consecutive days of oral administration.
- To investigate the potential effects on memory associated with REM sleep
- To investigate the relationship between plasma concentrations of GW679769 and all the sleep or cognitive parameters and to develop a PK/PD model.

Endpoint(s)

Primary

- Wake time after sleep onset (WASO) derived from polysomnographic (PSG) recording.

Secondary

- Objective PSG measures of sleep continuity including: Total Sleep Time (TST), latency to persistent sleep (LPS), wake during sleep (WDS), wake after sleep (WAS), and number of awakenings during sleep.
- Objective PSG measures of sleep structure: Non-REM sleep time, Slow-Wave Sleep (SWS) time (stage 3 and 4), Stage 2 non-REM sleep time; REM sleep time, REM activity, REM density.
- Spectral analysis of EEG output
- Subjective Post-Sleep Questionnaire: TST, WASO, SOL, number of awakenings, and sleep quality (SQ) to be applied on each morning following PSG recording.
- Daytime cognitive function data on the morning following dosing, including tests of alertness, memory, attention and fine motor control (i.e. Romberg, VAS for sleepiness/alertness, DSST, and immediate and delayed word recall).
- HVLT-R (verbal memory tests)

- Changes of TST, SOL, SQ, WAS and number of awakenings measured with the Post-Sleep Questionnaire score collected on specified mornings at home during the 3-day period following each 2-night PSG sessions.
- Plasma concentration of GW679769 and its major metabolite (GSK 525060).

Study Design

This is a randomized, double-blind, placebo-controlled, cross-over study using a complete set of orthogonal Latin Squares. Potential subjects will participate in a screening period consisting of a clinical screening visit and 2-night PSG recording in the sleep laboratory. Subjects with primary insomnia that qualify will participate in 3 separate 2-night PSG sessions in which they will be randomized to receive placebo or GW679769 (30 mg or 90 mg), one treatment for each session in a balanced order. Each session will be separated by a minimum of 12 days and will occur on the same day of the week (± 1 day).

Study Population

Male and female subjects, 18-64 years of age (inclusive), with a primary diagnosis of primary insomnia who have had symptoms for at least three months, as defined by Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) criteria 307.42. Subjects will be recruited from approximately 5-7 sites in the United States.

Approximately 48 subjects will be enrolled in the study. A minimum of 43 evaluable subjects is required to complete the study, covering a maximum drop-out rate of 10%.

Study Assessments and Procedures

Study assessments and procedures are presented in Section 14.1, Time and Events Table.

Investigational Product(s)

Subjects will receive each of the following:

- Placebo
- GW679769 30 mg
- GW679769 90 mg

1. INTRODUCTION

1.1. Background

1.1.1. NK1 Antagonists as Candidate Anxiolytic and Sleep-Improving Drugs

The NK1 receptor is one of the three 7-transmembrane receptors that bind tachykinins, a family of peptide neurotransmitters than include substance P, neurokinin A, and neurokinin B. Both tachikins and NK1 receptors are expressed in mammalian brains in various sub-cortical and cortical structures involved in emotional control and mood regulation [Kramer, 1998]. Evidence of the involvement of NK1 receptor in such regulatory functions were obtained by administering agonist and antagonist drugs in animals, in particular gerbils, guinea pigs and marmosets, whose NK1 receptor share a higher homology with the human receptor. For example, NK1 agonists induce anxiogenic-like responses when injected directly into the brain and NK1 receptor antagonists show anxiolytic-like properties in elevated maze and social interaction tests in rodents [File, 1997; Rupniak, 1994]. In humans, repeated administration of the NK1 antagonist GW 205171 has been associated with anxiolytic effects in patients suffering from Social Anxiety Disorder(NKD10013).

Acute anxiolytic-like effects were also observed with the NK1 antagonist GW597599. Two sets of data support this evidence: 1) Preclinical studies using the Social Interaction Test in gerbils and the Human Threat Test in monkeys (i.e., marmoset) showed dose-dependent anxiolytic effects of GW597599; 2) one Experimental Medicine study performed in healthy volunteers selected for their liability to panic-like attacks when challenged with 7%CO2 breathing for 20 minutes (NKD10013). In this work, run in the GSK Clinical Pharmacology Unit in Verona, acute pre-treatment with a single dose of 25 mg GW597599 was significantly effective in reducing the anxiety scores reported at the end of the 7%CO2 breathing period in a cross-over design. These effects were also compared to the effects of 0.75 mg alprazolam on panic symptoms, escape reaction, and heart rate changes, showing a similar profile. These data suggest that acute administration of 25 mg GW597599 can produce anxiolysis in humans.

Evidence that NK1 receptor antagonists have antidepressant effects in humans is gained from observations in depressed subjects [Kramer, 1998]. In this study, a selective NK1 receptor antagonist, MK-869 (300mg/day) was tested in a six-week clinical trial, and its effect was both significantly superior to placebo, and comparable to paroxetine (20mg/day). MK-869 was well tolerated, with fewer side effects than paroxetine (less insomnia, sexual dysfunction and gastrointestinal effects). Interestingly, it also showed effects on the patients' insomnia score, suggesting that NK1 antagonists can be used to approach sleep disorders [see also Holsboer, 2003].

1.1.2. The NK1 antagonist GW679769

Preclinical evidence indicates that GW679976 shares the same acute anxiolytic-like properties of GW597599 and GR 205171 in gerbils and marmoset (see Version 2 - May 2003 - GW 679796 Investigator's Brochure).

GW679769 was first administered to man in October 2002 and has been evaluated in humans in four single-dose studies and one repeat dose study, with doses ranging from 2.5 to 150 mg. A total of 182 subjects have been enrolled in these studies (see Table 1).

Table 1 Summary of GW 679769 studies completed as of 15 April 2004

Study	Description	SD/RD[1]	GW679769 DOSE MG	No of subjects administered GW679769
NKF10001	FTIH	SD	5, 15, 30, 60, 80, 100, 120, 150	21
NKF10002	PET %RO	SD	2.5, 5, 20, 50, 120	8
NKF10004	Repeat dose and PK	SD&RD	30, 50, 60, 70, 90	52
NKF10007	CYP450 interaction	SD	50, 100	48
NKF10010	Food effect; rel bio.	SD	50, 100	36

1. SD=single dose; RD=repeat dose (7 and 28 days)
Total of 165 subjects treated on active (113 SD; 52 RD) of which 4 post menopausal, 1 after SD and 3 after RD

GW679769 is safe and well tolerated with headache, fatigue and somnolence (drowsiness) being the most commonly reported adverse events (AEs). None of the AEs were considered severe and the majority were graded as mild. All AEs resolved spontaneously and the majority did not require treatment. There were no deaths. An overview of adverse events following single and repeat oral dosing for seven and twenty-eight days, respectively, is provided in the Table 2 and Table 3:

Table 2 Summary of Adverse Events in the Multiple Oral Dose Study after Single and 7-day Dosing (NKF10004)

	GW679769				
Preferred Term	**50 mg N=8 n(%)**	**90 mg N=8 n(%)**	**70/120 mg N=8 n(%)**	**Total N=24 n(%)**	**Placebo N=6 n(%)**
Sub. with AE					
Headache	1 (13%)	5(63%)	1(13%)	7(29%)	2 (33%)
Somnolence	2 (25%)	5(63%)	1 (13%)	8 (33%)	2 (33%)
Fatigue	-	-	-	-	2 (33%)
Disturbance in attention	-	2 (25%)	-	2 (8%)	-

Table 3 Summary of Adverse Events in the Multiple Oral Dose Study after Single and 28-day Dosing (NKF10004)

	GW679769			
Preferred term	**30 mg N=12 n(%)**	**60 mg N=13 n(%)**	**Total N=25 n(%)**	**Placebo N=9 n(%)**
Sub. with AE				
Fatigue	5 (42%)	10(77%)	15 (60%)	2 (22%)
Headache	1 (8%)	3 (23%)	4 (16%)	2 (22%)
Somnolence	2 (17%)	1 (8%)	3 (12%)	-
Dizziness	1 (8%)	1 (8%)	2 (8%)	-
Disturbance in attention	-	-	-	2 (22%)
Eye irritation	2 (17%)	-	2 (8%)	-

As of 6 May 2004, three serious adverse events have been reported following administration of GW679769. One serious adverse event (SAE) was documented in a study conducted in support of a psychiatry indication (peritonsillar cellulitis in study NKF10007) and believed to be unrelated to GW679769 treatment. Another SAE was reported in a study conducted in support of the indication for chemotherapy-induced nausea and vomiting (gastric perforation in study NKV 10001) in a patient with an undisclosed history of peptic ulcer disease. This SAE was also believed to be unrelated to treatment with GW679769. The third SAE also occurred in study NKV 10001. This SAE (tuberculosis) was considered unlikely to be related to GW679769.

There were no trends in laboratory parameters of clinical concern, although two subjects were withdrawn from Study NKF10004 (one on Day 1 and one on Day 16) due to moderate isolated elevations in liver transaminases. In both cases, the increase in liver transaminases was reversible. Clinical observations, including heart rate, blood pressure and 12-lead ECGs did not reveal any changes believed to be of clinical significance although analysis of the QTc data from the repeat dose study is ongoing. The key finding in toxicological studies with GW679769 was a reduction in gastric chief cells in rat and dog (clear NOAEL identified). There were no relevant changes in serum pepsinogen I and II level monitored during the repeat dose study in human volunteers. However, as a result of these toxicological findings, subjects with active peptic ulcer disease or a history of peptic ulcer disease of unknown etiology are excluded from the study. Subjects with a medical history of peptic ulcer disease with a known etiology must provide documentation by a gastroenterologist of the etiology of the PUD, that effective treatment was provided with full eradication of ulcers and symptoms, and that all steps have been taken to minimize reoccurrence risk. Finally Pepsinogen levels will be monitored throughout the study.

The "fatigue" described in repeat dose studies in healthy volunteers seemingly imply a relationship with "sedation," but it appears more likely only to a component of sedation. The self-reported AEs were about "being tired" rather than "sleepy" or "drowsy." In addition, no cognitive impairment possibly related to hypnotic residual effects was reported after 60 mg for 28 days or 90 mg for 7 days.

For additional information on the preclinical and clinical data for GW679769, please refer to Version 2 (May 2003) of the Investigator's Brochure.

1.2. Rationale

As noted in the introduction, primary insomnia is a major health problem that is not fully recognized or treated successfully by currently available medications. The majority of currently available treatments have significant side effects, including addictive liability and residual cognitive effects i.e., memory and attention deficits. These treatments are effective by decreasing sleep latency and improving total sleep time, but often do not improve sleep continuity or maintenance at the doses used clinically.[Nowell, 1997; Holbrook, 2000] A trade-off between improvement of sleep continuity and appearance of residual effects has been described for this classes of compounds.[Roth, 1985; Holbrook, 2000] In particular, there is no evidence of sustained improvement when the medication is withdrawn.[Smith, 2002] The development of a novel therapy for primary insomnia delivering efficacy in both short and long-term treatment scenarios with no residual effects or abuse liability is highly desirable

During the past few years, emerging data suggests that substance P and neurokinin receptors can be involved in the control of arousal and sleep. Substance P is known to be released by several brain structures,[Carrasco, 2003] and is liberated as a result of exposure toenvironmental stressors. It is also known to reduce the total sleep time in preclinical species and humans.[Hetta, 2002] In particular, substance P (acting through NK1 receptor) is active on locus coeruleus and raphe nuclei, both structures involved in REM sleep regulation.[Sakai, 1991; Ma, 2002; Kohlmeier, 2002] The awakening effects of an infusion of substance P were recently studied in healthy volunteers, showing a decreased total sleep time and an increased sleep onset latency.[Lieb, 2002] NK1 antagonists, like benzodiazepines, also show anxiolytic-like effects in several preclinical models.[File, 1997; Rupniak, 1994; van der Hart, 2002] In humans, repeated administration of an NK1 antagonist, GW 205171, has been associated with anxiolytic effects in patients suffering from Social Anxiety Disorders [NKD10013] and has shown antidepressant effects in patients with recurrent depression.[Kramer, 1998] Improvement on the measures associated with insomnia was reported in the latter studies, suggesting possible efficacy of NK1 antagonists in sleep disorders.[Holsboer, 2003]

The theory that NK1 antagonists may be of potential benefit for primary insomnia and act through a novel mechanism, different from benzodiazepines or related GABA-A receptor modulators is supported by data from a recent study using an investigational NK1 antagonist (GW597599). When administered at 15 mg and 25 mg, GW597599 produced transient pharmaco-EEG consisting of increases in delta and theta waves and decreases in alpha and beta rhythms modifications primarily in the first 2 hours after dosing in resting conditions when compared with placebo. Overall, the EEG pattern transiently produced by GW597599 was interpreted as reduced vigilance. At both doses, GW597599 improved sleep continuity, the sleep efficiency index and the Total Sleep Time. The sleep onset time and the time spent in non-REM sleep were found unchanged. However, the sleep architecture was altered, with stage 2 non-REM sleep being augmented at the expense of slow wave sleep (SWS). In particular, time spent in SWS stage 3 and 4 was significantly decreased. These effects were mostly observed during the first third of the

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The evidence of effects on insomnia of NK1 antagonist MK869 on Major Depression is based on a study done by Merck using the "compound-A" L-759274 in patients with melancholic depression. The 6-week treatment was associated with changes from baseline LOCF of -0.4 (ES=0.25) p=0.028).[Kramer, 1998] In our 8 week treatmentstudy in patients with Major Depression using GW597599 (15 mg/day) treatment showed a difference from baseline of 0.17 (ES=0.27), p=0.100 (NKD20006) The statistical variance in the latter study was higher, reflecting a non-significant p value. However, the effect size was about the same, suggesting sleep improving properties of the two compounds.

The aim of the present experiment is to assess the short-term efficacy of one NK1 antagonists for use in the treatment of primary insomnia. The NK1 antagonist GW679769 is being proposed for use in this protocol based on the reasoning that GW679769 will deliver similar hypnotic affects to GW597599 if those effects are mediated by NK1 receptors. Furthermore, GW679769 shows a rapid brain penetrability and allows full brain NK1 receptor occupancy when used in the range of 60-90 mg.

2. OBJECTIVE(S)

2.1. Primary

- To evaluate the acute efficacy of on sleep continuity in adults with Primary Insomnia as determined objectively by polysomnography (PSG).

2.2. Secondary

- To study the changes induced by GW679769 on various PSG sleep parameters.
- To investigate the effects of GW679769 on daytime cognitive functioning on the morning following dosing, including tests of alertness, memory, attention and fine motor control.
- To investigate the effects of GW679769 on subjective sleep quality using self reported Post-Sleep Questionnaires.
- To investigate the safety and the pharmacokinetic (PK) profile of GW679769 in subjects with primary insomnia after 2 consecutive days of oral administration.
- To investigate the potential effects on memory associated with REM sleep
- To investigate the relationship between plasma concentrations of GW679769 and all the sleep or cognitive parameters and to develop a PK/PD model.

3. ENDPOINT(S)

3.1. Primary

- Wake time after sleep onset (WASO) derived from polysomnographic (PSG) recording.

3.2. Secondary

- Objective PSG measures of sleep continuity including: Total Sleep Time (TST), latency to persistent sleep (LPS), wake during sleep (WDS), wake after sleep (WAS), and number of awakenings during sleep.
- Objective PSG measures of sleep structure: Non-REM sleep time, Slow-Wave Sleep (SWS) time (stage 3 and 4), Stage 2 non-REM sleep time; REM sleep time, REM activity, REM density.
- Spectral analysis of EEG output
- Subjective Post-Sleep Questionnaire: TST, WASO, SOL, number of awakenings, and sleep quality (SQ) to be applied on each morning following PSG recording.
- Daytime cognitive function data on the morning following dosing, including tests of alertness, memory, attention and fine motor control (i.e. Romberg, VAS for sleepiness/alertness, DSST, and immediate and delayed word recall).

- HVLT-R (verbal memory tests)
- Changes of TST, SOL, SQ, WAS and number of awakenings measured with the Post-Sleep Questionnaire score collected on specified mornings at home during the 3-day period following each 2-night PSG sessions.
- Plasma concentration of GW679769 and its major metabolite (GSK 525060).

4. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, cross-over study using a complete set of orthogonal Latin Squares. Potential subjects will participate in a screening period consisting of a clinical screening visit and 2-night PSG recording in the sleep laboratory. Subjects with primary insomnia that qualify will participate in 3 separate 2-night PSG sessions in which they will be randomized to receive placebo or GW679769 (30 mg or 90 mg), one treatment for each session in a balanced order. Each session will be separated by a minimum of 12 days and will occur on the same day of the week (± 1 day).

5. STUDY POPULATION

Male and female subjects, 18-64 years of age (inclusive), with a primary diagnosis of primary insomnia who has had symptoms for at least three months, as defined by Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) criteria 307.42. Subjects will be recruited from approximately 5-7 sites in the United States.

5.1. Number of Subjects

Approximately 48 subjects will be enrolled in the study. A minimum of 43 evaluable subjects is required to complete the study, covering a maximum drop-out rate of 10%.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. The subject must be able to read and understand the informed consent form and provide written informed consent, indicating the subject's understanding of the purpose of the study and willingness to comply with all study procedures described in the protocol, including all sleep-laboratory restrictions and procedures.
2. The subject must be 18 through 64 years (inclusive).
3. Diagnosis of primary insomnia, as defined by Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) criteria 307.42. A complaint of difficulty initiating or maintaining sleep or of non-restorative sleep, which lasts for at

least 3 months along with clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance in sleep does not occur exclusively during the course of another sleep disorder or occur exclusively during the course of another mental disorder. Lastly, the disturbance is not due to the direct physiological effects of a substance or a general medical condition.

4. The subject's self-reported sleep history includes at least three months of a usual TST of less than 6.5 hours, SOL of at least 30 minutes and at least 3 awakening per night in at least 3 nights per week.
5. On two screening PSGs (on single-blinded placebo administration at each night):
   - TST between 240 and 420 minutes on both nights.
   - Mean LPS of 30 minutes or more, but not < 20 minutes on either night.
   - Mean WASO of 30 minutes or more, with neither night < 20 minutes.
6. Time in bed between 6.5 and 9 hours for at least 5 nights per week over the preceding 3 months
7. Bed time between 21.00 and 24.00 hours that does not vary by more than ±1 hour
8. Women of childbearing potential must be able to commit to consistent and correct use of an acceptable method of birth control; GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of a physician, are as follows:
   a Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal. For purposes of this study, postmenopausal is defined as one year without menses); or,
   b child-bearing potential, has a negative serum pregnancy test result at screen and a negative urine dipstick pregnancy test at baseline (prior to study drug administration), and agrees to one of the following:
      - Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject,
      - Oral contraceptives (either combined or progestogen only),
      - Double-barrier method of contraception consisting of spermicide with either condom or diaphragm;
      - IUD with a documented failure rate of less than 1% per year; or
      - Complete abstinence from intercourse for two weeks before exposure to the study drug, throughout the clinical trial, and for a period after the trial to account for elimination of the drug (minimum of three days, equivalent to five half lives).
9. If subjects indicate they will remain abstinent during the period described above, they must agree to follow GSK guidelines for the consistent and correct use of an acceptable method of birth control should they become sexually active.

10. The subject is in good health as determined by medical and psychiatric history, physical examination, ECG, and serum chemistry, hematology, serology, and urinalysis results.
11. Subjects with a medical history of peptic ulcer disease with a known etiology must provide documentation from a gastroenterologist of the etiology of the PUD and that effective treatment was provided with full eradication of ulcers and symptoms. Also that all steps have been taken to minimize reoccurrence risk (i.e. if NSAID induced that subject is no longer taking NSAIDs, if cause was H. Pylori, then subject should have negative antibody or breath test).

5.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Any clinically significant unstable medical or surgical condition (treated or untreated).
2. Any history of a clinically significant abnormality of the neurological system (including cognitive disorders or significant head injury) or any history of seizure (including febrile seizure).
3. Subject has a history of depression, anxiety or other Axis I or II disorders.
4. Current or recent (within six months) documented gastrointestinal disease; a history of malabsorption, esophageal reflux, or irritable bowel syndrome; frequent (more than once a week) occurrence of heartburn, or any surgical intervention (e.g. cholecystectomy) which would be expected to influence the absorption of drugs.
5. Subjects with active PUD and/or history of PUD of an unknown etiology, except as indicated in inclusion criterion number 11.
6. Subject has an unstable medical disorder; or a disorder that would interfere with the action, absorption, distribution, metabolism, or excretion of GW679769; or interfere with the accurate assessment of safety or efficacy.
7. Subjects having clinically significant abnormalities in hematology, blood chemistry, ECG, urinalysis, physical exam, vital signs, or other protocol-specified screening test which are not resolved by the baseline visit.
8. Subjects with a history of clinically significant hepatic, cardiac (e.g. including myocardial infarction), renal, neurologic (e.g. including seizures), cerebrovascular, metabolic or pulmonary disease.
9. Known seropositivity for human immunodeficiency virus (HIV), Hepatitis B, or Hepatitis C.
10. Women having a positive serum HCG pregnancy test at Screening Visit, a positive urine pregnancy dipstick or serum pregnancy test at Baseline Visit (Randomization), or who are lactating or planning to become pregnant within the 3 months following the Screening Visit

11. Any clinically significant psychiatric disorder other than primary insomnia as defined by DSM-IV-TR.
12. History of alcohol, narcotic, benzodiazepine, or other substance abuse or dependence (with the exception of tobacco use) within the past 12 months as defined by DSM-IV-TR.
13. Symptoms/signs that are consistent with any primary sleep disorder other than primary insomnia.
14. Body mass index of 34 or more.
15. Apnea-hypopnea index of 10 or more/hour of sleep on screening PSG.
16. Movement arousal index of 10 or more/hour of sleep on screening PSG.
17. Nightshift or rotating-shift work within the last 2 work weeks or during the study period.
18. Planned travel across more than 3 time zones during the study or in the 2 weeks prior to screening.
19. Consumption of 300 mg or more per day on average of xanthine-containing beverages (eg, coffee, cola, tea, chocolate) over the preceding 1 month [**NOTE**: 12 oz soda = ~50 mg, 7 oz coffee or 2 oz espresso = ~100 mg, 7 oz tea = ~75 mg of caffeine].
20. Smoking more than 1 pack of cigarettes per day on average over the preceding 1 month, or inability to stop smoking during the sleep.
21. Typical consumption of more than 14 alcoholic units in any week, or more than 5 alcoholic units in any single day, over the preceding 1 month [**NOTE**: 1 unit = 8 oz beer, 3 oz wine, or 1 oz hard liquor].
22. LFTs elevated above the reference range at pre-study screening that remain elevated with a repeat LFT (to be discussed with the sponsor, if necessary).
23. Subjects who are not euthyroid as evidenced by normal TSH. Subjects maintained on thyroid medication must be euthyroid for a period of at least six months prior to the screening visit; with no dose changes.
24. Subjects with a history or with evidence of clinically significant renal impairment (serum creatinine > 1.4 mg/dL) not resolved by the baseline visit.
25. Subjects with anemia and low Mean Corpuscular Volume (<80 fL) at the screening visit (to avoid entering subjects with iron deficiency anemia).
26. Use of any psychotropic medications or other medications, including over-the-counter (OTC) and herbal products, that may affect sleep/wake function within 1 week or 5 half-lives (whichever is longer) prior to screening or need to use any of these medications at any time during the study.
27. Subjects (i.e. asthmatics) who have used systemic corticosteroids within 1 week or 5 half-lives (whichever is longer) prior to the screening visit.
28. All other (non-psychotropic) drugs metabolized via the P450 3A4 pathway must be discontinued from baseline visit and are not allowed until completion of Session 3.

29. Use of any investigational drug within 30 days or 5 half-lives of the study compound prior to the Screening Visit.
30. Positive urine drug screen (i.e., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, or opiates).
31. Exhibited intolerance to NK1 antagonists.
32. Any serious medical disorder or condition that would in the Investigator's opinion, preclude the administration of study medication.
33. Subjects who, in the opinion of the investigator, would be noncompliant with the visit schedule or study procedures.

5.2.3. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study:

- the CIB or equivalent documentation for GW679769

5.2.4. Lifestyle Guidelines/Other Restrictions

- Subjects will be required to arrive in the unit before dosing and to stay in the unit until all assessments are completed during each study related visit.
- Participants will be instructed to refrain from grapefruit and grapefruit juice for 48 hours prior to and throughout each visit to the clinic.
- Subjects will be instructed to refrain from alcohol and caffeine- or xanthine-containing products for 6 hours prior to and throughout each visit to the clinic. Subjects' use of tobacco products is forbidden only during subjects' stay in the sleep unit.
- Water is allowed *ad libitum*.
- Subjects will be required to refrain from taking any other medication (either prescribed or over the counter) starting 12 hours before each visit to the clinic.
- Subjects will be required to refrain from activities that have the potential to change circadian rhythm (i.e. travel covering more than 3 time zones, occasional shift work, etc.)

6. STUDY ASSESSMENTS AND PROCEDURES

Please refer to Section 14.1 for a detailed listing of procedures for Time and Events Table.

6.1. Demographic and Baseline Assessments

6.1.1. Screening

6.1.1.1. Initial Screening (Visit 1)

The following procedures will be performed to determine subject eligibility after written informed consent has been obtained:

- Inclusion/Exclusion Criteria review
- Medical/Surgical/Psychiatric history
- Sleep history
- Prior medication history review (*within past 30 days*)
- Full previous sleep medication history review (*with detailed account of all medications within 30 days prior to screening*)
- Physical examination
- 12-lead ECG
- Sitting Vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Clinical laboratory tests (*Section 14.2*)
- Serum Pregnancy Test
- Urine illicit drug screen
- Alcohol breath test

In the event any clinical significant findings are observed, the subject will not be enrolled into the study and will be referred for appropriate follow-up.

6.1.1.2. Polysomnographic Screening (Visits 2/3)

Subjects who complete the screening procedures, identified above, will return for up to 2 consecutive nights of PSG screening (PSG1 and PSG2) within 2 to 10 days of the initial Screening visit.

Subjects should report to the sleep laboratory for Visit 2/Night 1 (V2/N1) – as for all PSG Visit nights – in sufficient time to complete the pre-dose assessments and to maintain the appropriate sleep schedule.

On Visit 2/Night 1 (V2/N1) -- the first PSG Screening visit night -- the following will be performed:

- Inclusion/exclusion criteria review
- Concomitant medication review

- Adverse events inquiry
- Medical/Surgical/Psychiatric/Sleep history update
- Alcohol Breath Test
- Urine or serum pregnancy test
- Urine illicit drug screen
- 12-lead ECG (*approximately 30 minutes before single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Pre-sleep questionnaire
- Memory HVLT-R list
- Single-blind placebo administration (*60 minutes before lights-out*)

Lights-out will occur at approximately 21:00 hours to 00:00 hours (midnight).

Approximately 60 minutes after this single-blind placebo administration, the following will also be performed:

- 12-lead ECG (just before lights-out)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Nocturnal PSG

At Visit 2/Day 1 (V2/D1) – the morning after V2/N1 – the following will be performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (*about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes*)
- Psychometric testing (*about 35 minutes (± 15 minutes) after lights-on*)
  a Digit Symbol Substitution Test (DSST)
  b Memory HVLT-R list
- VAS for sleepiness/alertness (*about 35 minutes (± 15 minutes) after lights-on*)
  a Leeds Sleep Evaluation Questionnaire
  b Stanford Sleepiness Scale
- 12-lead ECG (*approximately 10 hours after single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature, collected about 10 hours after single-blind dose*)
- Adverse events inquiry (last activity before Romberg, heel-to-toe tests)
- Romberg test, heel-to-toe test

Subjects will be allowed to leave the sleep laboratory at V2/D1 and throughout the study, once they are able to perform the Romberg and heel-to-toe gait tests at a performance level that confirms to the clinician that no residual effects exist. Residual effects, present to the extent that subjects are unable to leave the sleep laboratory, should be recorded as adverse events.

The PSG at Visit 2 will be used to exclude subjects with sleep-related breathing disorders or PLMS or both. Subjects without such breathing disorders or PLMS will return for the second Screening PSG night, Visit 3/Night 2 (V3/N2), if the following:

- LPS is greater than or equal to 20 minutes;
- WASO is greater than or equal to 20 minutes; and
- TST is between 240 and 420 minutes.

At Visit 3/Night 2 (V3/N2) – later in the day of V2/D1 – the following procedures will be performed:

- Inclusion/exclusion criteria review
- Concomitant medication review
- Adverse events inquiry
- Medical/Surgical/Psychiatric/Sleep history update
- Alcohol Breath Test
- Urine illicit drug screen
- 12-lead ECG (*approximately 30 minutes before single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Pre-sleep questionnaire
- Single-blind placebo administration (*60 minutes before lights-out*)

Approximately 60 minutes after this single-blind placebo administration, the following will also be performed:

- 12-lead ECG (*just before lights-out*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Nocturnal PSG

At Visit 3/Day 2 (V3/D2) – the morning after V3/N2 – the following will be performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (*about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes*)

- Psychometric testing (*about 35 minutes (± 15 minutes) after lights-on*)
  a Digit Symbol Substitution Test (DSST)
  b Memory HVLT-R list
- VAS for sleepiness/alertness (*about 35 minutes (± 15 minutes) after lights-on*)
  a Leeds Sleep Evaluation Questionnaire
  b Stanford Sleepiness Scale
- Question about the kind of treatment they received *(unmasking/masking effects*)
- 12-lead ECG (*approximately 10 hours after single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature, collected about 10 hours after single-blind dose*)
- Adverse events inquiry (*last activity before Romberg, heel-to-toe tests*)
- Romberg test, heel-to-toe test

As always, subjects are free to leave the sleep laboratory in the morning following PSG nights, once the Romberg and heel-to-toe gait tests confirm that no residual effects exist. Residual effects that prevent subjects from promptly leaving the sleep laboratory should be recorded as adverse events.

All subjects who qualify for the study will be scheduled to return a minimum of seven (7) days (± 1 day) after the V2/N1 date, for the first double-blind treatment period. Subjects who do not qualify for the double-blind portion of the study will be notified not to return.

Those subjects scheduled to return for the first double-blind treatment period will also be required to complete a SUBJECT DIARY. The diary consists of three sets of each of the following items:

- one pre-sleep questionnaire
- one post-sleep questionnaire
- one Leeds Sleep Evaluation Questionnaire
- one Stanford Sleepiness Scale

Starting on the night of V3/D2 and continuing on each of the succeeding two nights, subjects will complete three sets of forms, as are identified, immediately above.. Subjects will be required to return the completed diaries to the clinic at Visit 4/Night 1 (V4/N1) for study-record maintenance.

6.2. Treatment Period

6.2.1. Double-Blind Treatment Period (Visits 4/5, 6/7, and 8/9)

If all screening criteria are met, subjects will be required to return to the sleep laboratory for 3 sessions, each consisting of two consecutive nights of polysomnographic recording

(PSG3 - PSG8). Each session will be separated by a minimum of 12 days and will occur on the same day of the week (± 1 day).

Subjects will be required to report to the sleep laboratory in sufficient time to complete the pre-dose assessments and to maintain the appropriate sleep schedule.

At each of the following study visits:

Visit 4/Night 1 (V4/N1)
Visit 5/Night 2 (V5/N2)
Visit 6/Night 1 (V6/N1)
Visit 7/Night 2 (V7/N2)
Visit 8/Night 1 (V8/N1)
Visit 9/Night 2 (V9/N2)

the study procedures, below, must be performed prior to dosing:

- Concomitant medication review
- Adverse events inquiry
- Review of changes in subject's sleep habits
- Alcohol breath test
- Urine or serum pregnancy test
- Urine illicit drug screen
- Blood sample for Pharmacogenetics (*V4/N1 only*)
- pK sample collection
- 12-lead ECG (*approximately 30 minutes before study-drug administration*)
- Pre-sleep questionnaire
- Memory HVLT-R list (*only at V4/N1, V6/N1, V8/N1*)

Double-blind study-drug administration will occur 60 minutes before lights-out. As with all PSG visit nights in this study, lights out will occur at approximately 21:00 hours to 00:00 hours (midnight).

Approximately 60 minutes after the double-blind study-drug administration, the following will also be performed:

- 12-lead ECG (*just before lights-out*)
  - Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
  - Nocturnal PSG

At each of the following study visits:

Visit 4/Day 1 (V4/D1)
Visit 5/Day 2 (V5/D2)
Visit 6/Day 1 (V6/D1)
Visit 7/Day 2 (V7/D2)
Visit 8/Day 1 (V8/D1)

the assessments, below, will be performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (*about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes*)
- Psychometric testing (*about 35 minutes (± 15 minutes) after lights-on*)
  a Digit Symbol Substitution Test (DSST)
  b Memory HVLT-R list
- VAS for sleepiness/alertness (*about 35 minutes (± 15 minutes*) after lights-on)
  a Leeds Sleep Evaluation Questionnaire
  b Stanford Sleepiness Scale
- Question about the kind of treatment they received (*unmasking/masking effects) (only V5/D2, V7/D2, and V9/D2*)
- 12-lead ECG (*approximately 10 hours after single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature), collected about 10 hours after double-blind dose*)
- pK blood sample (*10 hours from time of dosing the night before*)
- Adverse events inquiry (*last activity before Romberg, heel-to-toe tests*)
- Romberg test, heel-to-toe test

At Visit 9/Day 2 (V9/D2), the following assessments will be performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (*about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes*)
- Psychometric testing (*about 35 minutes (± 15 minutes) after lights-on*)
  a Digit Symbol Substitution Test (DSST)
  b Memory HVLT-R list
- VAS for sleepiness/alertness (*about 35 minutes (± 15 minutes) after lights-on*)
  a Leeds Sleep Evaluation Questionnaire
  b Stanford Sleepiness Scale

- Question about the kind of treatment they received (*unmasking/masking effects) (only V5/D2, V7/D2, and V9/D2*)
- Physical examination
- 12-lead ECG (*approximately 10 hours after single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature, collected about 10 hours after double-blind dose*)
- Laboratory tests (*Section 14.2*)
- Serum Pregnancy Test
- pK blood sample (*10 hours from time of dosing the night before*)
- Adverse events inquiry (*last activity before Romberg, heel-to-toe tests*)
- Romberg test, heel-to-toe test

Subjects will be permitted to leave the sleep laboratory once they are able to perform the Romberg and heel-to-toe gait testing at a level of performance to indicate to the clinician that there are no residual effects. Residual effects, present to the extent that the subject is unable to leave the sleep laboratory, should be recorded as adverse events.

As after Visit 3, subjects will also be required to complete a subject diary after each of Visits 5, 7, and 9. Like that completed after Visit 3, the diary consists of three sets of each of the following items:

- one pre-sleep questionnaire
- one post-sleep questionnaire
- one Leeds Sleep Evaluation Questionnaire
- one Stanford Sleepiness Scale.

Starting on the night of V5/D2 and continuing on each of the succeeding two nights, subjects will complete three sets of forms, as are identified immediately above. Similarly, subjects will complete a subject diary, starting on each of the nights of V7/D2 and V9/D2. Subjects will be required to return the completed diaries to the clinic at their next study visit for study-record maintenance.

During the 12 days between sessions, no other drugs will be allowed, in particular hypnotics. No changes of life-style or extreme exercise will be allowed.

6.2.2. Early Withdrawal Visit Assessment

For subjects who are withdrawn from the study the following assessments will be performed as promptly as can be scheduled:

- Post-Sleep Questionnaire
- Physical examination
- 12-lead ECG

- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Concomitant medications
- Adverse events inquiry. (The Investigator will contact the medical monitor regarding any gastric AEs regardless of relationship to study drug.)
- Thyroid function tests
- Serum pregnancy test
- Blood draw for clinical labs (in particular for LFT) and pK (Any significant abnormal results will be repeated until resolution.)

6.2.3. Follow-up Visit(s) Assessments

A follow-up visit will be conducted 14 days (± 3 days) after the last night of PSG recording (Visit 9). The following will be performed at the follow-up visit:

- Post-Sleep Questionnaire
- Leeds Sleep Evaluation Questionnaire; Stanford Sleepiness Scale
- Physical examination
- 12-lead ECG
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Concomitant medications
- Adverse events inquiry. (The Investigator will contact the medical monitor regarding any gastric AEs regardless of relationship to study drug.)
- Thyroid function tests
- Serum Pregnancy Test
- Clinical laboratory tests (Section 14.2) (Any significant abnormal results from the end of study visit (Visit 9) will be repeated until resolution.)

6.3. Safety

Safety measurements will be obtained as detailed in Section 14.1.

The Investigator, or medically-qualified delegate, will be responsible for reviewing safety data on an ongoing basis throughout the study. The Investigator will exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant and report to the sponsor, as appropriate.

6.3.1. Vital Signs

Vital signs will be measured at the initial Screening visit, and approximately 30 minutes before, 60 minutes after, and 10 hours after dosing (either single-or double-blind) on Screening PSG and treatment PSG nights. Vital signs to be measured include the following:

- sitting blood pressure
- heart rate
- respiratory rate
- oral temperature

Before blood pressure and heart rate are measured, the subject must be in a seated position and resting for at least 5 minutes. (The same position should be used each time vital signs are measured for a given subject). Any vital sign value that is judged by the Investigator as a clinically significant change (worsening) when compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored until the event has resolved or stabilised.

6.3.2. Electrocardiography

A 12-lead ECG will be conducted at the following times with respect to nocturnal PSG performance in Study GW 679769/903:

- Thirty (30) minutes before dosing (either single- or double-blind)
- Approximately 60 minutes after dosing (either single- or double-blind)
- Approximately ten (10) hours after dosing (either single- or double-blind)

A qualified physician will be responsible for providing interpretation of the electrocardiograph. Any electrocardiogram finding that is judged by the Investigator as a clinically significant change (worsening) when compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored until the event has resolved or stabilized.

6.3.3. Assessment of morning residual effects

Residual effects relative to morning alertness and psychomotor function will be measured by the use of psychometric tests (DSST and HVLT-R) and two VAS instruments for sleepiness/alertness (Leeds Sleep Evaluation Questionnaire and Stanford Sleepiness Scale). These assessments will be made on the mornings following nights spent in the sleep laboratory. The HVLT-R will also be completed at V2/N1, V4/N1, V6/N1, and V8/N1.

The two VAS instruments for sleepiness/alertness and the psychometric tests will be completed approximately 35 minutes (±15 minutes) after lights on. The HVLT-R tests to be completed at V2/N1, V4/N1, V6/N1, and V8/N1 may be completed at anytime prior to single- or double-blind dosing.

After each night, subjects will be permitted to leave the sleep laboratory once they are able to perform the Romberg and heel-to-toe gait testing at a level of performance to indicate to the clinician that there are no residual effects. Residual effects that are present to the extent that the subject is unable to leave the sleep laboratory should be recorded as adverse events

6.3.4. Hepatic Safety Monitoring

In the case of hepatic clinical findings detected during Early Withdrawal, at the End of the study (visit 9) or during the Follow-Up visit, the following procedure is followed:

A liver function test (LFT) elevation (including ALT, AST, ALP, GGT, direct bilirubin or total bilirubin) greater than or equal to twice the upper limit of the reference range (ULRR) occurs in any subject, weekly LFT monitoring will be performed for that subject until the results are within the normal range. Measurement of CK isoenzymes can be performed on isolated AST values to rule out a muscular origin if deemed clinically necessary by the medical monitor or the investigator. Individuals with isolated elevations in indirect bilirubin and no reason to suspect hemolysis likely have Gilbert's syndrome and may be kept in the study after repeat testing confirms absence of hemolysis (stable Hemoglobin, Hematocrit, and RBC morphology in peripheral smear, platelet count, LHD, haptoglobin and reticulocyte count are all normal) and persistent normality of liver enzymes. Isolated elevations in direct bilirubin are not expected and should be reported to the sponsor.

The investigator shall notify the sponsor in the event of a hepatic adverse event (e.g. LFT elevations less than 3 times ULRR), hepatomegaly, jaundice, hepatitis, etc.

6.3.5. Peptic Ulcer Disease

All subjects will be asked to report any peptic ulcer symptoms to the investigating physician.

If, during the course of the study, a subject with a history of PUD reports peptic ulcer symptoms, the subject will be referred to a gastroenterologist for evaluation with the possibility that an endoscopy and biopsy may be recommended. In the event of any of the above, termination of study drug will also be considered.

The investigator must inform GSK of all such cases within 24 hours of learning of the peptic ulcer symptoms.

During the course of the study, pepsinogen levels will be measured. In the event of a drop in pepsinogen (either within or outside the laboratory reference range), the GSK Medical Monitor must be notified within 24 hours to assess appropriate follow-up. Subjects will be considered for withdrawal from the study if the circulating levels of PGI are below the lower limit of the normal range on two consecutive readings performed at least four days apart. Such subjects will continue to be followed-up and should be offered to undergo further evaluation, namely gastric biopsy.

6.3.6. Pregnancy

6.3.6.1. Pregnancy testing

A serum pregnancy test must be completed for women of childbearing potential at the Screen Visit and again at the 14-Day Follow-up Visit. Serum samples will be processed through a designated laboratory. Urine dipstick pregnancy tests or serum pregnancy tests will be obtained prior to dosing on the first evening of each session and the morning following the final dose of study medication.

6.3.6.2. Time period for collecting pregnancy information

Pregnancies reported after administration of the first dose of randomized study medication and on or before the final scheduled study visit (14-Day Follow-up Visit) must be reported using the Pregnancy Notification Form in the CRF.

6.3.6.3. Action to be taken if pregnancy occurs

In the event a subject becomes pregnant during the reporting period described in Section 6.3.6.2, study drug for that subject will be stopped immediately

The investigator, or his/her designee, will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Section 10.6, "Recording of AEs and SAEs" and will be followed as described in Section 10.8, "Follow-up of AEs and SAEs."

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 10, “Adverse Events (AE) and Serious Adverse Events (SAE).” Furthermore, any SAE occurring as a result of a post-study pregnancy **and** is considered reasonably related to the investigational product by the investigator, will be reported to GSK as described in Section 10.11, "Post-study AEs and SAEs." While the investigator is not obligated to actively seek this information in former study subjects, he/she may learn of an SAE through spontaneous reporting.

6.4. Efficacy

The chosen efficacy measurements are well substantiated in literature. PSG and subjective Sleep Questionnaires are routinely used to assess the hypnotic properties of pharmaceutical compounds. The principal end-points for efficacy will be TST, WASO,

and LPS as measured with PSG. Correlation with the corresponding subjective scores of the Sleep Questionnaire on the same sleep parameters will be assessed.

Sleep questionnaires (Section 14.10 and Section 14.11) will be performed as described in Section 6.2.

6.5. Pharmacokinetics

6.5.1. Blood sample for PK

Blood samples for pharmacokinetic analysis will be obtained at all double-blind treatment visits in the following order: at pre-dose and 10 hours post-dose, following cognitive testing on the next morning.

In case of deviation from the times specified here for pK sampling, the actual time of the collection must be annotated.

Blood samples (5 mL) for the analysis of GW 679769 and its major metabolite (GW525060) will be collected into tubes containing EDTA, and immediately chilled on crushed ~~water~~ ice. Plasma will be separated by refrigerated centrifugation (approximately 4°C, 500xg for 15 minutes) within 1 hour of collection. (Where refrigerated centrifugation is not possible, the blood samples may be centrifuged, unrefrigerated, as long as they have been maintained at 4°C just prior to centrifugation.)

The resultant plasma samples will be removed, transferred to 3.6 mL polypropylene (Nunc) pre-labelled storage tubes and stored frozen at approximately -20°C pending shipment for drug analysis. Plasma concentration-time data of unlabelled GW679769 and its major metabolite (GSK525060) will be evaluated by standard non-compartmental methods and population-based mixed models.

6.5.2. Sample Transfer and Assay Methodology

All plasma samples will remain frozen at approximately -20ºC until transferred on solid carbon dioxide for analysis. Drug analysis for the determination of GW679769 and its major metabolite (GSK525060) will be carried out using a validated assay methodology (LC/MS/MS) by Worldwide Bioanalysis, DMPK, GlaxoSmithKline, Verona, Italy.

All plasma samples will be shipped for analysis to:

[redacted] and [redacted]
GlaxoSmithKline S.p.A.
DMPK
Via Fleming, 4
37135 Verona – Italy

Phone: [redacted]

Fax: [redacted]

6.6. Pharmacodynamics

6.6.1. PSG measurements

- All the PSG parameters related to sleep continuity, sleep architecture and not included in the Efficacy chapters will be considered for this analysis (e.g., REM sleep time, REM activity, SWS time, etc.).
- PSG will be collected using methodology on file and will be processed for spectral analysis using rapid FFA approach [Krystal, 1999].

6.6.2. Neurocognitive Measures

The Digit Symbol Substitution Test (DSST)

The Hopkins Verbal Learning Test - Revised [Lacritz, 2001] will be used in this study. THE HVLT-R offers a brief assessment of verbal learning and memory (recognition and recall) and its use has been validated with brain-disordered populations (e.g., Alzheimer's disease, Huntington's disease, amnesic disorders).

Eight distinct forms of the HVLT-R are available, eliminating practice effects on repeated administrations. Each form consists of a list of 12 nouns (targets) with four words drawn from each of three semantic categories. The semantic categories differ across the eight forms, but the forms are very similar in their psychometric properties. The HVLT-R tasks include three learning trials, a delayed recall trial (20-25 minute delay), and a yes/no delayed recognition trial. This latter trial consists of a randomized list that includes the 12 target words and 12 non-target words, 6 of which are drawn from the same semantic categories as the targets. Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index.

6.7. Pharmacogenetics

Details for pharmacogenetic sampling are provided in Section 14.4.

7. INVESTIGATIONAL PRODUCT(S)

7.1. Description of Investigational Product

The investigational products used in this study will be shipped to the site in subject-specific packaging. Clinical supplies will consist of GW679769 30 and 45 mg tablets and placebo.

GW679769 30 mg and 45 mg are white to off-white, film-coated, round tablets containing 30 mg and 45 mg of GW679769X (as the mesylate salt, GW679769B).

Placebo tablets visually match the active GW679769 tablets.

Tablets for clinical trials are packaged in opaque, white, high-density polyethylene (HDPE) bottles, with child-resistant closures that include induction seal liners. A dessicant is also utilized.

7.2. Dosage and Administration

GW679769 will be administered po at 30 mg or 90 mg day for 2 consecutive evenings at approximately 60 minutes prior to lights out.

Placebo will be administered po for 2 consecutive evenings at approximately 60 minutes prior to lights out.

7.3. Dose Rationale

Concentration-dependent effects on sleep in healthy volunteers were seen using 25 mg of GW597599 (NKD10014), suggesting that at high concentration, or at high brain NK1 receptor occupancy, the effects on REM sleep and on sleep continuity are higher. Exposures following a 30 mg dose of GW679769 (Cmean 14-62 ng/mL) are similar to those obtained following a 25 mg dose of GW597599 (Cmean = 16-40 ng/mL). Therefore, a 30 mg dose of GW679769 is being used in this study in order to obtain exposures and, as a result, NK1 receptor occupancy similar to that following administration of 25 mg GW597599.

The selection of the 30 mg dose for GW679769 as low dose for this study was based on a relatively loose relationship with GW597599. The two compounds show a similar brain penetration (1.2 for both drugs from i.v. administration) and occupy NK1 receptors with similarly high affinity (pKi = 10.20 for both) and protein binding (about 99%). However, the GW679769 PK profile allows for higher exposure than GW597599. For example, 5 mg GW679769 occupies the same 75% receptor in the temporal cortex as 15 mg GW597599. It is concluded that the plasma concentration following a single dose of 30 mg GW679769 (Cmean 14-62 ng/mL) will partially overlap the receptor occupancy delivered by the higher concentration of the single dose 25 mg GW597599 (Cmean = 16-40 ng/mL).

The selection of the dose of 90 mg dose for GW 679769 represents the near maximal tolerated dose under acute or sub-acute administration. According to the Phase I studies using PET 90 mg GW 679769 would deliver a full (95-100%) occupancy of NK1 receptor in the brain. In addition, according to the results of the Phase I studies both compounds are safe and well tolerated when administered at these doses from 1 up to 28 days.

7.4. Blinding

The randomization numbers for each subject will be provided to the Site by GlaxoSmithKline. The randomization schedule will not be broken until the study has completed and all data queries are resolved in order to maintain the study blind.

Only in the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the subject, the Investigator may unblind a subject's treatment assignment. If the blind is broken for any reason, the Investigator must notify GSK **immediately** of the unblinding incident without revealing the subject's study treatment assignment. In addition, the Investigator will record the date and reason for revealing the blinded treatment assignment for that subject in the appropriate CRF.

If a serious adverse event (SAE; as defined in Section 10.2., "Definition of a SAE") is reported to GSK, Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for the individual subject. If an expedited regulatory report to one or more regulatory agencies is required, the report will identify the subject's treatment assignment. When applicable, a copy of the regulatory report may be sent to Investigators in accordance with relevant regulations, GSK policy, or both.

7.5. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule generated by GSK Clinical Pharmacology Statistics and Programming (CPSP).

7.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

7.7. Preparation

No additional preparation of study medication is required.

7.8. Handling and Storage

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the Investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements.

Prior to dispensing, all study medication will be kept safely locked stored at a temperature between 15 - 30°C (59 - 86°F).

7.9. Product Accountability

The Investigator is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain investigational product accountability

records throughout the course of the study. This person(s) will document the amount of investigational product received from GSK, the amount supplied and/or administered to and returned by subjects, if applicable.

7.10. Assessment of Compliance

Study medication will be administered under the supervision of study personnel. The oral cavity of each subject will be examined following dosing to assure that study medication was taken.

7.11. Treatment of Investigational Product Overdose

An overdose is defined as an excessive dose taken by a subject, either accidentally or intentionally, irrespective of whether it involves study medication or non-study medication. Overdose may be suspected or confirmed and may or may not be associated with clinical signs and symptoms.

It would definitely include, but not be limited to those events which based on the investigators clinical judgement were considered to be of medical concern and/or require clinical observation and/or medical intervention.

As a guide, an overdose would include any dose greater than the highest daily dose included in the protocol.

Deviations to study drug administration (i.e. resulting from poor subject compliance) must be recorded in the study medication compliance section of the CRF.

To date, there have been no cases of overdose with GW679769. Treatment of any suspected or confirmed overdose with GW679769 should therefore be symptomatic. Supportive care, as per clinical judgment of the Investigator, is recommended in cases where overdose is suspected. While the potential for overdose is considered small, GW679769 is an investigational compound and the potential for unexpected reactions is not known.

7.12. Occupational Safety

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1. Permitted Medications

All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

In addition, all prior medications will be recorded at the screening visit in the CRF with indication, dose information, and dates of administration. The Clinical Investigator Brochure must be consulted for information relating to possible drug interactions.

8.2. Prohibited Medications

- The concomitant use of other psychotropic medications including antidepressants, sedatives, hypnotics and herbal treatments, is not permitted.
- Subjects are not permitted to take psychotropic drugs or antidepressants (including monoamine oxidase inhibitors, MAOIs) within the time frames specified below prior to the Screening visit until ~~following~~ completion of the follow-up visit:
    - At least 12 weeks: depot neuroleptics
    - At least 4 weeks: MAOIs or Fluoxetine
    - At least 14 days or 5 half-lives (whichever is longer): hypnotics, benzodiazepines, and all other sedatives (including sedating antihistamines)
    - At least 14 days: Antidepressants other than MAOIs or fluoxetine (e.g. TCAs, SSRIs, SNRIs), lithium and oral antipsychotics
    - At least 14 days: Any CNS-active herbal/natural supplement or preparation known or thought to have any psychoactive effects
- Systemic corticosteroids are not permitted to be used for at least 1 week or five half-lives prior to the screening visit until completion of the final follow-up visit
- All other (non-psychotropic) drugs metabolised via the P450 3A4 pathway must be discontinued from baseline visit and are not allowed until completion of the final study session. (Section 14.9)
- Use of any other investigational drugs within 30 days or 5 half-lives of the study compound prior to the Screening Visit is not permitted until completion of the final follow-up visit

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject Completion

A subject will be considered to have completed the study if they participate in the full active treatment period.

9.2. Subject Withdrawal

A withdrawal is any subject who has been dispensed randomized study medication but does not complete the full treatment phase (i.e., through session 3).

9.2.1. Subject Withdrawal from Study

A subject who does not complete the full treatment phase will be considered prematurely discontinued from the study. Subjects who are prematurely discontinued from the study will not be replaced.

A subject may voluntarily discontinue participation in this study at any time. The Investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. The Investigator shall notify the Sponsor if a subject is withdrawn due to a hepatic adverse event (e.g. any LFT elevation, hepatomegaly, jaundice, hepatitis, etc.). If a subject is prematurely discontinued from participation in the study for any reason, the Investigator must make every effort to perform the evaluations listed for the Early Withdrawal Visit in the Time and Events Table (Section 14.1).

The reason for termination will be recorded on the End of Study Record page of the CRF. A subject may withdraw (or be withdrawn) from the study prematurely for the following reasons:

1. Voluntary withdrawal of informed consent
2. Adverse event (Adverse Event section must be completed)
3. Insufficient therapeutic effect
4. Protocol deviation (including non compliance)
5. Lost to follow-up
6. Other (must be specified)

In the event that a subject is prematurely discontinued from the study at any time due to an AE (as defined in Section 10.1., “Definition of an AE”) or SAE (as defined in Section 10.2., “Definition of a SAE”), the procedures stated in Section 10, (“AEs and SAEs”) must be followed.

The Investigator shall notify the Sponsor if a subject is withdrawn due to an adverse event.

9.2.2. Subject Withdrawal from Investigational Product

Every attempt should be made to carry out the study assessments described in Section 14.1.

For all subjects who are prematurely withdrawn during the treatment phase of the study, the early withdrawal visit should be scheduled as soon as possible following the discontinuation of study medication.

The End of Study Record page of the CRF must be completed and the medication records should be brought up to date as far as possible. A safety Follow-up Visit will be scheduled to take place 14 days following the early termination visit for all subjects.

9.3. Screen and Baseline Failures

Subjects who withdraw from the study following informed consent, but prior to randomisation to study treatment will be classed as Screen or Baseline failures based on the visit at which withdrawal from the study occurs. Screen/Baseline failures logs will be maintained at the site. CRFs from Screen and Baseline failures will not be collected.

10. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

10.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE **includes**:

- Significant or unexpected worsening or exacerbation of the condition/indication under study. See Section 10.3., “Lack of Efficacy”, for additional information.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).

Examples of an AE **does not include** a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For GSK clinical studies, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

10.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a results in death.

b is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the Patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e is a congenital anomaly/birth defect.

f Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3. Lack of Efficacy

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

10.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., recording of vital signs and 12-lead ECG) that are judged by the Investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 10.1 ("Definition of an AE"), or SAE, as defined in Section 10.2 ("Definition of a SAE"). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.5. Time Period, Frequency, and Method of Detecting AEs and SAEs

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. before informed consent) should be recorded on the Medical/Surgical history section within the CRF.

All AEs occurring after administration of the first dose of study medication (beginning of placebo run-in), and on or before the final visit must be reported on the Adverse Event form in the CRF. All adverse events must be recorded irrespective of whether they are considered drug related.

SAEs that are related to study participation (e.g. procedures, invasive tests, a change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged. All other AEs and SAEs will be collected from the time of administration of study medication until discharge from the study.

As a means of assessing adverse events, the investigator should ask questions such as:

- "How are you feeling?"
- "Have you had any medical problems since your last visit/assessment?"
- "Have you taken any new medicines since your last visit/assessment?"

Questions should then be asked to pinpoint the onset of any events in relation to administration of investigational product in order to determine if the event should be recorded as an AE. However, if an event that is ongoing at the time of administration of study medication worsens following study drug administration, it will be collected as an AE or SAE.

At each visit/assessment in the period defined above, AEs will be evaluated by the Investigator and recorded in the appropriate AE/Serious AE section of the CRF.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the CRF should be completed. If an AE changes in intensity/frequency, then this should be recorded as a separate event (i.e. a new record started).

10.6. Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding an AE/SAE on the CRF. It is not acceptable for the Investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the appropriate AE/SAE CRF pages. However, there may be instances when copies of medical records for certain cases

are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

AEs and subject-completed questionnaires (e.g. HADS) are independent components of the study. Responses to each question in the questionnaires will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

10.7. Evaluating AEs and SAEs

10.7.1. Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.2, "Definition of a SAE".

10.7.2. Assessment of Causality

The Investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The Investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The Investigator will also consult the CIB/IB and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, it is very important that the Investigator always make an assessment of causality for every event prior to transmission

of the SAE CRF to GSK. The Investigator may change his/her opinion of causality in light of follow-up information, amending the SAE CRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The Investigator will provide the assessment of causality as per instructions on the SAE form in the CRF.

10.8. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject and provide further information to GSK on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The Investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed "SAE" CRF, with all changes signed and dated by the Investigator. The updated SAE CRF should be resent to GSK within the time frames outlined in Section 10.9.1.

10.9. Prompt Reporting of SAEs to GSK

SAEs will be reported promptly to GSK as described in the following table once the Investigator determines that the event meets the protocol definition of an SAE.

10.9.1. Timeframes for Submitting SAE Reports to GSK

	Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Type of SAE	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hrs	"SAE" CRF pages	24 hrs	Updated "SAE" CRF pages

10.9.2. Completion and Transmission of the SAE Reports

Once an Investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours as outlined in Section 10.9, "Prompt Reporting of SAEs to GSK". The SAE CRF will always be completed as thoroughly as possible with all available details of the event, signed by the Investigator (or designee), and forwarded to GSK within the designated time frames. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional information is received.

The Investigator will always provide an assessment of causality at the time of the initial report as described in Section 10.7.2, "Assessment of Causality".

Facsimile transmission of the "SAE" CRF is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the "SAE" CRF sent by overnight mail. Initial notification via the telephone does not replace the need for the Investigator to complete and sign the SAE CRF within the time frames outlined in Section 10.9, "Prompt Reporting of SAEs to GSK".

GSK will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.

The following pages of the CRF must accompany the SAE forms that are forwarded to GSK: "Demography," "Medical History," "Concomitant Medications," "Study Medication Records," and "Form D" (if applicable).

10.10. Regulatory Reporting Requirements For SAEs

The Investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 10.9., "Prompt Reporting of SAEs to GSK." GSK has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The Investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

This protocol has been filed under an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA). A given SAE may qualify as an IND Safety Report if the SAE is both attributable to the investigational product and unexpected. In this case, all Investigators filed to the IND (and associated INDs for the

same compound) will receive an Expedited Investigator Safety Report (EISR), identical in content to the IND Safety Report submitted to the FDA.

EISRs are prepared according to GSK policy and are forwarded to Investigators as necessary. An EISR is prepared for a SAE that is both attributable to investigational product and unexpected. The purpose of the EISR is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

When a site receives from GSK an Initial or Follow-up EISR or other safety information (e.g., revised Clinical Investigator's Brochure/Investigator's Brochure), the responsible person according to local requirements is required to promptly notify his or her IRB or IEC.

10.11. Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period defined in Section 10.5, "Time Period, Frequency, and Method of Detecting AEs and SAEs", of the protocol.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify GSK.

10.12. SAEs Related to Study Participation

An SAE considered related to study participation (e.g., procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly to GSK (see Section 10.9., "Prompt Reporting of SAEs to GSK").

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1. Hypotheses

The null hypothesis (HO) states there is no difference among the treatment groups in the efficacy end-points, while the alternative hypothesis (H1) assumes a difference between the treatment groups, in particular among the active treatments vs placebo.

11.2. Treatment Comparisons of Interest

11.2.1. Primary Comparisons of Interest

The primary comparison of interests are

GW679769 90 mg vs placebo

GW679769 30 mg vs placebo

11.2.2. Other Comparisons of Interest

Another comparison of interest is

GW679769 30 mg vs GW679769 90 mg

11.3. Interim Analysis

An interim analysis is planned after about half of the subjects (approximately 24 subjects) have been treated and after the data for those subjects are available. The focus of this interim analysis will be the total sleep time (TST) which is a sensitive parameter even though the primary endpoint is wake time after sleep onset (WASO). To maintain the blind, only aggregate data will be released to GSK personnel and will not be communicated to any study site. The study team and the investigators will remain blinded throughout the entire study. The result of the interim analysis should not affect the conduct of the remainder of the study. Only in the rare chance that both doses of GW679769 are statistically significantly inferior to placebo will the study be stopped. The study will not be terminated after the interim analysis due to superior efficacy.

11.4. Sample Size Considerations

11.4.1. Sample Size Assumptions

The final sample size was based on the primary efficacy end-point "wake time after sleep onset (WASO)". In the previous study (NKD10014) a within subjects standard deviation of about 14 min was observed. So assuming a difference vs. placebo of at least 10 min, 43 subjects completing the study would provide a 90% power to detect a difference between active drugs and placebo.

A greater power is expected on the most important of the secondary endpoint (TST) where, in the previous study, a within subjects standard deviation of about 17 min was observed and where differences vs. placebo of at least 20 min are expected.

11.4.2. Sample Size Sensitivity

With a real effect of 8 min or a within subjects standard deviation of 18 min, 43 subjects completing the study would provide a power greater than 70% to detect a difference between active drugs and placebo.

11.4.3. Sample Size Re-estimation

No sample size re-estimation is planned.

11.5. Analysis Populations

Safety Population: including all subjects dosed at least once

Intent-to-Treat Population (ITT): including all subjects dosed at least once, with efficacy measures for at least one night in the double-blind phase

PD Population: including all subjects dosed at least once with evaluable PD measures for at least one night in the double-blind phase

PK Concentration Population: including all subjects for whom at least a pharmacokinetic sample was obtained and analyzed

11.5.1. Data Sets

Data sets will be based on the actual data collected.

11.6. General Considerations for Data Analysis

11.6.1. Withdrawal

Subjects who withdraw from the study will not be replaced.

11.6.2. Missing Data

Mixed effects models will be used. Such approach is suitable for mildly unbalanced data when cases are missing at random.

11.6.3. Derived and Transformed Data

For each session and subject, mean values over the two nights will be obtained for PSG and the other measures collected during both the two nights.

11.6.4. Assessment Windows

Not applicable

11.6.5. Other Issues

Any deviation from the planned analysis will be documented in the RAP and in the final study report.

11.7. Efficacy Analysis

11.7.1. Primary Analysis

WASO measures will be analyzed using a mixed effect model with session and treatment as fixed effect and subject as random effect.

Additional analyses will be performed to investigate the carry-over effect (effect of the treatment received in the previous period) and the treatment by period interaction. In both the cases additional terms will be added to the original model. Tests of significance will be performed at the 5% level. Least squares mean values will be evaluated for each treatment. Estimates for treatment differences expressed in pair-wise basis will be calculated together with 95% corresponding confidence intervals. Error diagnostics from the residuals will be examined to ensure that the model does not depart from the assumptions underlying analysis of variance. If the assumptions are seriously violated, transformations of the data or nonparametric methods will be considered.

11.7.2. Secondary Analysis

Other efficacy measures will be analyzed using the same approach described for the primary analysis.

11.8. Safety Analyses

No formal statistical analysis is planned on safety data. All safety parameters will be reported according to the specific treatment the subject received.

11.8.1. Extent of Exposure

This will be summarized as the number of subjects exposed to the different treatments and the time period.

11.8.2. Adverse Events

All adverse events will be summarised and listed by treatment period according to MedDra coding dictionary. Drug related AE's will be highlighted.

11.8.3. Clinical Laboratory Evaluations

Results of laboratory safety analysis (Biochemistry, Haematology and Urinalysis) will be listed as appropriate. Values of clinical concern will be flagged with 'HT' or 'LT' and then reported in the listing of Biochemistry/Haematology data for subjects with at least one value outside threshold range.

11.8.4. Other Safety Measures

Vital signs and ECG data will be summarised by treatment and listed by subject and time.

11.9. Clinical Pharmacology Data Analyses

11.9.1. Pharmacokinetic Analyses

Blood sampling times will be related to the time of dosing. Actual sampling times will be used to calculate all parameters. All plasma concentration data will be listed. The concentration at each time point will be summarised as arithmetic mean, standard deviation, median, minimum, and maximum.

According to the SOP-CPK-0001 v01 "Standard methods for the Non-Compartmental Analysis of Pharmacokinetic Data" values below the LLOQ of the assay (BQL) will be considered as zero in the determination of the summary statistics. If the resulting mean, median, minimum, maximum values are BQL, then they will be presented as BQL

Population PK analysis will be performed using NONMEM Version V software. This software implements the non-linear mixed effects model, which allows simultaneous estimation of all curves, while preserving inter-individual differences in parameter values. A common structural model is estimated, and population parameters are obtained describing location and inter-individual spread of the model parameters. Based on the estimated population parameters, as a prior, and the individual data, individual specific parameters may be generated

Derived PK parameters will be listed by subject and treatment.

11.9.2. Pharmacodynamic Analyses

PD endpoints will be analyzed using a mixed effect model with session and treatment as fixed effect and subject as random effect.

Additional analyses will be performed to investigate the carry-over effect (effect of the treatment received in the previous period) and the treatment by period interaction. In both the cases additional terms will be added to the original model. Tests of significance will be performed at the 5% level. Least squares mean values will be evaluated for each treatment. Estimates for treatment differences expressed in pair-wise basis will be calculated together with 95% corresponding confidence intervals. Error diagnostics from the residuals will be examined to ensure that the models do not depart from the assumptions underlying analysis of variance. If the assumptions are seriously violated, transformations of the data or nonparametric methods will be considered.

11.9.3. Pharmacokinetics/Pharmacodynamics Analyses

This analysis will be the responsibility of CPK/M&S, GSK, Verona.

PK/PD relationships will be evaluated and, where appropriate, suitable modelling techniques will be applied to describe the functional link between plasma concentration and PSG parameters, sleep questionnaires, and cognitive readouts.

12. STUDY ADMINISTRATION

12.1. Regulatory and Ethical Considerations

12.1.1. Regulatory Authority Approval

GSK will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

12.1.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the October, 1996 version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. GSK will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before investigational product(s) and CRFs can be shipped to the site, GSK must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to GSK promptly.

12.1.3. Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

12.1.4. Investigator Reporting Requirements

As indicated in Section 10.10, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of GSK.

12.2. Study Monitoring

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.

This will be done in order to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 12.4., "Study and Site Closure."

12.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate

his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

12.4. Study and Site Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

- Return of all study data to GSK.
- Data queries.
- Accountability, reconciliation, and arrangements for unused investigational product(s).
- Review of site study records for completeness.
- Return of treatment codes to GSK.
- Shipment of PK/PGx samples to assay laboratory(ies).

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but are not limited to, safety or ethical issues or severe non-compliance. If GSK determines such action is needed, GSK will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, GSK will provide advance notification to the Investigator of the impending action prior to it taking effect.

GSK will promptly inform all other Investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study.

Financial compensation to Investigators and/or institutions will be in accordance with the agreement established between the Investigator and GSK.

12.5. Records Retention

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before

such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

12.6. Provision of Study Results and Information to Investigators

When a clinical study report is completed, GSK will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subject.

12.7. Information Disclosure and Inventions

Ownership:

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study.

These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period of at least thirty (30) days [or, for abstracts, at least five (5) working days] to review the proposed Publication. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

12.8. Data Management

Subject data are collected by the investigator or designee using the Case Report Form (CRF) defined by GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures. Database freeze will occur when data management quality control procedures are completed. Original CRFs will be retained by GSK, while the investigator will retain a copy.

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14. APPENDICES

14.1. Appendix 1: Time and Events Table

Procedures and Assessments	Screen Visit	Pair of Screening PSG Nights				Pairs of Double-Blind Treatment Sessions												Early Withdrawal or F/U Visit
						First				Second				Third				
	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9		
		N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	
Informed Consent	X																	
Inclusion/Exclusion Criteria Review	X	X		X														
Medical/Surgical/Psychiatric/ Sleep History	X	X		X														
Prior Medication History[a]	X																	
Concomitant Med Review		X		X		X		X		X		X		X		X		X
Adverse Events Inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep-habit Changes Review						X		X		X		X		X		X		
Physical Examination	X						X		X		X		X		X		X	X
12-lead ECG[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sitting Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Lab Tests (*Section 14.2*)	X																X	X
pK Sample Collection						X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacogenetic Sampling[d]						X												
Pregnancy Test[e]	X	X				X				X				X			X	X
Urine Illicit Drug Screen	X	X		X		X		X		X		X		X		X		

a. Within past 30 days; including sleep medication
b. 30 min, 60 min, and 10 hours after single- or double-blind dosing.
c. Blood pressure, heart rate, respiratory rate, oral temperature
d. Pre-dose
e. Serum test at V1, V9/D2, and Early W/D or F/U; for all other visits, serum or urine test

Appendix 1: Time and Events Table (Continued)

Procedures and Assessments	Screen Visit	Pair of Screening PSG Nights				Pairs of Double-Blind Treatment Sessions												Early Withdrawal or F/U Visit
						First				Second				Third				
	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9		
		N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	
Alcohol Breath Test	X	X		X		X		X		X		X		X		X		
Pre-sleep Questionnaire		X		X		X		X		X		X		X		X		
Study Drug Administration[f]		X		X		X		X		X		X		X		X		
Nocturnal PSG		X		X		X		X		X		X		X		X		
Post-sleep Questionnaire			X		X		X		X		X		X		X		X	X
DSST			X		X		X		X		X		X		X		X	
Memory HVLT-R List[g]		X	X		X	X	X		X	X	X		X	X	X		X	
Leeds Sleep Evaluation Questionnaire			X		X		X		X		X		X		X		X	
Stanford Sleepiness Scale			X		X		X		X		X		X		X		X	
Romberg/Heel-to-toe Tests			X		X		X		X		X		X		X		X	
Masking Question					X		X		X		X		X		X		X	
Subject Diaries (*Dispensed and/or Collected*)[h]					X				X				X				X	
Schedule Next Clinic Visit[i]	X		X		X		X		X		X		X		X		X	

f. 60 minutes before lights-out

g. HVLT-R form to be completed dictated by HVLT Randomisation List

h. Completion required, starting on the evening of this visit, and concluding on the morning, three days later

i. 2-10 days between V1 and V3; 7 days (± 1 day) between V3/N2 and V4/N1; 12 days minimum (± 1 day) between V5 and V6 and between V7 and V8; and 14 days (± 3 days) for F/U visit completion after V9/D2

14.2. Appendix 2: Clinical Laboratory Tests

Serum Chemistry

The following serum chemistry tests will be performed:

- sodium
- potassium
- chloride
- bicarbonate
- glucose
- blood urea nitrogen (BUN)
- creatinine
- calcium
- magnesium
- phosphorus
- uric acid
- total and conjugated bilirubin
- total protein
- albumin
- cholesterol
- triglycerides
- aspartate transaminase (AST)
- alanine transaminase (ALT)
- gamma-glutamyl transferase (GGT)
- alkaline phosphatase

Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- RBC
- mean corpuscular volume (MCV)
- mean corpuscular hemoglobin concentration (MCHC)

- platelet count
- WBC count and differential count, polymorphonuclear leukocytes (neutrophils), lymphocytes, eosinophils, monocytes, basophils, atypical lymphocytes
- Pepsinogen I and II

Urinalysis

Urinalysis will include testing for the following:

- protein
- glucose
- ketones
- blood (hemoglobin)
- pH
- specific gravity
- bilirubin
- nitrites
- microscopic: bacteria, red blood cells (RBC), white blood cells (WBC) casts, crystals

Other Clinical Laboratory Tests

- Urine drug screen: includes a means to detect the presence of drugs prohibited according to the protocol, including opiates, cocaine, amphetamine, cannabinoids, barbiturates, benzodiazepines, phencyclidine, methadone, propoxyphene, antidepressants, phenothiazines, and methaqualone. A positive result for any of the above drugs, without explanation, will preclude the subject from enrollment or continued participation in the study.
- Pregnancy Test (serum at screening and follow-up and urine or serum prior to dose #1 in each session and the morning following the last dose of study medication)
- HIV, Hepatitis B & C (screening only)
- Thyroid Stimulating Hormone (Screening Visit, Early Withdrawal Visit or Follow-up Visit)

14.3. Appendix 3: Country Specific Requirements

No country-specific requirements exist.

14.4. Appendix 4: Pharmacogenetics

Pharmacogenetics-Background

Patients show inter-individual variability in response to drugs both in terms of clinical response and pharmacokinetics as well as in term of occurrence of adverse events. Part of this subjective variability to drug response is likely to be determined by genetic variations in genes that code for protein involved in the drug mechanism of action as well as in drug disposition and elimination. The genetic variations that characterise every individual genetic make up are determined by the presence of variation in the sequence of the DNA. The most common form of diversity in the genome is represented by the variation (polymorphism) of single nucleotide named 'single nucleotide polymorphisms' (SNPs). SNPs may fall into the coding sequence of a gene and may determine an altered structure of the protein that can lead to an altered function of the protein. Pharmacogenetics aim to study how individual genetic differences influence the variability that patients show in response to drug administration. The study of the genome variability is performed determining every individual set of polymorphism (e.g. assessing SNPs) at a given gene or at nearby region of the DNA. Genes that code for proteins that are relevant to the mechanism of action of a specific drug or that code for proteins involved in drug methabolism or disposition are chosen as candidate genes. Very often the understanding of the mechanism of action of drug used in psychiatry is limited, particularly when dealing with drugs that appear to act with unprecedented mechanisms. It is therefore difficult in these circumstances to choose the right candidate gene. Modern technologies allow testing rapidly, and with relatively low cost, a large number of polymorphisms. For example, it is now possible to scan 100 of thousands of SNPs that span across the entire human genome. The screening of the whole genome allow then to test virtually all human genes simultaneously providing an unprecedented great opportunities in identifying genes that play a role in the individual variation to drug response and occurrence of adverse reactions even when the precise mechanism of the drug is uncertain.

In addition to subjective variability to drug response patients show quite a large range of variability in term of response to placebo. Several studies suggest that subjects with high response to placebo share at least in part a common biologic substrate with patients that respond to antidepressant. It is likely that this biological substrate diversity is in part contributing to the individual susceptibility to respond to placebo. Genes that are related with the function of brain areas that activate in patients that show placebo response are likely to determine variability in term of placebo response. Candidate genes for placebo response will be looked within those biochemical pathways that constitute the neurobiologic underpinnings of emotion, stress response, adaptive behaviour that appear to be relevant to placebo response.

Drug	Disease	Gene	Outcome
Clozapine	Schizophrenia [Ancoli-Israel, 1999; Arranz, 1995]	5HT2A	Patients homozygous for the C102 allele appear more frequently in the non-responder (53%) than in the responder group (26%)
Pravastatin	Coronary Atherosclerosis [Kuivenhoven, 1998]	Cholesteryl ester transfer protein (CETP)	Progression of coronary atherosclerosis slowed in B1/B1 homozygotes but not in B2/B2 homozygotes receiving pravastatin
Desipramine	Depression [Daly, 1995]	CYP2D6	Poor metabolizing genotypes at risk of drug accumulation and associated toxicity
Isoniazid	Tuberculosis [Nebert, 1997]	NAT-2 (N-acetyl transferase)	High incidence of peripheral neuropathy in patients with slow acetylator genotypes
Abacavir	HIV [Hetherington, 2002; Ma, 2002; Mallal, 2002]	HLA (human leukocyte antigen)	Caucasian males with HLA B57 variant were at increased risk for experiencing hypersensitivity to abacavir
Tranilast	Restenosis prevention following coronary bypass [Roses, 2002]	UGT1A1	Drug induced hyperbilirubinemia explained by high proportion of affected patients having 7/7 TA repeat genotype, consistent with clinically benign Gilbert's Syndrome
ABT-761	Asthma [Drazen, 1999]	ALOX5	ALOX5 Sp1 promoter genotype (x,x) associated with reduced response to 5-lipoxygenase inhibitor ABT-761

A key component to successful PGx research is the collection of samples during the conduct of clinical studies. Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in handling or response to GW679769.

Inter-individual variability in terms of clinical response and adverse events associated with NK1 antagonists is known. Part of this variability is likely to be determined by genetic variations in genes that are involved in the drug transformation and disposition of these compounds as well as in genes that code for proteins relevant to the mechanism of action of the drug.

In addition, the placebo response that each individual can generate can be related to a given genetic background, still partially unknown. For example, preliminary data

presented by Pfizer show an association between the 5HTT promoter polymorphism (i.e., the "l" form or "s" form, respectively) and both onset of efficacy as well as placebo response in a study on Major Depressive Disorder. The l/l subject group (~30% of population, n~30 in data shown) showed a faster onset of response to the SSRI sertraline compared to the s/s and s/l group (~70%: n~70 in data shown). Interestingly, the l/l group showed a clinical response distinguishable from placebo as early as 2 weeks after the initiation of treatment. Efficacy at 6 weeks or more was similar for all genotypes (~50-60%). According to the Pfizer communication, the l/l group had a lower placebo response (12%) as compared to the s/s and s/l group (~40%) at 6 weeks. If confirmed, this data can open the door to the use of polymorphism as criteria for clinical trials data assessment.

Rationale

Blood samples are collected in this clinical study to enable PGx to be conducted. PGx analyses may help to explain subjective response to GW679769 both as variability to clinical efficacy and pharmacokinetics as well as occurrence of adverse reactions. In these circumstances the genes that would be analyzed will be dependent on the clinical response observed.. For example, the genes analyzed will be dependent of whether the analysis conducted is to help explain clinical efficacy, a PK finding or safety issue. In all cases, however, the PGx analysis conducted will be limited to PGx analysis of GW679769 handling or response and may include the evaluation of specific candidate genes. Depending on the outcome of this study or similar studies the conduction of a wholegenome linkage disequilibrium scan that will make use of SNPs or other markers will be considered.

Candidate genes will be identified among those genes that are believed to be relevant to the mechanism of action drug disposition and metabolism ofGW679769. For example: NK1 receptorgene (*TACR1*) 5-HT transporter gene (*5HTT*). A non exhaustive list of candidate genes that may be considered for this study to address subjective response to GW679769 and to placebo is indicated in the section below. In addition, continuing research may identify novel enzymes/transporters/ proteins/receptors that are relevant to response or handling of GW679769. Genes of these enzymes, transporters, proteins and/or receptors may also be studied as candidate genes.

For the whole genome SNP scan approach, SNP or other genetic marker sets across the genome may be evaluated to identify those markers associated with differential drug handling or response.

The need to conduct PGx analysis may be identified after a study (or set of studies) of GW679769 has been completed and the study data reviewed. For this reason, samples may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples before then. In special cases, the samples may not be studied. This might happen if there are not enough subjects, if the study is stopped for other reasons, or if no questions are raised about how people respond to or handle GW679769.

In the performance of the PGx analysis, GSK may use subjects' medical information, samples, and/or research results. This PGx research is not designed to determine whether other members of the subject's family are at risk of developing insomnia or their response to or handling of GW679769.

Sample Quality Control (QC)

If DNA is extracted from blood samples taken from the clinical study, the DNA may be subjected to sample quality control (QC) analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

Pharmacogenetic Research Objectives

If at any time it appears there is potential variability in GW679769 response or handling (e.g., pharmacokinetics, safety, and/or efficacy) in this clinical trial or in a series of clinical trials, the following objectives may be investigated (assuming sample number is adequate and the availability of genotyping assays):

- to investigate the relationship between polymorphisms in the selected candidate genes and the subjective variability observed in response to GW679769 as measured by PSG and subjective questionnaires on sleep quality.
- Dependent on the clinical study data additional analysis may be performed to investigate the relationship between genetic polymorphisms and tolerability of GW679769 using adverse events.
- Relationship between genetic variants and efficacy of investigational product as well as placebo effects.

Endpoints

Genes and/or polymorphisms that may be studied include:

HTR1A	NM_000524	5-hydroxytryptamine (serotonin) receptor 1A
HTR1B	NM_000863	5-hydroxytryptamine (serotonin) receptor 1B
HTR2A	NM_000621	5-hydroxytryptamine (serotonin) receptor 2A
HTR2C	NM_000868	5-hydroxytryptamine (serotonin) receptor 2C
SERT (SLC6A4)	NM_001045	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLC6A4),
TPH	NM_004179	tryptophan hydroxylase 1 (tryptophan 5-monooxygenase)
VMAT1	NM_003053	vescicular monoamine transporter 1, solute carrier family 18 (vesicular monoamine), member 1 (SLC18A1),
VMAT2	NM_003054	vescicular monoamine transporter 2, solute carrier family 18 (vesicular monoamine), member 2 (SLC18A2)
ADRA2A	NM_000681	adrenergic, alpha-2A-, receptor
ADRA2B	NM_000682	adrenergic, alpha-2B-, receptor
ADRA2C	NM_000683	adrenergic, alpha-2C-, receptor
ADRB1	NM_000684	adrenergic, beta-1-, receptor
ADRB2	NM_000024	adrenergic, beta-2-, receptor, surface
ADRB3	NM_000025	adrenergic, beta-3-, receptor,
TH	NM_000360	tyrosine hydroxylase
NET (SLC6A2)	NM_001043	solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2 (SLC6A2)
DRD1	NM_000794	dopamine receptor D1

DRD2	NM_000795 NM_016574	dopamine receptor D2, transcript variant 1, transcript variant 2
DRD3	NM_000796 NM_033658 NM_033659 NM_033660 NM_033663	dopamine receptor D3, transcript variant a, transcript variant b, transcript variant c, transcript variant d, transcript variant e,
DRD4	NM_000797	dopamine receptor D4
DAT (SLC6A3)	NM_001044	solute carrier family 6 (neurotransmitter transporter, dopamine), member 3
DBH	NM_000787	dopamine beta-hydroxylase (dopamine beta-monooxygenase)
COMT	NM_000754 NM_007310	catechol-O-methyltransferase variant M-COMT transcript variant S-COMT
MAO-A	NM_000240	monoamine oxidase A (MAOA)
MAO-B	NM_000898	monoamine oxidase B (MAOB)
TAC1	NM_003182 NM_013996 NM_013997 NM_013998	tachykinin, precursor 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, or gamma) ranscript variant beta transcript variant alpha transcript variant gamma transcript variant delta
NK1 (TACR1)	NM_001058 NM_015727	tachykinin receptor 1 transcript variant long transcript variant short
NK2 (TACR2)	NM_001057	tachykinin receptor 2
NK3 (TACR3)	NM_001059	tachykinin receptor 3

Enzymes and /or transporters involved in the absorption, metabolism, and/or transport of Novel NK1 Antagonist, e.g. CYP3A4 and CYP2C19.

DNA samples may also be used for assessing polymorphisms related to genes of interest for the pathophysiology of Sleep Disorders, particularly insomnia.

A SNP or sets of SNPs (Haplotypes) play a role in the subjective variability to clinical response to GW679769.

A SNP or sets of SNPs (Haplotypes) play a role in the subjective variability to pharmacokinetics of GW679769.

A SNP or sets of SNPs (Haplotypes) play a role in the occurrence of adverse event related to the administration of GW679769.

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the criteria required for entry into the clinical study, and receives investigational product may take part in the PGx research. Any subject who has received a bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

No administration of investigational product beyond that detailed in the clinical study is associated with the PGx research.

Subject Withdrawal from Study - Pharmacogenetics

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options concerning the PGx sample if already collected:

- PGx research continues per the subject's consent; or,
- Any remaining sample is destroyed.

If a subject withdraws consent from the PGx research or requests sample destruction, the Investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the Investigator study files. In either case, GSK will only keep and study information collected/generated up to that point.

Screen and Baseline Failures - Pharmacogenetics

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the inclusion and exclusion criteria for participation in the clinical study, then the Investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the Investigator study files.

Blood Sample for PGx

In addition to any blood samples taken for the clinical study, a whole blood sample (~10ml) will be collected for the PGx research using a tube containing EDTA. The PGx sample is labeled (or"coded") with a study specific number that can be traced or linked back to the subject by the Investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. It is recommended that the blood sample be taken at the first available opportunity, but may be taken at any time while the subject is participating in the clinical study.

Pharmacogenetics Analyses

The genotypic frequencies of each candidate gene polymorphism will be evaluated in conformity to those expected under normal conditions by employing Hardy-Weinberg Equilibrium testing: For pairs of polymorphisms located within a given gene, the degree

to which alleles from the two sites are correlated (linkage disequilibrium) will also be evaluated. If the genotypes at two polymorphic sites within a gene are shown to be statistically associated with a response to investigational product, the degree of linkage disequilibrium will aid interpretation in that it will indicate the extent to which the two sites are exerting independent effects. Further, a decision regarding the construction and analysis of marker haplotypes -- combinations of alleles from different polymorphic sites that are inherited from one parent -- will be guided by the assessment of linkage disequilibrium. For example, if there is no linkage disequilibrium between polymorphic sites, then haplotype construction will be uninformative. Differences in baseline clinical characteristics and potential contributing covariates will be summarized and compared among genotype (or haplotype) subgroups. Analyses will be carried out to evaluate the degree of association between subject genotype (or haplotype) and selected efficacy and safety parameters. In addition to evaluating the main effects of the genotypes (or haplotypes) on the selected efficacy and safety parameters, the possibility of a treatment group by genotype (haplotype) interaction will also be explored. Under certain circumstances, such as low recruitment of subjects into the pharmacogenetic research or premature discontinuation of the clinical study, it may be decided that the samples will not be used for pharmacogenetic research and the samples will be destroyed.

Sample Size Considerations

The ability to detect differential drug response or handling among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete.

Estimates of sample sizes required to demonstrate genotype effects vary considerably, depending on the assumptions made about allele frequency, genetic effect size, and mechanism of inheritance.[Ancoli-Israel, 1999; Cardon, 2000] In the work by Palmer and Cookson [Palmer, 2001], which assumed a genotype relative risk of 1.5, it was estimated that more than 300 cases and 600 controls would be needed to conduct a genetic association analysis. In contrast, McCarthy and Hilfiker [McCarthy, 2000] showed that with a genotype relative risk of 2.16 and a relatively commonly occurring genotype, only 30 cases and 30 controls would be needed to demonstrate an association. Consequently, it is quite possible that effects with relatively large genotype relative risks may be detectable in individual Phase I or Phase II studies. A range of examples exist to demonstrate robust and clinically relevant PGx data may be generated from PGx studies with sample sizes far less than the sizes proposed by Palmer and Cookson [Palmer, 2001].

Published PGx examples include abacavir hypersensitivity reaction [Hetherington, 2002; Ma, 2002; Mallal, 2002] and tranilast induced hyperbilirubinemia [Roses, 2002] where genetic markers have been found to significantly associate with hypersensitivity reaction (abacavir) and hyperbilirubinemia (tranilast). These examples show that small sample sizes typically encountered in Phase I and Phase II studies may be sufficient to identify clinically relevant genetic associations.

Administrative Matters

Ethical Conduct of the Study and Ethics Approval - Pharmacogenetics

IEC/IRB approval of the PGx consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before IEC/IRB approval can be sought.

Informed Consent - Pharmacogenetics

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. For each subject, informed consent must be obtained prior to any blood being taken for PGx research. The informed consent for the PGx research must be obtained **in addition to** the subject's consent to participate in the clinical study.

Provision of Study Results and Information to Investigators - Pharmacogenetics

GSK may list and summarize the PGx research results from coded samples by subject number in the clinical study report. In this event, the Investigator and study staff would have access to the research results and would be able to link the results to a particular subject. The Investigator and study staff would be directed to hold this information confidentially.

Information Disclosure and Inventions

Pharmacogenetic Data

Data from the case report forms and PGx research using the coded sample will be stored electronically. International regulations for information on computers and relevant laws on processing personal information will be followed.

Confidentiality of Subject's PG Data

GSK advises that participation in this PGx research, withdrawal from this research, sample destruction, and/or PGx results should not be documented in the subject's medical records. Storage of information regarding the PGx research with source documents for the study is permissible if stored in the Investigator study files.

Coded PGx samples and results will be associated with the subject's study specific number in computer databases. Coded PGx research results may be submitted to regulatory agencies as part of an investigational product submission and/or included in a research publication.

Individual genotype results will only be shared with a subject through the Investigator if the subject requests to see their results and it is a requirement of a governmental agency or other legal authority that GSK make these results available. GSK will not release

individual PGx results to anyone else (e.g., family members, primary care physicians, insurers, or employers) under any circumstance, unless required by law.

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14.5. Appendix 5: PSG - Study Instructions

During the study please maintain your usual sleep habits and sleep schedule, and in addition, follow these instructions:

1. Do not change the number or duration of naps you normally take, except do not nap on the days you will be in the sleep clinic.
2. Do not change your normal alcohol intake, except do not consume any alcohol 24 hours prior to study drug administration.
3. Do not change your normal caffeine intake, except do not consume or take any caffeine 8 hours before study drug administration.
4. No exercise 4 hours before study drug administration.
5. Complete your dinner at least 3 hours before study drug administration. Have a snack with HS Dose
6. Do not change your normal nicotine intake.
7. Arrive at the sleep laboratory according to investigator instructions.

Recording Procedure:

The following signals are to be recorded in all PSGs:

- Electroencephalogram: 3 mandatory channels with C3/A2, C4/A1 and O1/A2 montage and a back-up channel: O2/A1 (according to the International 10-20 System of electrode placement)
- Electro-oculogram using infraorbital and supraorbital electrodes: 2 channels
- Chin electromyogram using mentalis and submentalis electrodes: 1 channel
- Electrocardiogram: 1 channel
- For the first screening nights PSG the following signals will be added:
- Oral or/and nasal flow using a thermistor or thermocouple: 1 channel
- Leg electromyogram using 2-leg anterior tibialis electrodes: 2 channels
- Chest and abdominal motion will be measured via strain gauges.

Time in bed (from lights out to lights on) for each NPSG will be approximately 8 hours. The duration of the PSG study will be the amount of time necessary to record exactly 960 pages.

Scoring Procedure:

Sleep staging using the criteria of Rechtshaffen and Kales (1968) will be performed epoch by epoch. Each 30-second epoch is to be manually scored. This epoch duration shall be maintained for the duration of the record. Each epoch is to be assigned a single score. Portions of 2 epochs may not be combined to create a new epoch. The scoring will start at the epoch of lights off and stop at the epoch of lights on. The original numbering of epochs by the investigating site shall not be modified. When an epoch is half/half, it should be scored as the preceding epoch.

14.6. Appendix 6: Sleep Staging

Wake: The EEG contains alpha activity and/or low voltage, mixed frequency activity.

Stage 1: Characterized by absence of alpha activity, low amplitude predominantly theta frequency range EEG activity, and slow-rolling eye-movements.

Stage 2: Onset requires the presence of either: 1) a K-complex defined as a negative sharp wave followed by a slower positive component that lasts more than 0.5 sec or 2) a Sleep Spindle defined as at least 0.5 sec of a centrally-predominant 12-14 Hz waveform. This occurs in the setting of a predominantly theta frequency background. Stage 2 is continued until either: an epoch of waking, SWS criteria are met, or a rapid eye-movement occurs signaling the onset of REM.

Stage SWS: At least 20% of the epoch is comprised of frontally-maximal waveforms that have a period of at least 0.5 sec with an amplitude of at least 75 microvolts.

Stage REM sleep: Onset defined by the presence of a rapid eye-movement defined as phasic lateral eye-movement of wave form period less than 1 sec with both rising and falling phases lasting for 50-200 msec. Electromyogram (EMG) is characterized by tonic suppression with phasic burst activity. EEG is relatively low voltage, mixed frequency with sawtooth waves (vertex maximal notched theta frequency waves). Once REM is identified, it continues until either: an epoch of waking, a spindle, or K complex.

Movement Time (MT): This is a scoring epoch, during which the polygraph record is obscured by movements of the subject. This score is assigned to epochs which immediately precede or follow sleep stages, but in which the EEG and EOG tracings are obscured in more than half the epochs by muscle tension and/or amplifier blocking artifacts associated with movements of the subject. When such an epoch is immediately preceded and followed by Wake, the epoch is scored Wake rather than MT. Discrete body movements and movement arousals should not be scored as MT.

14.7. Appendix 7: Definitions of Variables

Variable	Abbreviation	Definition
Time in bed (minutes)	TIB	From lights off to lights on
Latency to persistent sleep (minutes)	LPS	Measured from lights off to the first epoch of 20 consecutive non-wake epochs (sleep onset). Calculation: number of epochs from lights off to the first of 20 consecutive non-wake epochs (sleep onset) divided by 2.
Total sleep time (minutes)	TST	Duration of REM plus non-REM (Stage 1, Stage 2, Stages 3/4) sleep from lights off to lights on. Calculation: number of REM plus non-REM (Stage 1, Stage 2, Stages 3/4) epochs from lights off to lights on divided by 2.
Wake after sleep onset (minutes)	WASO	Measured from persistent sleep onset to lights on. Calculation: number of wake epochs from persistent sleep onset to lights on divided by 2.
Number of awakenings		Number of periods of awakening from persistent sleep onset to lights on. Calculation: number of times after persistent sleep onset that there is a wake entry on the PSG recording of at least 1 minute duration (at least 2 consecutive wake epochs). Pairs of awakenings must be separated an epoch of non-REM sleep or REM sleep. NOTE: Two wake entries of at least one minute separated by stage 1 sleep is considered as a single awakening.
Sleep efficiency	SE	(total sleep time)/ (time in bed)x100 (%).
Apnea		At least 90% decrease in air flow lasting 10 seconds or longer.
Hypopnea		A 50-90% decrease in nasal or oral flow lasting 10 seconds or longer which is associated with an arousal, an awakening, or a greater than 3% decrease in oxygen saturation.
Apnea/Hypopnea Index	AHI	Number of apnea and hypopnea episodes divided by the TST expressed in hours.

Continued

Variable	Abbreviation	Definition
Periodic Leg Movement	PLM	A leg movement (LM) is defined as a burst of anterior tibialis muscle with a duration between onset and resolution of 0.5-5.0 seconds and with an amplitude of at least 25% of the leg movements recorded during calibration. The LM must be separated from a subsequent LM by at least 5 seconds and not more than 90 seconds. Movements are only counted if they are part of a series of 4 or more consecutive movements meeting these criteria. The LM must be associated with an arousal/awakening to be considered an event (LMA); and to score LMA, the arousal or awakening must follow the LM onset by not more than 3 seconds. Leg movements associated with "Wake" and respiratory events are not counted. (ASDA criteria; see Recording and scoring leg movements. Sleep 1993; 16:749-59) Note: For definition of arousal use ASDA criteria (EEG arousals scoring rules and examples. Sleep 1992;15:174-84).
Periodic Leg Movement Arousal Index	PLMAI	Number of Periodic Leg Movements associated with arousals or awakening divided by the TST expressed in hours.

14.8. Appendix 8: Sleep Montage

SUBJECT: Digital Acquisition Apnea Montage for Baseline, CPAP, Split-night, Insomnia

Label	Jack Inputs	Sens	LFF	HFF	Polarity
C_4 A_1	6-7	7Φv/mm	.3sec	30Hz	---
O_2 A_1	12-7	7Φv/mm	.3sec	30Hz	---
C_3 A_2	5-8	7Φv/mm	.3sec	30Hz	---
O_1 A_2	11-8	7Φv/mm	.3sec	30Hz	---
LOC	23-8	10Φv/mm	.3sec	35Hz	---
ROC	24-8	10Φv/mm	.3sec	35Hz	---
MChin	19-21	3Φv/mm	5sec	35Hz	---
EKG	4-10	30Φv/mm	.3sec	35Hz	---
L tibial	13-17	3Φv/mm	5sec	35Hz	---
R tibial	14-18	3Φv/mm	5sec	35Hz	---
Nasal	29	10Φv/mm	.15sec	15Hz	---
Oral	30	10Φv/mm	.15sec	15Hz	---
Thorax	31	30Φv/mm	.15sec	15Hz	---
Abdomen	32	32Φv/mm	.15sec	15Hz	---
SAO_2	il	150Φv/mm	DC	10Hz	+

14.9. Appendix 9: Excluded Medications

This is a guide and is **not** meant to be an all-inclusive listing of excluded medications. Please contact the Medical Monitor for this protocol if you have questions or concerns regarding any medication your patients may be taking p to or during the course of this study.

AntiAnxiety Agents
Ativan
Librium
Limbitrol
Limbitrol DS
Tranxene
Tranxene SD
Valium
Xanax
Atarax
Effexor XR
Miltown
Paxil
Sinequan
Vistaril

AntiDepressants
Effexor
Effexor XR
Remeron
Serzone
Thioridazine Hydrochloride
Vivactil
Wellbutrin
Wellbutrin SR

Monoamine Oxidase Inhibitors
Nardil
Parnate

Selective Serotonin Reuptake Inhibitors (SSRI)
Celexa
Paxil
Prozac
Zoloft
Lexapro
Serafem
Serzone
Remeron
Effexor
Luvox

Tricyclic Antidepressants and Combinations
Etrafon
Etrafon-Forte

AntiPsychotic Agents
Clozaril
Geodon
Haldol Decanoate
Haldol
Loxitane
Moban
Navane
Orap
Risperdal
Seroquel
Thiothixene
Zyprexa

Herbal Supplements
Bilberry Fruit
Black Cohosh
Cayene
Echinacea
Ephedra (Ma Haung)
Eleutherococcus
Siberian Gingseng
Evening Primrose Oil
Ginkgo Biloba
Ginseng (Panax)
Gotu Kola
Kava-Kava
Lobelia
St. John's Wort

Cytochrome 3A4 Isoenzyme Inhibitors

Antiarrythmics
Cordarone
Quinamm

Antifungal Agents
Diflucan
Sporanox
Nizoral
Monistat

Antiinfectives
Biaxin
erythromycin
Flagyl
Noroxin
troleandomycin

Calcium channel blockers
Posicor

Leukotriene modifiers
Accolate

Proton pump inhibitors
Prilosec

Protease inhibitors
Agenerase
Crixivan
Viracept
Norvir
Invirase

SSRIs
Prozac
Luvox
Zoloft

Miscellaneous
Cannabinoids
Tagamet
Grapefruit juice
Serzone

Cytochrome 3A4 Isoenzyme Inducers

Anticonvulsants
Zarontin
Phenobarbital
Dilantin
Mysoline
Tegretol

Antitubercular Agents
Mycobutin
Rifadin
Rimactane

Corticosteroids
Decadron

Miscellaneous
Rezulin
St. John's Wort

Cytochrome 3A4 Isoenzyme Substrates

Angiotensin II Inhibitors
Cozaar

Antiarrhythemics
Cordarone
Norpace
Xylocaine
Quinaglute
Drua-Tabs
Quinamm

Anticonvulsants
Tegretol
Zarontin

Antiemetics
Marinol
Zofran

Antifungal Agents
Nizoral
Monistat

Antihistamines
Hismanal
Allegra
Claritin
Seldane

Antiinfectives
Cleocin
Dapsone
Erythromycin

Antitubercular Agents
Rifadin
Rimactane

Benzodiazepines
Xanax
Klonopin
Valium
Versed
Restoril
Halcion

Calcium Channel Blockers
Norvasc
Cardizem

DynaCirc
Posicor
Cardene
Adalat
Procardia
Nimotop
Sular
Calan
Isoptin

Chemotherapeutic Agents
Myleran
Cytoxan
Neosar
Adraimycin
Rubex
Toposar
VePesid
Ifex
Taxol
Nolvadex
Vumon
Alkaban-AQ
Velban
Oncovin
Vincasar
Navelbine

Corticosteroids
dexamethasone
methylprednisolone
prednisolone
prednisone

Estrogens, Oral Contraceptives
Estraderm
Estrace

HMG-CoA Reductase Inhibitor
Dilacor
Tiazac
Plendil
Lipitor
Mevacor
Pravachol
Zocor

Immunosupressants
Neoral
Sandimmune
Prograf

LeukotrieneModifiers
Zyflo
Singulair

Narcotic Analgesics
Alfenta
Cocaine
Duragesic
Sublimaze

Protease Inhibitors
Agenerase
Crixivan
Viracept
Norvir
Invirase

Proton Pump Inhibitors
Prevacid
Prilosec

SSRIs
Zoloft
Celexa

TCAs
Elavil
Anafranil
Tofranil

Miscellaneous
Cannabinoids
Propulsid
Flexeril
Dextromethorphan
Aricept
Glynase
Micronase
Serzone
Viagra
Testosterone
Effexor

Cytochrome 2D6 Isoenzyme Inhibitors

Antiarrythmics
Cordarone
Rythmol
Quinaglute
Dura-tabs

Antihistamines
Brompheniramine
Chlorpheniramine
Diphenhydramine
Triprolidine

Antipsychotics
Prolixin
Haldol
Mellaril

Calcium Channel Blockers
Posicor

Protease Inhibitors
Norvir

TCAs
Anafranil
Norpramin

SSRIs
Paxil
Prozac
Luvox
Zoloft

Miscellaneous
Tagamet
Serzone
Darvocet

Cytochrome 2D6 Isoenzyme Inducers

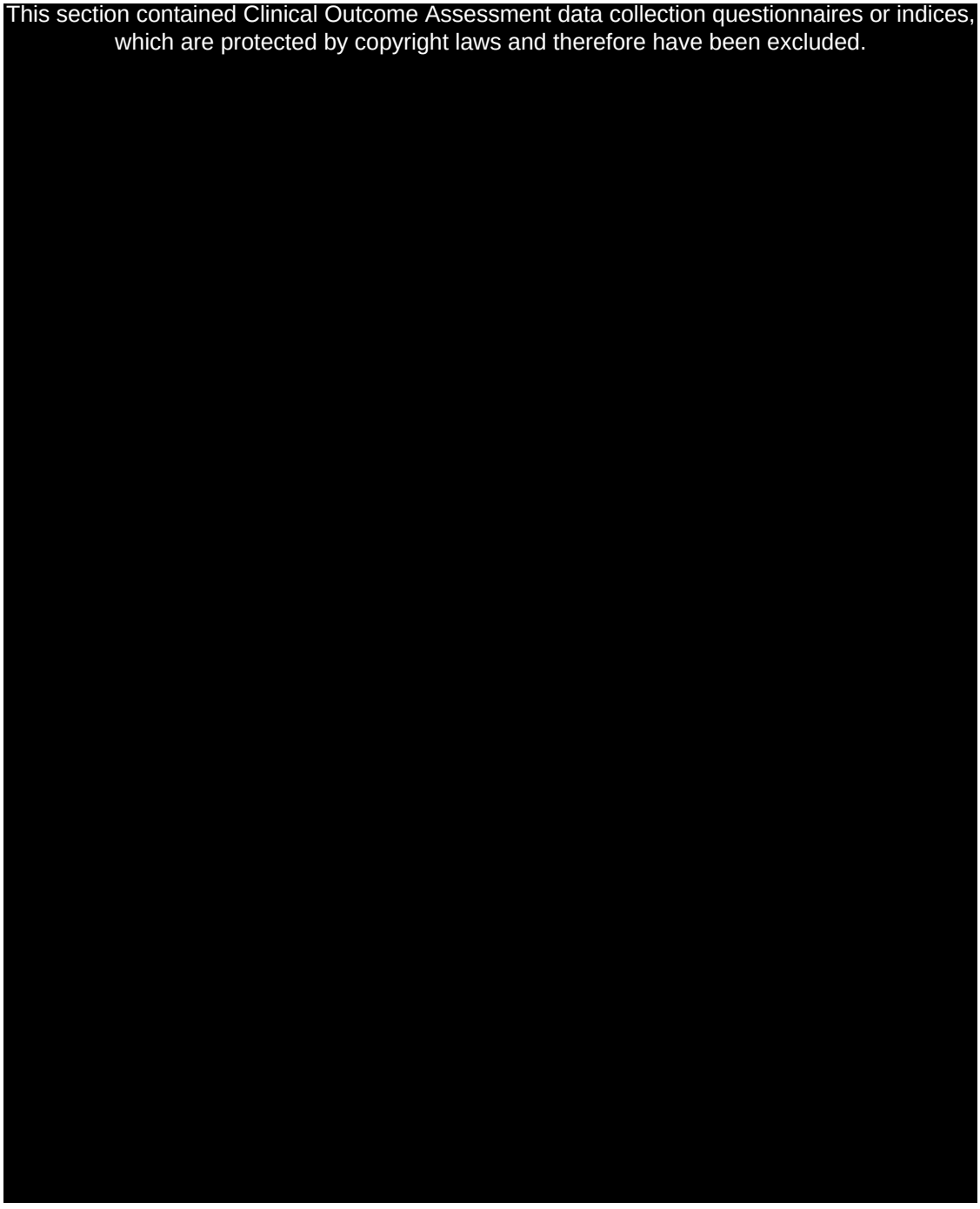
Anticonvulsants
Tegretol
Phenobarbital
Dilantin

Protease Inhibitors
Norvir

Antitubercular Agents
Rifadin
Rimactane

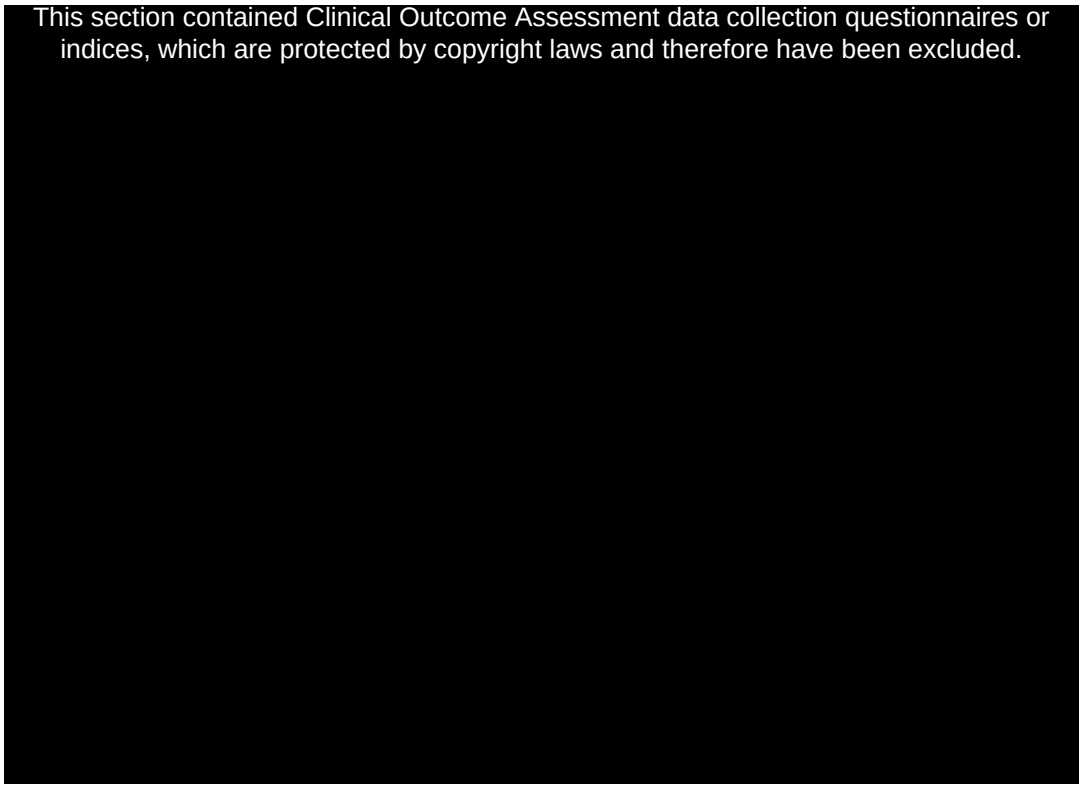
14.10. Appendix 10: Pre-Sleep Questionnaire

PRE-SLEEP QUESTIONNAIRE



14.11. Appendix 11: Post-Sleep Questionnaire

POST-SLEEP QUESTIONNAIRE



14.12. Appendix 12: Protocol Changes

Amendment 1

5.2.1 Inclusion Criteria

Change from

5. On two screening PSGs (on single-blinded placebo administration at each night):
   - TST between 240 and 420 minutes on both nights.
   - Mean LPS of 30 minutes but not < 20 minutes on either night.
   - Mean WASO of 30 min with neither night < 20 min

Change to

5. On two screening PSGs (on single-blinded placebo administration at each night):
   - TST between 240 and 420 minutes on both nights.
   - Mean LPS of 30 minutes or more, but not < 20 minutes on either night.
   - Mean WASO of 30 minutes or more, with neither night < 20 minutes.

5.2.2 Exclusion Criteria

Change from

5. Subjects with active PUD and/or history of PUD of an unknown etiology, except as indicated in inclusion criteria number 10.

Change to

5. Subjects with active PUD and/or history of PUD of an unknown etiology, except as indicated in inclusion criterion number 11.

Change from

29. Use of any investigational drug within 6 months before the screening visit.

Change to

29. Use of any investigational drug within 30 days or 5 half-lives of the study compound prior to the Screening Visit.

5.2.4 Lifestyle Guidelines/Other Restrictions

Change from

- Participants will be instructed to refrain from tobacco, alcohol, and caffeine- or xanthine-containing products for 6 hours prior to and throughout each visit to the clinic.

Change to

- Subjects will be instructed to refrain from alcohol and caffeine- or xanthine-containing products for 6 hours prior to and throughout each visit to the clinic. Subjects' use of tobacco products is forbidden only during subjects' stay in the sleep unit.

Change from

- Subjects are required to be fasting for three hours each visit to the clinic; water is allowed *ad libitum*.

Change to

- Water is allowed *ad libitum*.

6.1.1.2 Initial Screening (Visit 1)

Change from

The following procedures will be performed to determine subject eligibility after obtaining written informed consent:

- Medical/psychiatric history
- Sleep history
- Prior medication history review (within past 30 days)
- Full previous sleep medication history review (with detailed account of all medications within 30 days prior to screening)
- Physical examination
- 12-lead ECG
- Sitting Vital signs
- Laboratory tests (Section 14.2)
- Serum Pregnancy Test
- Urine illicit drug screen
- Alcohol breath test
- Training for cognitive tests and Post-Sleep Questionnaire

- In the event any clinical significant findings are observed, the subject will not be enrolled into the study and will be referred for appropriate follow-up.

Change to

The following procedures will be performed to determine subject eligibility after written informed consent has been obtained:

- Inclusion/Exclusion Criteria review
- Medical/Surgical/Psychiatric history
- Sleep history
- Prior medication history review (*within past 30 days*)
- Full previous sleep medication history review (*with detailed account of all medications within 30 days prior to screening*)
- Physical examination
- 12-lead ECG
- Sitting Vital signs (blood *pressure, heart rate, respiratory rate, oral temperature*)
- Clinical laboratory tests (*Section 14.2*)
- Serum Pregnancy Test
- Urine illicit drug screen
- Alcohol breath test
- ~~Training for cognitive tests and Post-Sleep Questionnaire~~

In the event any clinical significant findings are observed, the subject will not be enrolled into the study and will be referred for appropriate follow-up.

6.1.1.2 Polysomnographic Screening (Visits 2/3)

Change from

Subjects who meet the screening criteria above will return for up to 2 consecutive nights of PSG screening (PSG1 and PSG2) within 2 to 10 days of the initial screening visit. PSG screening will not be done until clinical laboratory test results and ECG results are available.

At the first PSG screening visit (Visit 2), the following will be performed:

- Review of inclusion/exclusion criteria
- Concomitant medication review
- Single-blind placebo administration (1.5 hours before sleep)

- Baseline blood sampling for PK at 1 hour before sleep
- AE review
- Medical/psychiatric/sleep history update
- Alcohol Breath Test
- Presleep questionnaire
- PSG
- Urine or serum pregnancy test
- Urine illicit drug screen
- 12-Lead ECG
- Sitting vital signs

The PSG at Visit 2 will be used to exclude subjects with sleep-related breathing disorders and/or PLMS.

Subjects who do not have sleep-related breathing disorders or PLMS and also have a mean LPS of 30 minutes or more (not < 20 minutes on either night) and TST between 240 and 420 minutes will return for the second screening PSG (Visit 3).

All pre-PSG procedures detailed for Visit 2 above will also be performed at Visit 3. In addition, patients will be required to complete presleep training for HVLT-R (verbal memory tests)

For all PSGs in the study (including screening), the following assessments will be performed upon awakening each morning (8 hours after lights out):

- Postsleep questionnaire (approximately 25 minutes but not before 15 minutes after lights on, lasting 5 minutes
- VAS for sleepiness/alertness
- Neurologic assessment to include Romberg Test and heel-to-toe gait.
- Adverse event assessment (last activity before leaving)

Upon awakening at approximately 8 hours after lights out on the morning following the first PSG night (Visit 2), psychometric testing (DSST and word recall) will also be performed. Psychometric testing will commence approximately 35 min [±15 minutes] after lights on and will last approximately 15 minutes.

Upon awakening at approximately 8 hours after lights out on the morning following the second PSG night (Visit 3), the following procedures will also be performed:

- Cognitive test for sleep-dependent memory. This assessment will be done using the HVLT (verbal memory tests)
- Question about the kind of treatment they had received (unmasking/masking effects)

Throughout the study, subjects will be permitted to leave the sleep laboratory once they are able to perform the Romberg and heel-to-toe gait testing at a level of performance that indicates to the clinician that there are no residual effects. Residual effects that are present to the extent that the subject is unable to leave the sleep laboratory should be recorded as adverse events. Subjects will return home and will be asked to follow study instructions. All subjects who qualify for the study will be scheduled to return a minimum of 12 days later on the same day of the week (± 1 day) for the first double-blind treatment period. Subjects who do not qualify for the double-blind portion of the study will be notified not to return.

Change to

Subjects who complete the screening procedures, identified above, will return for up to 2 consecutive nights of PSG screening (PSG1 and PSG2) within 2 to 10 days of the initial Screening visit.

Subjects should report to the sleep laboratory for Visit 2/Night 1 (V2/N1) – as for all PSG Visit nights – in sufficient time to complete the pre-dose assessments and to maintain the appropriate sleep schedule.

On Visit 2/Night 1 (V2/N1) -- the first PSG Screening visit night -- the following will be performed:

- Inclusion/exclusion criteria review
- Concomitant medication review
- Adverse events inquiry
- Medical/Surgical/Psychiatric/Sleep history update
- Alcohol Breath Test
- Urine or serum pregnancy test
- Urine illicit drug screen
- 12-lead ECG (*approximately 30 minutes before single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Pre-sleep questionnaire
- Memory HVLT-R list
- Single-blind placebo administration (60 minutes before lights-out)

Lights-out will occur at approximately 21:00 hours to 00:00 hours (midnight).

Approximately 60 minutes after this single-blind placebo administration, the following will also be performed:

- 12-lead ECG (just before lights-out)

- Sitting vital signs (blood pressure, heart rate, respiratory rate, oral temperature)
- Nocturnal PSG

At Visit 2/Day 1 (V2/D1) – the morning after V2/N1 – the following will be performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (*about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes*)
- Psychometric testing (*about 35 minutes (± 15 minutes) after lights-on*)
  a Digit Symbol Substitution Test (DSST)
  b Memory HVLT-R list
- VAS for sleepiness/alertness (*about 35 minutes (± 15 minutes) after lights-on*)
  a Leeds Sleep Evaluation Questionnaire
  b Stanford Sleepiness Scale
- 12-lead ECG (*approximately 10 hours after single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature, collected about 10 hours after single-blind dose*)
- Adverse events inquiry (*last activity before Romberg, heel-to-toe tests*)
- Romberg test, heel-to-toe test

Subjects will be allowed to leave the sleep laboratory at V2/D1 and throughout the study, once they are able to perform the Romberg and heel-to-toe gait tests at a performance level that confirms to the clinician that no residual effects exist. Residual effects, present to the extent that subjects are unable to leave the sleep laboratory, should be recorded as adverse events.

The PSG at Visit 2 will be used to exclude subjects with sleep-related breathing disorders or PLMS or both. Subjects without such breathing disorders or PLMS will return for the second Screening PSG night, Visit 3/Night 2 (V3/N2), if the following:

- LPS is greater than or equal to 20 minutes;
- WASO is greater than or equal to 20 minutes; and
- TST is between 240 and 420 minutes.

At Visit 3/Night 2 (V3/N2) – later in the day of V2/D1 – the following procedures will be performed:

- Inclusion/exclusion criteria review
- Concomitant medication review
- Adverse events inquiry

- Medical/Surgical/Psychiatric/Sleep history update
- Alcohol Breath Test
- Urine illicit drug screen
- 12-lead ECG (approximately *30 minutes before single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Pre-sleep questionnaire
- Single-blind placebo administration (*60 minutes before lights-out*)

Approximately 60 minutes after this single-blind placebo administration, the following will also be performed:

- 12-lead ECG (*just before lights-out*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Nocturnal PSG

At Visit 3/Day 2 (V3/D2) – the morning after V3/N2 – the following will be performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (*about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes*)
- Psychometric testing (*about 35 minutes (± 15 minutes) after lights-on*)
  a Digit Symbol Substitution Test (DSST)
  b Memory HVLT-R list
- VAS for sleepiness/alertness (*about 35 minutes (± 15 minutes) after lights-on*)
  a Leeds Sleep Evaluation Questionnaire
  b Stanford Sleepiness Scale
- Question about the kind of treatment they received *(unmasking/masking effects*)
- 12-lead ECG (*approximately 10 hours after single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature, collected about 10 hours after single-blind dose*)
- Adverse events inquiry (*last activity before Romberg, heel-to-toe tests*)
- Romberg test, heel-to-toe test

As always, subjects are free to leave the sleep laboratory in the morning following PSG nights, once the Romberg and heel-to-toe gait tests confirm that no residual effects exist. Residual effects that prevent subjects from promptly leaving the sleep laboratory should be recorded as adverse events.

All subjects who qualify for the study will be scheduled to return a minimum of seven (7) days (± 1 day) after the V2/N1 date, for the first double-blind treatment period. Subjects who do not qualify for the double-blind portion of the study will be notified not to return.

Those subjects scheduled to return for the first double-blind treatment period will also be required to complete a SUBJECT DIARY. The diary consists of three sets of each of the following items:

- one pre-sleep questionnaire
- one post-sleep questionnaire
- one Leeds Sleep Evaluation Questionnaire
- one Stanford Sleepiness Scale

Starting on the night of V3/D2 and continuing on each of the succeeding two nights, subjects will complete three sets of forms, as are identified, immediately above.. Subjects will be required to return the completed diaries to the clinic at Visit 4/Night 1 (V4/N1) for study-record maintenance.

6.2.1 Double-Blind Treatment Period (Visits 4/5, 6/7, and 8/9)

Change from

If all screening criteria are met, subjects will be required to return to the sleep laboratory for 3 sessions consisting of two consecutive nights of polysomnographic recording (PSG3 - PSG8). Each session will be separated by a minimum of 12 days and will occur on the same day of the week (± 1 day). Subjects will be required to report to the sleep laboratory approximately 2 hours prior to the start of their PSG.

At each visit, a blood sample for pharmacokientics will be obtained prior to study medication administration. The following procedures must be performed prior to PSG at each visit (may be before or after study medication administration):

- Sitting Vital signs
- Presleep questionnaire
- Concomitant medication usage
- AE assessment
- Changes in sleep habits
- Alcohol breath test
- Urine or serum pregnancy test (pre-dose first night of PSG during each session)
- Blood sample for Pharmacogenetics (pre-dose Visit 4 only)

In addition, a 12-lead ECG will be obtained within 30 minutes following administration of study medication in each session on the first PSG night only.

Also, a sample for pharmacokinetics will be obtained when the subjects returns to the unit for the second PSG night in each session.

Subjects will then receive double-blind study medication (GW679769 or placebo) according to the randomization schedule approximately 60 minutes prior to lights out. Lights out will occur at approximately 21:00 to 23:00. For all PSGs in the study, the following assessments will be performed upon awakening each morning (aproximately 8 hours after lights out):

- Postsleep questionnaire (approximately 25 minutes but not before 15 minutes) after lights on, lasting 5 minutes
- VAS for sleepiness/alertness
- Neurologic assessment to include Romberg Test and heel-to-toe gait.
- Adverse event assessment (last activity before leaving)
- PK blood sample (aproximately 10 hours from time of dosing the night before)

Upon awakening at approximately 8 hours after lights out on the morning following the first PSG night of each session (Visits 4, 6, and 8), psychometric testing (DSST, word recall) will also be performed. Psychometric testing will commence approximately 35 min [±15 minutes] after lights on and will last approximately 15 minutes.

Upon awakening at approximately 8 hours after lights out on the morning following the second PSG night of each session (Visits 5, 7, and 9), the following procedures will also be performed:

- Cognitive test for sleep-dependent memory. This assessment will be done using the HVLT-R (verbal memory tests) .
- Question about the kind of treatment they had received (unmasking/masking effects)

Subjects will also be required to complete post-sleep questionnaires for the first three mornings at home after their clinical visits in each session.

On the morning after the final PSG night only (Visit 9), the following will be performed:

- Physical examination
- Sitting Vital signs
- Clinical laboratory tests (Section 14.2)
- Urine or serum pregnancy test, if applicable
- 12-Lead ECG

Throughout the study, subjects will be permitted to leave the sleep laboratory once they are able to perform the Romberg and heel-to-toe gait testing at a level of performance to indicate to the clinician that there are no residual effects. Residual effects that are present to the extent that the subject is unable to leave the sleep laboratory should be recorded as adverse events.

During the 12 days between sessions, no other drugs will be allowed, in particular hypnotics. No changes of life-style or extreme exercise will be allowed.

Change to

If all screening criteria are met, subjects will be required to return to the sleep laboratory for 3 sessions, each consisting of two consecutive nights of polysomnographic recording (PSG3 - PSG8). Each session will be separated by a minimum of 12 days and will occur on the same day of the week (± 1 day).

Subjects will be required to report to the sleep laboratory in sufficient time to complete the pre-dose assessments and to maintain the appropriate sleep schedule. Sitting vitals signs to be collected and 12-lead ECGs to be conducted throughout the study should always be performed prior to the collection of blood samples.

At each of the following study visits:

Visit 4/Night 1 (V4/N1)
Visit 5/Night 2 (V5/N2)
Visit 6/Night 1 (V6/N1)
Visit 7/Night 2 (V7/N2)
Visit 8/Night 1 (V8/N1)
Visit 9/Night 2 (V9/N2)

the study procedures, below, must be performed prior to dosing:

- Concomitant medication review
- Adverse events inquiry
- Review of changes in subject's sleep habits
- Alcohol breath test
- Urine or serum pregnancy test
- Urine illicit drug screen
- Blood sample for Pharmacogenetics (*V4/N1 only*)
- pK sample collection
- 12-lead ECG (*approximately 30 minutes before study-drug administration*)
- Pre-sleep questionnaire
- Memory HVLT-R list (*only at V4/N1, V6/N1, V8/N1*)

Double-blind study-drug administration will occur 60 minutes before lights-out. As with all PSG visit nights in this study, lights out will occur at approximately 21:00 hours to 00:00 hours (midnight).

Approximately 60 minutes after the double-blind study-drug administration, the following will also be performed:

- 12-lead ECG (*just before lights-out*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Nocturnal PSG

At each of the following study visits:

Visit 4/Day 1 (V4/D1)
Visit 5/Day 2 (V5/D2)
Visit 6/Day 1 (V6/D1)
Visit 7/Day 2 (V7/D2)
Visit 8/Day 1 (V8/D1)

the assessments, below, will be performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (*about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes*)
- Psychometric testing (*about 35 minutes (± 15 minutes) after lights-on*)
  a Digit Symbol Substitution Test (DSST)
  b Memory HVLT-R list
- VAS for sleepiness/alertness (about *35 minutes (± 15 minutes) after lights-on*)
  a Leeds Sleep Evaluation Questionnaire
  b Stanford Sleepiness Scale
- Question about the kind of treatment they received (*unmasking/masking effects) (only V5/D2, V7/D2, and V9/D2*)
- 12-lead ECG (*approximately 10 hours after single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature), collected about 10 hours after double-blind dose*)
- pK blood sample (*10 hours from time of dosing the night before*)
- Adverse events inquiry (*last activity before Romberg, heel-to-toe tests*)
- Romberg test, heel-to-toe test

At Visit 9/Day 2 (V9/D2), the following assessments will be performed upon awakening (approximately 8 hours after lights-out):

- Post-sleep questionnaire (*about 25 minutes, but not before 15 minutes after lights-on, lasting 5 minutes*)

- Psychometric testing (*about 35 minutes (± 15 minutes*) after lights-on)
  a Digit Symbol Substitution Test (DSST)
  b Memory HVLT-R list
- VAS for sleepiness/alertness (*about 35 minutes (± 15 minutes) after lights-on*)
  a Leeds Sleep Evaluation Questionnaire
  b Stanford Sleepiness Scale
- Question about the kind of treatment they received (*unmasking/masking effects) (only V5/D2, V7/D2, and V9/D2*)
- Physical examination
- 12-lead ECG (*approximately 10 hours after single-blind dose*)
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature, collected about 10 hours after double-blind dose*)
- Laboratory tests (*Section 14.2*)
- Serum Pregnancy Test
- pK blood sample (*10 hours from time of dosing the night before*)
- Adverse events inquiry (*last activity before Romberg, heel-to-toe tests*)
- Romberg test, heel-to-toe test

Subjects will be permitted to leave the sleep laboratory once they are able to perform the Romberg and heel-to-toe gait testing at a level of performance to indicate to the clinician that there are no residual effects. Residual effects, present to the extent that the subject is unable to leave the sleep laboratory, should be recorded as adverse events.

As after Visit 3, subjects will also be required to complete a subject diary after each of Visits 5, 7, and 9. Like that completed after Visit 3, the diary consists of three sets of each of the following items:

- one pre-sleep questionnaire
- one post-sleep questionnaire
- one Leeds Sleep Evaluation Questionnaire
- one Stanford Sleepiness Scale

Starting on the night of V5/D2 and continuing on each of the succeeding two nights, subjects will complete three sets of forms, as are identified immediately above. Similarly, subjects will complete a subject diary, starting on each of the nights of V7/D2 and V9/D2. Subjects will be required to return the completed diaries to the clinic at their next study visit for study-record maintenance.

During the 12 days between sessions, no other drugs will be allowed, in particular hypnotics. No changes of life-style or extreme exercise will be allowed.

6.2.2 Early Withdrawal Visit Assessment

Change from

For subjects who are withdrawn from the study the following will be performed:

- Sitting vital signs
- Physical exam
- Concomitant medications
- Adverse events probe. The investigator will contact the medical monitor regarding any gastric AEs regardless of relationship to study drug.
- 12-Lead ECG
- Thyroid function tests
- Blood draw for clinical labs (in particular for LPT) and PK
- Post-Sleep Questionnaire

Change to

For subjects who are withdrawn from the study the following assessments will be performed as promptly as can be scheduled:

- Post-Sleep Questionnaire
- Physical examination
- 12-lead ECG
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Concomitant medications
- Adverse events inquiry. (The Investigator will contact the medical monitor regarding any gastric AEs regardless of relationship to study drug.)
- Thyroid function tests
- Serum pregnancy test
- Blood draw for clinical labs (in particular for LFT) and pK (Any significant abnormal results will be repeated until resolution.)

6.2.3 Follow-up Visit(s) Assessments

Change from

A follow-up visit will be conducted at 14 days (+/- 3 days) after the last night of PSG recording (Visit 9). The following will be performed at the follow-up visit:

- Physical examination
- 12-lead ECG
- Sitting vital signs (BP, HR)
- Clinical laboratory tests (Section 14.2)
- Serum Pregnancy Test
- Any significant abnormal results from the end of study visit will be repeated until resolution
- Clinical ratings about insomnia
- Post-Sleep Questionnaire

Change to

A follow-up visit will be conducted 14 days (± 3 days) after the last night of PSG recording (Visit 9). The following will be performed at the follow-up visit:

- Post-Sleep Questionnaire
- Leeds Sleep Evaluation Questionnaire; Stanford Sleepiness Scale
- Physical examination
- 12-lead ECG
- Sitting vital signs (*blood pressure, heart rate, respiratory rate, oral temperature*)
- Concomitant medications
- Adverse events inquiry. (The Investigator will contact the medical monitor regarding any gastric AEs regardless of relationship to study drug.)
- Thyroid function tests
- Serum Pregnancy Test
- Clinical laboratory tests (Section 14.2) (Any significant abnormal results from the end of study visit (Visit 9) will be repeated until resolution.)

6.3.1 Vital Signs

Change from

Vital signs will be measured at the initial screening visit, and before and after PSG on screening and treatment nights. Vital signs include the following:

- sitting blood pressure
- sitting pulse
- respiratory rate

- oral temperature

Before blood pressure and pulse are measured, the subject must be in a seated position and resting for at least 5 minutes. (The same position should be used each time vital signs are measured for a given subject). Any vital sign value that is judged by the investigator as a clinically significant change (worsening) when compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored until the event has resolved or stabilized.

Change to

Vital signs will be measured at the initial Screening visit, and approximately 30 minutes before, 60 minutes after, and 10 hours after dosing (either single-or double-blind) on Screening PSG and treatment PSG nights. Vital signs to be measured include the following:

- sitting blood pressure
- heart rate
- respiratory rate
- oral temperature

Before blood pressure and heart rate are measured, the subject must be in a seated position and resting for at least 5 minutes. (The same position should be used each time vital signs are measured for a given subject). Any vital sign value that is judged by the Investigator as a clinically significant change (worsening) when compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored until the event has resolved or stabilized.

6.3.2 Electrocardiography

Change from

A 12-lead ECG will be conducted at the initial screening visit and the prior to dosing on the first evening of each pair of double-blind treatment nights. A qualified physician will be responsible for providing interpretation of the electrocardiograph. Any electrocardiogram finding that is judged by the investigator as a clinically significant change (worsening) when compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored until the event has resolved or stabilized.

Change to

A 12-lead ECG will be conducted at the following times with respect to study-drug administration in Study GW 679769/903:

- Thirty (30) minutes before dosing (either single- or double-blind)
- Approximately 60 minutes after dosing (either single- or double-blind)
- Approximately ten (10) hours after dosing (either single- or double-blind)

A qualified physician will be responsible for providing interpretation of the electrocardiograph. Any electrocardiogram finding that is judged by the Investigator as a clinically significant change (worsening) when compared to a baseline value will be considered an adverse event, recorded on the CRF, and monitored until the event has resolved or stabilized.

6.3.3 Assessment of morning residual effects

Change from

Residual effects relative to morning alertness and psychomotor function will be measured by the use of psychometric test (DSST) and a VAS for sleepiness/alertness, respectively. These assessments will be made on the mornings following nights spent in the sleep laboratory. The VAS for sleepiness/alertness and the psychometric test (DSST) will be completed 35 minutes (±15 minutes) after lights on.

Change to

Residual effects relative to morning alertness and psychomotor function will be measured by the use of psychometric tests (DSST and HVLT-R) and two VAS instruments for sleepiness/alertness (Leeds Sleep Evaluation Questionnaire and Stanford Sleepiness Scale). These assessments will be made on the mornings following nights spent in the sleep laboratory. The HVLT-R will also be completed at V2/N1, V4/N1, V6/N1, and V8/N1.

The two VAS instruments for sleepiness/alertness and the psychometric tests will be completed approximately 35 minutes (±15 minutes) after lights on. The HVLT-R tests to be completed at V2/N1, V4/N1, V6/N1, and V8/N1 may be completed at anytime prior to single- or double-blind dosing.

6.4 Efficacy

Change from

Sleep questionnaires (Section 14.8 and Section 14.9) will be performed as described in Section 6.2.

All questionnaires and cognitive tests administered on site will be integrated into a laptop computer and operated from a keyboard. In the case the subject is not able to self-operate the computer, an assistant will provide help as needed and may digit the information or supervise the execution of particular test.

Change to

Sleep questionnaires (Section 14.10 and Section 14.11) will be performed as described in Section 6.2.

~~All questionnaires and cognitive tests administered on site will be integrated into a laptop computer and operated from a keyboard. In the case the subject is not able to self-operate~~

~~the computer, an assistant will provide help as needed and may digit the information or supervise the execution of particular test.~~

6.5.1 Blood sample for PK

Change from

Blood samples for pharmacokinetic analysis will be obtained at each 2-night PSG session in the following order: at pre-dose and approximately 10 hours postdose following cognitive testing (morning of day 2), at pre-dose on day 2, and approximately 10 hours postdose following cognitive testing (morning of day 3).

In case of deviation the actual time of the collection must be annotated.

Blood samples (5 mL) for the analysis of GW 679769 and its major metabolite (GW525060) will be collected into tubes containing EDTA, immediately chilled on crushed water ice. Plasma will be separated by refrigerated centrifugation (approximately 4°C, 500xg for 15 minutes) within 1 hour of collection. The resultant plasma samples will be removed, transferred to 3.6 mL polypropylene (Nunc) pre-labelled storage tubes and stored frozen at approximately -20°C pending shipment for drug analysis. Plasma concentration-time data of unlabelled GW679769 and its major metabolite (GSK525060) will be evaluated by standard non-compartmental methods and population-based mixed models.

Change to

Blood samples for pharmacokinetic analysis will be obtained at all double-blind treatment visits in the following order: at pre-dose and 10 hours post-dose, following cognitive testing on the next morning.

In case of deviation from the times specified here for pK sampling, the actual time of the collection must be annotated.

Blood samples (5 mL) for the analysis of GW 679769 and its major metabolite (GW525060) will be collected into tubes containing EDTA, and immediately chilled on crushed ~~water~~ ice. Plasma will be separated by refrigerated centrifugation (approximately 4°C, 500xg for 15 minutes) within 1 hour of collection. (Where refrigerated centrifugation is not possible, the blood samples may be centrifuged, unrefrigerated, as long as they have been maintained at 4°C just prior to centrifugation.)

The resultant plasma samples will be removed, transferred to 3.6 mL polypropylene (Nunc) pre-labelled storage tubes and stored frozen at approximately -20°C pending shipment for drug analysis. Plasma concentration-time data of unlabelled GW679769 and its major metabolite (GSK525060) will be evaluated by standard non-compartmental methods and population-based mixed models.

6.6.2 Neurocognitive Measures

Change from

The Digit Symbol Substitution Test (DSST)

Immediate and delayed word recall [Vermeeren, 2002]

The Hopkins Verbal Learning Test - Revised [Lacritz, 2001] will be used in this study. THE HVLT-R offers a brief assessment of verbal learning and memory (recognition and recall) and its use has been validated with brain-disordered populations (e.g., Alzheimer's disease, Huntington's disease, amnestic disorders). Six distinct forms of the HVLT-R are available, eliminating practice effects on repeated administrations. Each form consists of a list of 12 nouns (targets) with four words drawn from each of three semantic categories. The semantic categories differ across the six forms, but the forms are very similar in their psychometric properties. The HVLT-R tasks include three learning trials, a delayed recall trial (20-25 minute delay), and a yes/no delayed recognition trial. This latter trial consists of a randomized list that includes the 12 target words and 12 nontarget words, 6 of which are drawn from the same semantic categories as the targets. Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index.

Change to

The Digit Symbol Substitution Test (DSST)

~~Immediate and delayed word recall [Vermeeren, 2002]~~

The Hopkins Verbal Learning Test - Revised [Lacritz, 2001] will be used in this study. THE HVLT-R offers a brief assessment of verbal learning and memory (recognition and recall) and its use has been validated with brain-disordered populations (e.g., Alzheimer's disease, Huntington's disease, amnesic disorders). Eight distinct forms of the HVLT-R are available, eliminating practice effects on repeated administrations. Each form consists of a list of 12 nouns (targets) with four words drawn from each of three semantic categories. The semantic categories differ across the eight forms, but the forms are very similar in their psychometric properties. The HVLT-R tasks include three learning trials, a delayed recall trial (20-25 minute delay), and a yes/no delayed recognition trial. This latter trial consists of a randomized list that includes the 12 target words and 12 non-target words, 6 of which are drawn from the same semantic categories as the targets. Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index.

8.2 Prohibited Medications

Change from

- Subjects are not permitted to take psychotropic drugs or antidepressants (including monoamine oxidase inhibitors, MAOI's) within the time frames specified below prior to the screening visit until following completion of the follow-up visit:
    - At least 12 weeks: depot neuroleptics
    - At least 4 weeks: MAOIs or Fluoxetine
    - At least 14 days or 5 half-lives (whichever is longer): hypnotics, benzodiazepines, and all other sedatives (including sedating antihistamines)
    - At least 14 days:
    - Antidepressants other than MAOIs or fluoxetine (e.g. TCAs, SSRIs, SNRIs), lithium and oral antipsychotics
    - Any CNS-active herbal/natural supplement or preparation known or thought to have any psychoactive effects

Change to

- Subjects are not permitted to take psychotropic drugs or antidepressants (including monoamine oxidase inhibitors, MAOIs) within the time frames specified below prior to the Screening visit until ~~following~~ completion of the follow-up visit:
    - At least 12 weeks: depot neuroleptics
    - At least 4 weeks: MAOIs or Fluoxetine
    - At least 14 days or 5 half-lives (whichever is longer): hypnotics, benzodiazepines, and all other sedatives (including sedating antihistamines)
    - At least 14 days: Antidepressants other than MAOIs or fluoxetine (e.g. TCAs, SSRIs, SNRIs), lithium and oral antipsychotics
    - At least 14 days: Any CNS-active herbal/natural supplement or preparation known or thought to have any psychoactive effects

Change from

- Use of any other investigational drugs is not permitted within 6 months before the screening visit until completion of the final follow-up visit

Change to

- Use of any other investigational drugs within 30 days or 5 half-lives of the study compound prior to the Screening Visit is not permitted until completion of the final follow-up visit.

14.1 Appendix 1: Time and Events Table

Changed from

14.1 Appendix 1: Time and Events Table

Procedures and assessments	Initial Screen Visit	Pair of Screening PSG Nights				First Pair of Double-Blind Treatment Nights				Second Pair of Double-Blind Treatment Nights				Third Pair of Double-Blind Treatment Nights				Follow-Up
		Night 1		Night 2		Night 1		Night 2		Night 1		Night 2		Night 1		Night 2		
		PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	
Informed consent	X																	
Inclusion/exclusion criteria review	X	X		X														
Medical/psychiatric/sleep history	X	X		X														
Question regarding any changes in sleep habits						X		X		X		X		X		X		
Prior medication review (including sleep medication)	X																	
Concomitant medication review		X		X		X		X		X		X		X		X		
Physical examination	X																X	X
Vital signs measurements	X	X		X		X		X		X		X		X		X	X	X
Clinical laboratory tests (Section 14.2)	X																X	X
Pregnancy test (Section 14.2)	X	X				X				X				X			X	X

Appendix 1: Time and Events Table (Continued)

Procedures and assessments	Initial Screen Visit	Pair of Screening PSG Nights				First Pair of Double-Blind Treatment Nights				Second Pair of Double-Blind Treatment Nights				Third Pair of Double-Blind Treatment Nights				Follow-Up
		Night 1		Night 2		Night 1		Night 2		Night 1		Night 2		Night 1		Night 2		
		PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	
12-lead electrocardiogram	X	X		X		X				X				X			X	X
Alcohol breathalyzer test	X	X		X		X		X		X		X		X		X		
Blood sample for PK		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for PGx[1]						X												
Adverse events inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Presleep questionnaire		X		X		X		X		X		X		X		X		
Administer study drug		X		X		X		X		X		X		X		X		
Nocturnal PSG		X		X		X		X		X		X		X		X		
Postsleep questionnaire			X		X		X		X		X		X		X		X	X
DSST			X				X				X				X			
Word recall - training				X														
Word recall baseline test			X															

Appendix 1: Time and Events Table (Continued)

Procedures and assessments	Initial Screen Visit	Pair of Screening PSG Nights				First Pair of Double-Blind Treatment Nights				Second Pair of Double-Blind Treatment Nights				Third Pair of Double-Blind Treatment Nights				Follow-Up
		Night 1		Night 2		Night 1		Night 2		Night 1		Night 2		Night 1		Night 2		
		PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	
Word recall HVLT-R list					X		X		X		X		X		X		X	
VAS for sleepiness/alertness			X		X		X		X		X		X		X		X	
Romberg test			X		X		X		X		X		X		X		X	
Heel-to-toe gait test			X		X		X		X		X		X		X		X	
Masking question					X				X				X				X	
Schedule next clinic visit	X		X		X		X		X		X		X		X		X	
Provide study instructions	X		X		X		X		X		X		X		X		X	

1. Pharmacogenetic sample can be obtained at anytiume during the study after separate pharmacogenetic consent has been obtained.

Changed to:

14.1. Appendix 1: Time and Events Table

Procedures and Assessments	Screen Visit	Pair of Screening PSG Nights				Pairs of Double-Blind Treatment Sessions												Early Withdrawal or F/U Visit
						First				Second				Third				
	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9		
		N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	
Informed Consent	X																	
Inclusion/Exclusion Criteria Review	X	X		X														
Medical/Surgical/Psychiatric/ Sleep History	X	X		X														
Prior Medication History[a]	X																	
Concomitant Med Review		X		X		X		X		X		X		X		X		X
Adverse Events Inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep-habit Changes Review						X		X		X		X		X		X		
Physical Examination	X						X		X		X		X		X		X	X
12-lead ECG[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sitting Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Lab Tests (*Section 14.2*)	X																X	X
pK Sample Collection						X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacogenetic Sampling[d]						X												
Pregnancy Test[e]	X	X				X				X				X			X	X
Urine Illicit Drug Screen	X	X		X		X		X		X		X		X		X		

j. Within past 30 days; including sleep medication
k. 30 min, 60 min, and 10 hours after single- or double-blind dosing.
l. Blood pressure, heart rate, respiratory rate, oral temperature
m. Pre-dose
n. Serum test at V1, V9/D2, and Early W/D or F/U; for all other visits, serum or urine test

Appendix 1: Time and Events Table (Continued)

Procedures and Assessments	Screen Visit	Pair of Screening PSG Nights				Pairs of Double-Blind Treatment Sessions												Early Withdrawal or F/U Visit
						First				Second				Third				
	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9		
		N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	N1	D1	N2	D2	
Alcohol Breath Test	X	X		X		X		X		X		X		X		X		
Pre-sleep Questionnaire		X		X		X		X		X		X		X		X		
Study Drug Administration[f]		X		X		X		X		X		X		X		X		
Nocturnal PSG		X		X		X		X		X		X		X		X		
Post-sleep Questionnaire			X		X		X		X		X		X		X		X	X
DSST			X		X		X		X		X		X		X		X	
Memory HVLT-R List[g]		X	X		X	X	X		X	X	X		X	X	X		X	
Leeds Sleep Evaluation Questionnaire			X		X		X		X		X		X		X		X	
Stanford Sleepiness Scale			X		X		X		X		X		X		X		X	
Romberg/Heel-to-toe Tests			X		X		X		X		X		X		X		X	
Masking Question					X		X		X		X		X		X		X	
Subject Diaries (*Dispensed and/or Collected*)[h]					X				X				X				X	
Schedule Next Clinic Visit[i]	X		X		X		X		X		X		X		X		X	

o. 60 minutes before lights-out

p. HVLT-R form to be completed dictated by HVLT Randomisation List

q. Completion required, starting on the evening of this visit, and concluding on the morning, three days later

r. 2-10 days between V1 and V3; 7 days (± 1 day) between V3/N2 and V4/N1; 12 days minimum (± 1 day) between V5 and V6 and between V7 and V8; and 14 days (± 3 days) for F/U visit completion after V9/D2

14.2 Appendix 2: Clinical Laboratory Tests

Other Clinical Laboratory Tests

Change from

- Thyroid Stimulating Hormone (screening only)

Change to

- Thyroid Stimulating Hormone (Screening Visit, Early Withdrawal Visit or Follow-up Visit)

14.10 Appendix 10: Pre-Sleep Questionnaire

Pre-Sleep Questionnaire added.

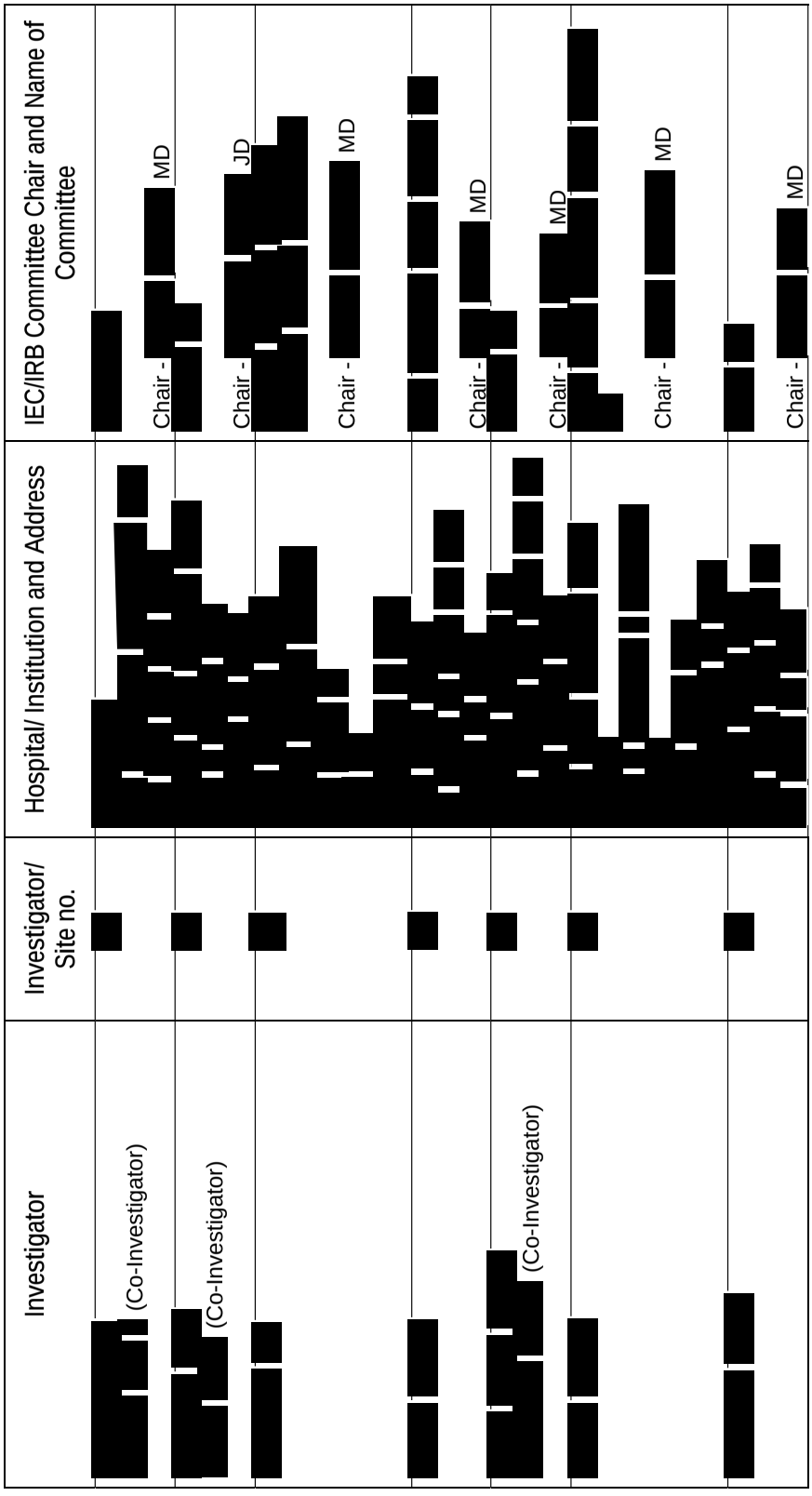
14.11 Appendix 11: Post-Sleep Questionnaire

Post-Sleep Questionnaire added.

ABBREVIATIONS

AE	Adverse Event

LIST OF INVESTIGATORS AND IECS/IRBS FOR GW679769/903 (ZM2005/00173/00)



This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

NOT TO BE USED FOR SUBJECT ENROLLMENT

INFORMED CONSENT
AGREEMENT TO BE IN A RESEARCH STUDY

NAME OF DRUG/DEVICE COMPANY:	SmithKline Beecham Corporation doing business as GlaxoSmithKline
CITY AND STATE:	Philadelphia, Pennsylvania
NUMBER AND NAME OF STUDY:	A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW679769 (30 mg and 90 mg) on sleep continuity, PSG sleep recordings, subjective sleep assessment, and daytime cognitive function in subjects with primary insomnia (GW 679769/903)
STUDY DOCTOR:	Dr. [redacted] Ph.D Dr. [redacted] M.D.
ADDRESS OF STUDY SITE:	[redacted]
TELEPHONE NUMBERS, DAYTIME: AFTER HOURS:	[redacted]

INTRODUCTION

You are being asked to volunteer for a medical research study. Before agreeing to participate in this study, it is important that you read this form. This form, called a consent form, describes the purpose, procedures, benefits, financial payment, risks, and discomforts of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time. No promises or guarantees can be made as to the results of the research study. Please ask as many questions as you need to so that you can decide whether you want to be in the study.

The information and any materials or items that you are given about or during this study- such as information regarding the study drug(s) or the type of study being performed - should be considered confidential business information of the study sponsor, GlaxoSmithKline. You are of course free to discuss such information under confidence with your doctor or with your friends and family while considering whether to participate in this study or at any time when discussing your present or future healthcare.

If you are not completely truthful with the study doctor and study staff regarding your health history, you may harm yourself by participating in this study.

The study doctor is being paid by the sponsor (GlaxoSmithKline) to conduct this medical research study.

PURPOSE OF STUDY

GW 679769 is an investigational drug that is being tested for use in patients with primary insomnia. "Investigational" means the drug being tested has not been approved by the United States Food and Drug Administration (FDA) for sale as a prescription or over-the-counter medication.

NOT TO BE USED FOR SUBJECT ENROLLMENT

The purpose of this study is to see if GW 679769 is effective in treating people with primary insomnia.

STUDY TREATMENT

If you qualify for the study, you will receive one of the following during each of three study sessions:

- GW 679769 30 mg
- GW 679769 90 mg
- placebo

A placebo is pill that looks like the study drug but has no active ingredients.

The treatment you receive will be assigned by chance, like the flip of a coin. All subjects will receive each of the study medications above sometime during the study.

This is a double-blind study, which means that neither you nor the study doctor will know which treatment you are receiving. However, the study staff can get this information quickly if you have a problem.

HOW LONG THE STUDY WILL LAST AND THE NUMBER OF SUBJECTS EXPECTED TO PARTICIPATE

It is expected that the maximum length of time you will participate in this study will be up to approximately 10 weeks. A minimum of 48 subjects are expected to participate in this study.

TO BE IN THIS STUDY

You cannot be in this study if you are currently in another study or if you have been in any other research study within the last 30 days or longer.

You cannot be in this study if you are taking any illegal drugs. A urine test will be performed to check for illegal drug use.

You should not volunteer for this study if you are breastfeeding, pregnant or trying to get pregnant.

Are There Other Restrictions?

- You may not consume grapefruit or grapefruit juice for 48 hours prior to and throughout each visit to the clinic.
- You may not use alcohol and caffeine- or xanthine-containing products for 6 hours before and throughout each visit to the clinic.
- You may not use tobacco products during your stay in the sleep unit.)
- You may not take any prescribed or over the counter medications starting 12 hours before each visit to the clinic.
- You must refrain from activities that have the potential to change your sleep patterns such as travel across time zones, changes in shift work.
- There are some other types of medication which you may not be permitted to take for a longer period of time. Your study doctor will tell you if you are currently taking one of these medications.

WHAT WILL HAPPEN DURING THE STUDY

First you will have screening tests done to help the study doctor decide if you qualify to be in the study. The screening tests to be performed at your first visit are:

- Medical/surgical/psychiatric history
- Sleep history
- Medication history (including use of sleep medications)
- Physical examination
- 12-lead EKG
- Vital signs (blood pressure, heart rate, breathing rate, and temperature by mouth)
- Blood and urine samples will be obtained for safety laboratory tests (including a pregnancy test for female subjects and a test for illegal drugs for all subjects)
- Alcohol breath test

If the results of all these tests indicate that you may qualify for the study, you will be

asked to return to the clinic within 2-10 days for a polysomnography (PSG) test. This part of the screening tests will require you to return to the clinic for two consecutive nights of sleep monitoring. During the PSG screening the following will be done one or more times before you go to sleep or after you wake up in the morning:

- Review of the medications that you are currently taking
- You will be asked how you are feeling
- Your medical, surgical, psychiatric, and sleep history information will be updated
- Alcohol Breath Test
- Pregnancy test (female subjects only)
- Testing for illegal drug use
- 12-Lead EKG
- Vital signs (blood pressure, heart rate, breathing rate, and temperature by mouth)
- Sleep questionnaire
- Administration of study medication (about 60 minutes before you go to sleep each night)
- Tests of memory, coordination, and alertness

Study Procedures Description

If you qualify for the study, you will be asked to return to the clinic for 3 study sessions. Each session will be approximately 2 weeks apart and will require you to report to the clinic for 2 consecutive nights of sleep monitoring. During each session, the following will be done one or more times before you go to sleep or after you wake up in the morning:

- Review of the medications that you are currently taking.
- You will be asked how you are feeling
- Review of changes in your sleep habit
- Alcohol Breath Test
- Pregnancy test (female subjects only)
- Testing for illegal drug use
- Blood samples to measure how much study medication is in your system.
- 12-Lead EKG
- Vital signs (blood pressure, heart rate, breathing rate, and temperature by mouth)
- Sleep questionnaire
- Administration of study medication (about 60 minutes before you go to sleep each night)
- Physical Examination
- Tests of memory, coordination, and alertness

On the morning following your last PSG night, the following will also be done:

- Blood and urine samples of safety laboratory tests

In addition, for several days after each PSG session, you will be asked to complete a subject diary about your sleep habits at home each day.

You must return to the clinic for a follow-up visit, about 14 days after your last PSG night. At the follow-up visit, the following will be done:

- Review of the medications that you are currently taking
- You will be asked how you are feeling
- Physical examination
- 12-lead ECG
- Vital signs (blood pressure, heart rate, breathing rate, and temperature by mouth)
- Safety laboratory tests (including a pregnancy test for female subjects)
- You will be asked about your insomnia and sleep habits

The total amount of blood drawn during the entire study will be a maximum of approximately **13 tablespoons** (approximately **200 mL**).

The text in the sub-section below is agreed with GSK legal. Do not edit this sub-section without input from legal.

NOT TO BE USED FOR SUBJECT ENROLLMENT

DISEASES OR CONDITIONS WHICH ARE REQUIRED TO BE REPORTED TO THE DEPARTMENT OF HEALTH

Your blood sample (or other biological samples being collected) will be tested during the study (or if follow-up testing is required) for human immunodeficiency virus (the AIDS virus) and hepatitis B and C viruses. A positive test result for the hepatitis viruses (B or C), or human immunodeficiency virus (HIV) is required by Ohio State law to be reported to the Department of Health. Your name will also be disclosed to the Ohio State Department of Health at that time.

In the event any study staff is exposed to your blood, you agree to have your blood tested for HIV and hepatitis viruses (B and C). You will be asked to sign a separate consent form before your blood is taken for the HIV test**.** Although testing is supposed to be private, you understand that this cannot be guaranteed. For example, it is possible for a court of law to get medical or study records without your permission.

Any subject with a positive hepatitis or a confirmed positive HIV test may not be able to stay in the study.

POSSIBLE SIDE EFFECTS AND RISKS OF THE TREATMENT

You may have no improvement of your symptoms, or they may get worse, especially if you receive the placebo.

One of the reasons for doing this study is to learn more about the possible side effects of the study medication. It is important that you tell the study staff about any side effects you have during the study. If you are not completely truthful with the study doctor and study staff regarding any side effects, you may harm yourself by participating in this study.

The current known risks for GW 679769 includes headache, fatigue, and drowsiness. In previous research studies, these complications were not serious, and the majority of the events were mild. In addition, all side effects ended quickly when the medicine was stopped.

GW 679769 has been studied in animals where it showed evidence of possible liver problems. As of June 2004, 182 humans have received GW 679769. Two of these humans had evidence of liver problems. These liver problems were not considered to be serious and were reversible.

In addition, one patient who participated in a study with GW 679769 had a history of stomach ulcers and experienced a serious gastrointestinal adverse event for which a surgical procedure was required to correct. One healthy volunteer receiving GW 679769 experienced a serious adverse event of inflammation for which the subject was hospitalized. One other patient in a study with GW 679769 was diagnosed with tuberculosis. These serious adverse events were considered not related to study medication.

Because this drug is investigational, all of its side effects may not be known. There may be rare and unknown side effects, including reactions that may be life threatening. Other medicines or supplements could cause side effects if they are used while you are taking the drug(s) given in this study. Because of this, you must tell the study doctor and/ or a member of the study staff about all your past and present illnesses and allergies of which you are aware, and all drugs, vitamins, supplements, and medicines that you are presently using.
Because this drug is investigational, all of its side effects may not be known. There may be rare and unknown side effects, including reactions that may be life threatening.

Possible side effects of having blood drawn or the insertion of the cannula (small plastic tube) include feeling faint, redness of the vein, pain, bruising or bleeding at the site of the needle puncture. There is also a slight chance of infection. If you feel faint, notify one of the study personnel immediately.

A cannula may be inserted into one of your forearms to take blood samples during this study. The cannula (small plastic tube) will be flushed (washed out) from time to time with a blood thinner called heparin to keep the cannula clear. The amount of heparin used is small, but in rare cases, it may lower platelet counts.

Platelets are cells in the blood which cause the blood to clot normally and help stop bleeding when it occurs. If you are known to be "allergic" to heparin or have had a side effect from heparin, you should not participate in this study.

PREGNANCY AND BIRTH CONTROL

- If you are female, it is very important that you do not become pregnant during this study. The only certain way to prevent pregnancy is to not have sex.
- If you are a woman who is not postmenopausal (has not gone through the change of life) or has not had a hysterectomy (surgical removal of the uterus or womb) it is recommended that you do not have sex beginning 14 days before the start of the study and continuing until you have completed your last study visit (follow-up visit).
- If you are a woman and choose to have sex during this study, you **must agree** to use a medically proven type of birth control beginning 14 days before the start of the study and continuing until you have completed your last study visit (follow-up visit).

Acceptable methods of birth control for this study include:

- condom AND diaphragm with spermicidal foam/gel/film/cream/suppository
- condom AND spermicidal foam/gel/film/ cream/suppository
- documented tubal ligation (tubes tied)
- documented placement of a copper-containing intrauterine device (IUD)
- oral birth-control medicines such as "the pill." Contraceptive medications taken after sex (e.g., 'morning after pill') are NOT permitted.

Even if you use a medically proven birth control method, there is a chance you could still become pregnant.

You will not be allowed to be in the study if you are pregnant, and you should not volunteer for this study if you are breastfeeding or planning to become pregnant. A pregnancy test could be wrong and if you become pregnant during the study you may be receiving study medication while pregnant. The effects of the study drug on an unborn baby are unknown. If you become pregnant during study, stop taking the study medication and call the study doctor at once.

POSSIBLE BENEFITS OF THE STUDY

You may receive the benefit of information about your health and a chance to be in a research study that may help others if the drug is found to be safe and effective. However you should know that there is no therapeutic benefit to you from your participation in this study. There is no guarantee that your symptoms will improve or that you will benefit from the study drug.

ALTERNATIVES TO PARTICIPATING IN THIS STUDY

This is not a treatment study. Your only other choice is not to participate.

RELEASE OF YOUR MEDICAL RECORDS AND PRIVACY *The text in this section is agreed with GSK legal. Do not edit this section without input from legal.*

It will be necessary for representatives of SmithKline Beecham Corporation or possibly drug or health regulatory agencies such as the FDA and the Institutional Review Board (IRB), or their authorized representative, to access and copy your medical records and your records from this study. Your participation in the study will be treated as confidential, that is, any personally identifiable information will be held and processed under secure conditions at SmithKline Beecham Corporation (or its agent) with access limited to appropriate SmithKline Beecham Corporation staff or other authorized agents having a requirement to maintain confidentiality of the information. You will not be referred to by name in any report of the study. Your identity will not be disclosed to any person, except for the purposes described above

NOT TO BE USED FOR SUBJECT ENROLLMENT

and in the event of a medical emergency or if required by law.

Your personal data will be processed electronically to determine the outcome of this study, and to provide it to drug or health regulatory agencies. Your data may be transferred to other countries for these purposes.

SmithKline Beecham Corporation complies with internal procedures to protect personal information even in countries whose data privacy laws are less strict than those of this country. The data may also be used for other medical research purposes.

You may be entitled under law to access your personal data and to have any justifiable corrections made. If you wish, you should request this from the study doctor conducting this study.

PAYMENT FOR INJURY RELATED TO THE STUDY *The text in this section is agreed with GSK legal. Do not edit this section without input from legal.*

In the event of any physical injury resulting from the research procedures, medical treatment will be provided without cost to you, but no other financial compensation is routinely provided by the Sponsor. If the injury is directly related to the investigational product/procedure, the Sponsor will reimburse only for medical expenses incurred by you as a result of participation in the study which are not covered by your third party payor. You or your third party payor, if any, may also be billed for medical expenses that are deemed medically necessary and would have been incurred independent of the study.

LEGAL RIGHTS

You will not lose any of your legal rights as a research subject by signing this consent form.

WHOM TO CONTACT

For answers to questions about this research or to report a research related injury, contact:

Dr. [redacted] Ph.D, Dr. [redacted] M.D.
DAYTIME: [redacted]
AFTER HOURS: [redacted]

To protect the rights and safety of subjects involved in research projects the FDA requires approval of this Informed Consent document by an Institutional Review Board (IRB). This means the IRB has approved the information provided in the Informed Consent for use when enrolling subjects into this study. An Ethical Review Board has approved this research study and informed consent document. The ethical review board is a group of scientific and non-scientific people that review research studies. Ethical review boards must follow the Food and Drug Administration (FDA) rules regarding the protection of the rights and welfare of human subjects involved in medical research studies. Questions about your rights as a study subject may be addressed to:

[redacted] J.D.

PAYMENT FOR BEING IN THE STUDY

Payment for Completion of Session 1	**$**_____
Payment for Completion of Session 2 *on, and on….*	**$**_____
Bonus for Completing Entire Study	**$**_____
Payment for Follow-up visits	**$**_____
Total for Completion of Entire Study (men) *if applicable*	**$**_____
Total for Completion of Entire Study (women) *if applicable*	**$**_____
Bonus for Being On-Time for all Study Day visits	**$**_____
Maximum Study Payment (men) *if applicable*	**$**_____
Maximum Study Payment	**$**_____

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(women) *if applicable*

If applicable. If you have a positive urine drug screen during treatment you will be dropped from the study. If you have already been dosed, you will remain in the CPU until 4 hours after dosing. You will then be discharged from the unit and receive payment for all the sessions **completed** plus $_____ for the session in which you have been dropped. If you are dropped prior to dosing in that session, you will receive payment only for the sessions completed and may leave the unit immediately.

PENALTY

1. The first time you are late by more than 20 minutes for any visit to the CPU, you will lose the on-time bonus - **$100.00**. If you are late by more than 20 minutes for your first stay day, you may be replaced and will not receive your payment.
2. The second time and each time you are late by more than 20 minutes for any visit to the CPU, you will have **$20.00** deducted from your total payment.
3. For each missed appointment or study day, you will have $35.00 deducted from your total payment.

If you are approved and then are withdrawn from the study by the investigator for medical reasons prior to dosing, you will receive the payment fee equal to that of an alternate which is **$100.00**.

If you choose to withdraw from the study you will only be paid for the part you have completed to that point.

This compensation is non-negotiable. You will receive the payment following completion of all study-related procedures.

YOUR PARTICIPATION IN THE STUDY

You cannot be forced to be in this study. You may not want to be in this study or you may leave the study at any time without punishment or loss of benefits to which you are entitled and without affecting your future medical care. The study doctor, the Sponsor, the IRB, or the FDA may take you out of the study without your permission at any time for the following reasons:

- if you do not follow the instructions of the study doctor
- if it is discovered that you do not meet the study requirements
- if the study is canceled
- if it appears to be medically harmful to you
- if you have a positive urine drug screen and alcohol test during the treatment phase of the study.

If you leave the study or if you are taken out of the study for any reason, you may be asked to return to the study doctor's office for a final visit. This is to make sure that you are in good health.

ADDITIONAL COSTS *Do not edit this section.*

There will be no additional costs to you for your participation in this study.

NEW INFORMATION

You will be told about any significant new findings about the study drug. This information can help you decide if you wish to continue your participation in the study.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a subject involved in an investigational drug study, you have the following rights. The following is the California Subject's Bill of Rights, which is required by California state law. However, the IRB feels that each subject should be made aware of these rights.

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.

3. Be given a description of any attendant discomforts and risk reasonably to be expressed from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that

might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time. The subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of a signed and dated written consent form when one is required.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

THE REASON FOR INSTITUTIONAL REVIEW BOARDS AND INFORMED CONSENT

What is a consent form?
The Informed Consent document contains the required information as found in and required by the United States regulations regarding the protection of human subjects (Code of Federal Regulations, Title 21, Part 50-Protection of Human Subjects). As required by this regulation, the informed consent must be reviewed and approved by an Institutional Review Board (IRB).

What is an Institutional Review Board (IRB)?
An Institutional Review Board (IRB) is any board, committee or other group which reviews, approves, and does continuing review of biomedical research involving human subjects. The primary purpose of such review is to guarantee the protection of the rights and welfare of the human subjects.

IRBs were established as the result of unfair treatment of human subjects. Prior to this, other committees existed as a requirement of the United States Public Health Service (USPHS) policy established in 1965. IRBs are regulated by the Food and Drug Administration and the National Institutes of Health (NIH).

What does an IRB mean to me?
The purpose of the IRB is to inform and protect human subjects through the information provided in the informed consent document. Therefore, the IRB is acting as a supporter for the research subject. This means that the IRB, during its review of the informed consent document, has the right and responsibility to ensure that the research subject is fully informed of the procedures involved in the study as well as the risks and other treatments that are available if participation in the study is refused.

How can I tell that an IRB has reviewed and approved this study?
The date that IRB approved the study design as well as the information in this Informed Consent document is printed on the top of each page of this Informed Consent form. **THIS DOES NOT MEAN THE IRB HAS APPROVED YOUR PARTICIPATION IN THE STUDY**. It is a FDA requirement that the study design (Protocol), Informed Consent form, any advertising materials, and other instructions to the subject (Subject Instructions, Patient Diaries, etc.) be reviewed and approved by an IRB. Although IRB approval is granted for the study doctor to conduct the study, you must evaluate the information in this Informed Consent form for yourself and decide whether or not you wish to participate.

The IRB for this study
[redacted] is an independent IRB whose board members are individuals who work in the [redacted] community. [redacted] provides services nation-wide to research professionals.

FDA regulations require that the committee have at least five members with varying backgrounds to provide complete and adequate review of research activities.

NOT TO BE USED FOR SUBJECT ENROLLMENT

To fulfill these requirements the IRB currently includes physicians, pharmacists, Ph.Ds., a toxicologist (someone who studies the harmful effects of chemicals), a psychologist, an oral surgeon, and lay members (non-scientific).

The telephone number of the Chair is available in every informed consent document under "Whom to Contact". You may contact the Chair with concerns regarding your rights as a subject.

AGREEMENT TO BE IN THE STUDY

This consent form contains important information to help you decide if you want to be in the study. If you have any questions that are not answered in this consent form, ask one of the study staff.

A)	Do you understand the information in this consent form?	Yes	No
B)	Have you been able to ask questions and talk about the study?	Yes	No
C)	Have all of your questions been answered to your satisfaction?	Yes	No
D)	Do you think you received enough information about the study?	Yes	No
E)	Do you understand that you can leave the study at any time without giving a reason and without affecting your medical care?	Yes	No
F)	Do you understand that your medical records from this study may be reviewed by the Drug Company and by government authorities?	Yes	No

If you answered NO to any of these six questions, you should not sign this consent form.

When you sign this consent form you agree that:

- you have had a chance to ask questions
- you understand English
- you want to be in the study

You will not lose any of your legal rights by signing this consent form.

Signature of Study Subject or Legally Authorized Representative Date
DO NOT SIGN AFTER

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KEEP FOR FUTURE REFERENCE

[redacted] **VERSION : (Date)** *Subject Initials* _____

NOT TO BE USED FOR SUBJECT ENROLLMENT

Printed Name of Study Subject Date

Signature of Person Explaining Informed Consent Date

Signature of Principle Investigator Date

You will be given a copy of this informed consent to keep.

Master Schedule Report

StudyID: *679769_903*
Description: *a randomized, db, placebo-controlled, cross-over study to evaluate the effects of two doses of GW679769 on sleep continuity in subjects with primary insomnia*

Treatments and Sequences defined for study

		Treatments	
Sequence	**Code**	**Description**	**Period**
A/B/C	A	Placebo	1
	B	GW679769 30 mg	2
	C	GW679769 90 mg	3
A/C/B	A	Placebo	1
	C	GW679769 90 mg	2
	B	GW679769 30 mg	3
B/A/C	B	GW679769 30 mg	1
	A	Placebo	2
	C	GW679769 90 mg	3
B/C/A	B	GW679769 30 mg	1
	C	GW679769 90 mg	2
	A	Placebo	3
C/A/B	C	GW679769 90 mg	1
	A	Placebo	2
	B	GW679769 30 mg	3
C/B/A	C	GW679769 90 mg	1
	B	GW679769 30 mg	2
	A	Placebo	3

Master Schedule Report

StudyID: *679769_903*
Description: *a randomized, db, placebo-controlled, cross-over study to evaluate the effects of two doses of GW679769 on sleep continuity in subjects with primary insomnia*

Schedule No: 1
Stratum None

Randomisation Number	Treatment / Sequence
[redacted]	B/A/C
	C/B/A
	A/C/B
	B/C/A
	A/B/C
	C/A/B
	A/C/B
	C/B/A
	B/C/A
	A/B/C
	C/A/B
	B/A/C
	B/A/C
	B/C/A
	A/C/B
	A/B/C
	C/B/A
	C/A/B
	C/B/A
	A/B/C
	B/A/C
	B/C/A
	C/A/B
	A/C/B
	C/A/B
	A/B/C
	A/C/B
	B/A/C
	C/B/A
	B/C/A

Randomisation Number	Treatment / Sequence
[redacted]	C/B/A
	A/C/B
	C/A/B
	A/B/C
	B/A/C
	B/C/A
	A/C/B
	C/A/B
	A/B/C
	C/B/A
	B/C/A
	B/A/C
	B/A/C
	B/C/A
	C/A/B
	A/B/C
	A/C/B
	C/B/A
	A/C/B
	A/B/C
	B/A/C
	C/A/B
	C/B/A
	B/C/A
	C/A/B
	B/A/C
	C/B/A
	B/C/A
	A/B/C
	A/C/B
	A/B/C

Report generated by: [redacted] **on:** 18-MAY-2006

Master Schedule Report

StudyID: *679769_903*
Description: *a randomized, db, placebo-controlled, cross-over study to evaluate the effects of two doses of GW679769 on sleep continuity in subjects with primary insomnia*

Randomisation Number	Treatment / Sequence	Randomisation Number	Treatment / Sequence
[redacted]	B/A/C	[redacted]	A/B/C
	C/B/A		B/C/A
	B/C/A		B/A/C
	C/A/B		C/B/A
	A/C/B		A/B/C
	A/C/B		B/C/A
	B/C/A		C/B/A
	C/B/A		A/C/B
	A/B/C		C/A/B
	C/A/B		B/A/C
	B/A/C		C/B/A
	C/A/B		A/C/B
	A/B/C		B/A/C
	A/C/B		B/C/A
	B/A/C		A/B/C
	C/B/A		C/A/B
	B/C/A		B/C/A
	A/B/C		C/A/B
	B/C/A		A/B/C
	C/B/A		A/C/B
	C/A/B		B/A/C
	A/C/B		C/B/A
	B/A/C		C/B/A
	A/C/B		A/B/C
	A/B/C		B/C/A
	C/A/B		B/A/C
	B/A/C		A/C/B
	C/B/A		C/A/B
	B/C/A		C/B/A
	A/C/B		B/A/C
	C/A/B		A/C/B

Report generated by: [redacted] **on:** 18-MAY-2006

Master Schedule Report

StudyID: *679769_903*
Description: *a randomized, db, placebo-controlled, cross-over study to evaluate the effects of two doses of GW679769 on sleep continuity in subjects with primary insomnia*

Randomisation Number	Treatment / Sequence	Randomisation Number	Treatment / Sequence
[redacted]	C/A/B	[redacted]	B/A/C
	B/C/A		B/C/A
	A/B/C		C/A/B
	C/B/A		B/C/A
	B/C/A		A/B/C
	A/C/B		C/B/A
	A/B/C		B/A/C
	C/A/B		A/C/B
	B/A/C		A/C/B
	A/C/B		B/A/C
	B/C/A		C/A/B
	C/A/B		A/B/C
	A/B/C		C/B/A
	B/A/C		B/C/A
	C/B/A		C/A/B
	C/B/A		A/C/B
	B/C/A		B/C/A
	C/A/B		B/A/C
	A/B/C		A/B/C
	A/C/B		C/B/A
	B/A/C		A/C/B
	C/A/B		A/B/C
	A/B/C		B/C/A
	A/C/B		C/B/A
	B/A/C		B/A/C
	C/B/A		C/A/B
	B/C/A		B/C/A
	C/A/B		C/B/A
	A/C/B		C/A/B
	C/B/A		A/B/C
	A/B/C		B/A/C

Report generated by: [redacted] **on:** 18-MAY-2006

Master Schedule Report

StudyID: *679769_903*
Description: *a randomized, db, placebo-controlled, cross-over study to evaluate the effects of two doses of GW679769 on sleep continuity in subjects with primary insomnia*

Randomisation Number	Treatment / Sequence
[redacted]	A/C/B
	B/C/A
	A/C/B
	B/A/C
	A/B/C
	C/B/A
	C/A/B
	A/B/C
	C/B/A
	B/C/A
	A/C/B
	C/A/B
	B/A/C
	C/A/B
	B/A/C
	A/C/B
	C/B/A
	B/C/A
	A/B/C

Master Schedule Report

StudyID: *679769_903*
Description: *a randomized, db, placebo-controlled, cross-over study to evaluate the effects of two doses of GW679769 on sleep continuity in subjects with primary insomnia*

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	C	GW679769 90 mg	2
	B	GW679769 30 mg	3
B/A/C	B	GW679769 30 mg	1
	A	Placebo	2
	C	GW679769 90 mg	3
B/C/A	B	GW679769 30 mg	1
	C	GW679769 90 mg	2
	A	Placebo	3
C/A/B	C	GW679769 90 mg	1
	A	Placebo	2
	B	GW679769 30 mg	3
C/B/A	C	GW679769 90 mg	1
	B	GW679769 30 mg	2
	A	Placebo	3

Schedule Summary

Schedule No.	Created by	Lock 1	Lock 2	Blind Status
1	[redacted]	Locked	Locked	Unblinded

Report generated by: [redacted] **on:** 18-MAY-2006

Master Schedule Report

StudyID: *679769_903*
Description: *a randomized, db, placebo-controlled, cross-over study to evaluate the effects of two doses of GW679769 on sleep continuity in subjects with primary insomnia*

Schedule Details

Schedule: 1 Main schedule

Date Generated: 28-JUN-2004
Date Unblinded: 19-SEP-2005
Generated by: [redacted]

Stratum	Block Size	Rand. No. Range	No. in Range
Main	6	[redacted]	204

Allocation Ratios

Treatment Sequence	Ratio
A/C/B	1
B/A/C	1
A/B/C	1
B/C/A	1
C/A/B	1
C/B/A	1

Investigator Signature Page

STUDY TITLE: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study to Evaluate the Effects of GW679769 (30mg and 90mg) on Sleep Continuity, PSG Sleep Recordings, Subjective Sleep Assessment, and Daytime Cognitive Function in Subjects with Primary Insomnia

I have read this report and confirm that to the best of my knowledge Study GW679769/903 was carried out as described in the GlaxoSmithKline Report ZM2005/00173/00

Name of Investigator: [redacted] MD, MS

Affiliation: [redacted]

Signature of Investigator: [redacted]

Date: 9/12/06

Sponsor Signatory Signature Page

STUDY TITLE: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study to Evaluate the Effects of GW679769 (30mg and 90mg) on Sleep Continuity, PSG Sleep Recordings, Subjective Sleep Assessment, and Daytime Cognitive Function in Subjects with Primary Insomnia

Study: GW679769/903 Development Phase: II

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted] M.D.

Title of Sponsor Signatory: VP, Clinical Molecular Imaging Translational Medicine and Genetics Acting Head, Psychiatry CPDM

Signature: [redacted]

Date: 29th Aug 06