Synopsis

Identifier: GM2007/00455/00 **Study Number:** MAD105516

Title: A randomized, double-blind, placebo-controlled, crossover study to evaluate the effects of morning administration of GW679769 (10 mg and 30 mg) on polysomnograph sleep recordings, subjective sleep assessment, daytime cognition and psychomotor function in subjects with primary insomnia

Investigator(s): This was a multicentre study conducted by 9 investigators.

Study center(s): This study was performed at 9 centers, 5 in the United States of America and 4 in Germany.

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

Study Period: 19 May 2006 to 13 Jul 2007

Phase of Development: IIB

Objectives:

Primary

The primary objective was to compare the efficacy of casopitant with placebo on night-time sleep parameters when casopitant was acutely and repeatedly administered in the morning to subjects with primary insomnia as determined objectively by polysomnography (PSG).

Secondary

- To compare the efficacy of casopitant and placebo acutely and repeatedly administered in the morning on subjective measures of sleep onset, continuity, duration and quality using self-reported Post-Sleep Questionnaires.
- To compare the effects of casopitant and placebo acutely and repeatedly administered in the morning on cognitive functioning; attention and alertness.
- To evaluate the safety and tolerability of casopitant compared with placebo.
- To evaluate the Pharmacokinetic-Pharmacodynamic (PK-PD) relationship between casopitant exposure and efficacy, safety, and tolerability.
- To potentially investigate changes in transcriptomic profiles of peripheral whole blood (PAXgene), and of proteomic profiles of plasma, following exposure to casopitant and placebo to establish relationships between profile changes and improvement of insomnia.

Methodology:

This was a double-blind, placebo-controlled, crossover study to explore the night-time sleep-promoting efficacy of 10 mg and 30 mg doses of casopitant when given acutely and repeatedly in the morning over 9 days to subjects diagnosed with primary insomnia. Potential subjects participated in a screening period consisting of a Screening Visit and a 2-night PSG recording session in the sleep laboratory. Eligible subjects with primary insomnia were randomized to three 9-day double-blind treatment periods (3-way cross-over) and received placebo, casopitant 10 mg or casopitant 30 mg (1 treatment in each double-blind treatment period) in the morning. Each double-blind treatment period consisted of 9 days of treatment with 2-night PSG sessions on the first 2 nights and the final 2 nights (Nights 8 and 9). Each double-blind treatment period was separated by 13 days (± 1 day) and PSG sessions preferably occurred on the same days of the week. PSG sessions were to be held consistently on either workdays or days of rest for a given subject.

Number of subjects:

	Placebo	Casopitant 10 mg	Casopitant 30 mg	Total
Randomized, N	62	60	61	68
Completed, n (%)	55 (89)	54 (90)	59 (97)	53 (78)
Total Number Subjects Withdrawn, n (%)	7 (11)	6 (10)	2 (3)	15 (22)
Withdrawn due to SAE, n (%)	0	0	0	0
Withdrawn due to AE, n (%)	3 (5)	4 (7)	0	7 (10)
Withdrawn due to Protocol Violation, n (%)	1 (2)	0	1 (2)	2 (3)
Voluntary Subject Withdrawal, n (%)	2 (3)	0	1 (2)	3 (4)
Lost to Follow-up, n (%)	1 (2)	0	0	1 (1)
Withdrawn due to Other Reasons, n (%)	0	2 (3)	0	2 (3)

In the Total column, a subject is defined as a completer if they have either a Night 8/PSG 13 or a Night 9/PSG 14 (or both) PSG record for the final (i.e. third) double-blind PSG session, otherwise they were defined as a withdrawal. If a subject was a withdrawal, the treatment group column indicated the treatment period during which the subject withdrew (whether during the On-Treatment part or the Follow-up part).
AE Adverse Event.

Diagnosis and main criteria for inclusion:

Male or female subjects aged 18 to 64 years with a principal diagnosis of primary insomnia based on the Diagnostic and Statistical Manual of Mental Disorders-Test Revision (DSM-IV-TR) criteria 307.42, but otherwise in good health. Minimum PSG entry criteria included: TST between 240 and 390 minutes on both Screening nights; mean LPS of 30 minutes or more but not less than 20 minutes on either Screening night; mean WASO of 60 minutes or more but not less than 45 minutes on either Screening night.

Treatment administration:

The investigational products used in this study consisted of white to off-white, film coated, round tablets, each containing 10 mg or 30 mg of GW679769X (as the mesylate salt, GW679769B). Placebo tablets visually matched the active casopitant tablets. Tablets were packaged in opaque, white, high-density polyethylene bottles. Lot numbers were as follows:

Product Description	Lot No.
EU Supplies	
Casopitant 10 mg (AT)	051101396
Casopitant 30 mg (AW)	051101399
Placebo (ATS)	051101118
US Supplies	
Casopitant 10 mg (AT)	051101396
Casopitant 30 mg (AW)	055101399
Placebo (ATS)	051101118
Placebo (ATS)	061125314

Subjects were randomized in balanced order to a sequence of three 9-day double-blind treatment periods at Visit 4 (Day 1 of first double-blind PSG session). The 3 treatments under study were casopitant 10 mg, casopitant 30 mg and placebo. Each of the 3 treatments was taken during 1 of 3 separate treatment periods. One double-blind placebo tablet or 1 casopitant tablet was administered to subjects at 10:00AM on the days of nocturnal PSG recordings. On the mornings between Treatment Period PSG sessions (i.e. Days 4, 5, 6, and 7 of each Treatment Period), subjects were instructed to take the double-blind medication in the morning between 8:00AM and 10:00AM.

Criteria for evaluation:

Primary

The primary endpoint was LPS, as a mean of the PSG recordings obtained on 2 consecutive nights.

Secondary

Key Secondary Endpoints

Key Secondary endpoints were the following objective PSG measures of sleep continuity: TST, WASO, Wake During Sleep (WDS), Wake After Sleep (WAS) and number of awakenings during sleep. All PSG variables were based on the mean of recordings on 2 consecutive nights.

Other Secondary Endpoints

The following additional variables were considered to be supportive of the primary and key secondary variables; all PSG variables are the mean of assessments performed at 2 consecutive nocturnal recordings, unless otherwise noted.

- Objective PSG measures of sleep structure: non-REM sleep time, Slow-Wave Sleep (SWS) time (Stage 3 and Stage 4), Stage 2 non-REM sleep time; REM sleep time.
- Subjective Pre-Sleep Questionnaire to be completed each evening before PSG recording and each evening on Days 3, 4, 5, 6, and 7 of each double-blind Treatment Period: daytime alertness, naps, alcohol or caffeinated beverage consumption, dinnertime, napping, drowsiness, ability to function, and well being.
- Subjective Post-Sleep Questionnaire: sTST, sWASO, Sleep Onset Latency (sSOL), number of awakenings, and Sleep Quality to be completed each morning following PSG recording and each morning on Days 4, 5, 6, 7 and 8 of each double-blind Treatment Period.
- Overall insomnia severity using the subject-rated Insomnia Severity Index, administered pre-dose on Day 1 and Day 9 of each Treatment Period and at the Day 14 Follow-up Visit.
- Transcriptomic profiles of whole blood (PAXgene), and proteomic profiles of plasma, were to be compared (depending on there being a sufficient number of subjects exhibiting a response to casopitant compared with placebo).

PK/PD Endpoints

PK and PK/PD assessments for the casopitant groups were to be performed to examine the correlation between clinical efficacy (LPS assessed by PSG) and plasma levels of the drug as well as its major metabolite GSK525060.

- PK samples were collected to estimate individual specific parameters such as exposure at steady state (AUC), C_{max}, C_{trough}, T_{max}, and plasma half-life.
- PK/PD relationships were to be evaluated and, where appropriate, suitable modeling techniques were to be applied to describe the functional link between plasma concentration and effects on LPS. Exploratory PK/PD analysis may include secondary endpoints of efficacy including TST and WASO.

Safety

The comparison of the safety and tolerability of casopitant versus placebo was based on various safety parameters assessed and recorded during the study. Safety and tolerability were assessed by monitoring the following:

- Adverse events (AEs)
- The percentage of subjects withdrawn due to AEs
- Daytime cognitive function tests before, and 1 and 3 hours following oral administration of study medication on the first and last day of each Treatment Period (i.e. Day 1 and Day 9 of each double-blind treatment period):
    - cognitive test battery: simple reaction time, digit vigilance test, choice reaction time, and Bond-Lader visual analogue scale of mood and alertness
- Standard tests for ataxia (Romberg test and Heel-to-toe test)
- Centrally interpreted 12-lead electrocardiograms (ECGs) at Screening, at Day 9 of each Treatment Period, and at the Day 14 Follow-Up visits
- Vital signs
- Pregnancy tests
- Clinical laboratory assessments at Screening, at Day 9 of each Treatment Period, and at the Day 14 Follow-Up visit
    - Special monitoring guidelines for liver enzymes, muscle markers (Creatine phosphokinase [CK], troponin) and pepsinogen
- Physical examination at Screening and Follow-up visits

Statistical methods:

The primary comparisons of interest in this study were each casopitant dose (10 and 30 mg) versus placebo in LPS for the Intent-to-treat (ITT) population following repeated administration (averaged over Nights 8 and 9 of treatment). A logarithm transformation was applied to the mean of the Nights 8 and 9 LPS before analysis.

Each dose was compared to placebo using a hierarchical approach with closed testing procedures. Firstly, the efficacy of casopitant 30 mg was compared with placebo at the 0.05 (2-sided) level of significance. If this comparison achieved statistical significance, the second comparison of casopitant 10 mg versus placebo was tested at the 0.05 (2-sided) level of significance. Note that if the first comparison of casopitant 30 mg versus placebo was not significant at level 0.05, no further inferential testing of the primary efficacy variable was to be carried out. In this instance, results presented for the comparison of casopitant 10 mg versus placebo would have been used for information only.

Since the primary comparisons were to be tested using a hierarchical approach, no multiplicity adjustment was performed.

The primary population was the ITT population and the comparisons were made using the Observed Cases dataset.

Treatment comparisons were also made between each casopitant dose level and placebo for the primary endpoint following acute dosing (averaged over Nights 1 and 2 of treatment) and for each individual PSG recording (Nights 1, 2, 8 and 9 separately).

The comparison of the primary endpoint was also performed using the Per Protocol (PP) population.

As the primary endpoint (LPS) and the lead secondary endpoint (WASO) were transformed logarithmically prior to analysis, a sensitivity analysis of the untransformed data was also performed in each case.

As these additional comparisons were considered secondary analyses, no adjustments for multiplicity were made and all tests were performed at a 5% significance level.

Note that for logarithm transformed endpoints, the differences between casopitant and placebo were estimated as 'casopitant/placebo'. For untransformed endpoints, the differences between casopitant and placebo were estimated as 'casopitant minus placebo'.

Results Summary:

Demography

A total of 68 subjects were randomized and all were included in the ITT population. The mean age of the total population was 43 years (range 18 to 63 years) and 71% of subjects were female. The majority of subjects (88%) were White. The mean BMI for the total population was 25 kg/m^2 (range 18 to 32 kg/m^2).

Primary Efficacy Endpoint

The first comparison in the hierarchical testing procedure was casopitant 30 mg versus placebo. The adjusted geometric mean LPS scores (mean of Nights 8 and 9) for subjects who received casopitant 30 mg was 30% less than for those who received placebo. This difference was statistically significant (p=0.004). The comparison of casopitant 10 mg versus placebo could therefore be performed. There was also a statistically significant difference between casopitant 10 mg compared with placebo at this timepoint; the adjusted geometric mean LPS score was 22% less with casopitant 10 mg compared with placebo (p=0.044). A summary of analysis for LPS Scores, based on the mean of Nights 8 and 9, is shown below:

	N	n	LPS Nights 8/9 Adjusted Geometric Mean (minutes)	Ratio of Treatment vs Placebo	95% CI	p-value
Placebo	62	58	27			
Casopitant 10 mg	60	58	21	0.78	0.61, 0.99	0.044
Casopitant 30 mg	61	60	19	0.70	0.55, 0.89	0.004

Note: The analysis method for the mean over 2 nights was analysis of covariance (model included: fixed effects - age, entry score, gender, centre group, period, treatment; random effect – subject).
CI Confidence Interval

The adjusted geometric mean LPS scores (mean of Nights 1 and 2) for subjects who received casopitant 30 mg was 17% less than for those who received placebo. This difference was not statistically significant. The adjusted geometric mean LPS score was 32% less for subjects who received casopitant 10 mg compared with those who received placebo. This difference was statistically significant (p=0.002). A summary of analysis for LPS Scores, based on the mean of Nights 1 and 2 is shown below:

	N	n	LPS Nights 1/2 Adjusted Geometric Mean (minutes)	Ratio of Treatment vs Placebo	95% CI	p-value
Placebo	62	62	25			
Casopitant 10 mg	60	60	17	0.68	0.54, 0.87	0.002
Casopitant 30 mg	61	61	21	0.83	0.65, 1.06	0.132

Note: The analysis method for the mean over 2 nights was analysis of covariance (model included: fixed effects - age, entry score, gender, centre group, period, treatment; random effect – subject).
CI Confidence Interval

The treatment ratios for geometric mean LPS were similar in the ITT and PP populations but a statistically significant difference was only observed in the casopitant 10 mg group compared with placebo at Nights 1 and 2. This may, however, be due to the smaller number of subjects in the PP analysis.

Key Secondary Endpoints

Total Sleep Time, Wake time After Sleep Onset, Wake During Sleep, Wake After Sleep and Number of Awakenings based on the mean of Nights 8 and 9

Total Sleep Time was longer after casopitant 30 mg treatment compared with placebo based on the mean of Nights 8 and 9 and the difference was statistically significant (p=0.001). Total Sleep Time was slightly longer but not statistically different after casopitant 10 mg treatment compared with placebo, as shown below:

	N	n	TST Nights 8/9 Least Squared Mean (SE) (minutes)	Difference of Treatment minus Placebo	95% CI	p-value
Placebo	62	58	385 (4.8)			
Casopitant 10 mg	60	58	389 (4.8)	3.89	-5.56, 13.34	0.416
Casopitant 30 mg	61	60	400 (4.8)	15.44	6.08, 24.80	0.001

Note: The analysis method for the mean over 2 nights was analysis of covariance (model included: fixed effects - age, entry score, gender, centre group, period, treatment; random effect – subject).
CI Confidence Interval. SE Standard Error.

Wake time After Sleep Onset was slightly shorter with casopitant 30 mg (8% less) and casopitant 10 mg (11% less) compared with placebo based on the adjusted geometric mean of Nights 8 and 9, but the differences were not statistically significant, as shown below:

	N	n	WASO Nights 8/9 Adjusted Geometric Mean (minutes)	Ratio of Treatment vs Placebo	95% CI	p-value
Placebo	62	58	53			
Casopitant 10 mg	60	58	47	0.89	0.78, 1.01	0.080
Casopitant 30 mg	61	60	48	0.92	0.81, 1.05	0.231

Note: The analysis method for the mean over 2 nights was analysis of covariance (model included: fixed effects - age, entry score, gender, centre group, period, treatment; random effect – subject).
CI Confidence Interval.

The differences in WDS, WAS and number of awakenings, between either casopitant 30 mg or casopitant 10 mg and placebo based on the mean of Nights 8 and 9 were not statistically significant, as shown below:

	N	n	Least Squared Mean (SE)	Difference of Treatment minus Placebo	95% CI	p-value
Wake During Sleep (minutes), mean of Nights 8 and 9						
Placebo	62	58	51 (3.1)			
Casopitant 10 mg	60	58	48 (3.0)	-2.50	-9.61, 4.61	0.487
Casopitant 30 mg	61	60	47 (3.0)	-3.45	-10.53, 3.62	0.335
Wake After Sleep (minutes), mean of Nights 8 and 9						
Placebo	62	58	11 (1.9)			
Casopitant 10 mg	60	58	9 (1.9)	-2.49	-7.01, 2.04	0.279
Casopitant 30 mg	61	60	11 (1.9)	-0.40	-4.90, 4.10	0.860
Number of Awakenings, mean of Nights 8 and 9						
Placebo	62	58	12 (0.6)			
Casopitant 10 mg	60	58	12 (0.6)	-0.10	-1.18, 0.97	0.848
Casopitant 30 mg	61	60	12 (0.6)	-0.52	-1.59, 0.54	0.332

Note: The analysis method for the mean over 2 nights was analysis of covariance (model included: fixed effects - age, entry score, gender, centre group, period, treatment; random effect – subject).
CI Confidence Interval. SE Standard Error.

Total Sleep Time, Wake time After Sleep Onset, Wake During Sleep, Wake After Sleep and Number of Awakenings based on the mean of Nights 1 and 2

Total Sleep Time was longer after casopitant 30 mg treatment compared with placebo based on the mean of Nights 1 and 2 and the difference was statistically significant (p=0.002). Total Sleep Time was slightly longer but not statistically different after casopitant 10 mg treatment compared with placebo, as shown below:

	N	n	TST Nights 1/2 Least Squared Mean (SE) (minutes)	Difference of Treatment minus Placebo	95% CI	p-value
Placebo	62	62	388 (4.5)			
Casopitant 10 mg	60	60	395 (4.5)	6.91	-3.40, 17.22	0.187
Casopitant 30 mg	61	61	404 (4.5)	16.16	5.84, 26.49	0.002

Note: The analysis method for the mean over 2 nights was analysis of covariance (model included: fixed effects - age, entry score, gender, centre group, period, treatment; random effect – subject).
CI Confidence Interval. SE Standard Error.

Wake After Sleep Onset was shorter with casopitant 30 mg compared with placebo based on the mean of Nights 1 and 2 and the difference was statistically significant (p=0.024). The difference in adjusted geometric mean WASO after casopitant 10 mg treatment compared with placebo was not statistically significant, as shown below:

	N	n	WASO Nights 1/2 Adjusted Geometric Mean (minutes)	Ratio of Treatment vs Placebo	95% CI	p-value
Placebo	62	62	51			
Casopitant 10 mg	60	60	52	1.01	0.89, 1.15	0.840
Casopitant 30 mg	61	61	44	0.86	0.76, 0.98	0.024

Note: The analysis method for the mean over 2 nights was analysis of covariance (model included: fixed effects – age, entry score, gender, center group, period, treatment; random effect – subject).
CI Confidence Interval.

There was no statistically significant difference in WDS, WAS or number of awakenings, between either casopitant 30 mg or casopitant 10 mg and placebo based on the mean of Nights 1 and 2, as shown below:

	N	n	Least Squared Mean (SE)	Difference of Treatment minus Placebo	95% CI	p-value
Wake During Sleep (minutes), mean of Nights 1 and 2						
Placebo	62	62	49 (3.0)			
Casopitant 10 mg	60	60	52 (3.0)	2.89	-3.99, 9.78	0.407
Casopitant 30 mg	61	61	44 (3.0)	-5.16	-12.05, 1.74	0.141
Wake After Sleep (minutes), mean of Nights 1 and 2						
Placebo	62	62	11 (2.1)			
Casopitant 10 mg	60	60	8 (2.1)	-2.59	-7.50, 2.32	0.299
Casopitant 30 mg	61	61	9 (2.2)	-1.46	-6.38, 3.46	0.557
Number of awakenings, mean on Nights 1 and 2						
Placebo	62	62	12 (0.6)			
Casopitant 10 mg	60	60	12 (0.6)	0.51	-0.70, 1.73	0.402
Casopitant 30 mg	61	61	11 (0.6)	-0.21	-1.42, 1.00	0.737

Note: The analysis method for the mean over 2 nights was analysis of covariance (model included: fixed effects - age, entry score, gender, centre group, period, treatment; random effect – subject).
CI Confidence Interval. SE Standard Error.

Other Secondary Endpoints

Sleep Architecture

Non-REM sleep duration was significantly longer in the casopitant 30 mg group compared with placebo based on the mean of Nights 8 and 9. Slow-Wave Sleep duration was also significantly shorter and Stage 2 sleep was significantly longer for both casopitant 30 mg and casopitant 10 mg versus placebo.

Slow-Wave Sleep, Stage 2 sleep and REM sleep duration were all significantly different for both casopitant 30 mg and casopitant 10 mg versus placebo based on the mean of Nights 1 and 2.

Post-Sleep Questionnaire

There were no statistically significant differences from placebo with either casopitant doses on any of the subjective secondary endpoints captured by the Post-Sleep Questionnaire.

Insomnia Severity Index

The Insomnia Severity Index Total Score decreased from pre-dose on Day 1 (Baseline) to pre-dose on Day 9 for both casopitant doses and placebo, however, there were no statistically significant differences between either casopitant dose and placebo.

Safety:

Adverse Events

A summary of AEs reported is shown below:

	Number (%) Subjects with AE		
	Placebo (N=62)	Casopitant 10 mg (N=60)	Casopitant 30 mg (N=61)
Number of subjects with an adverse event during the treatment phase	14 (23)	19 (32)	18 (30)
Number of subjects with a serious adverse event during the study	0	0	0
Number of subjects withdrawn due to an adverse event during the treatment or Follow-up phase	2 (3)	5 (8)	0

The most common AEs (i.e. reported by ≥2% of subjects in any treatment group) during the treatment phase were headache, fatigue, lethargy, somnolence and QRS axis abnormal. The incidence of these events in each treatment group is shown below:

	Number (%) Subjects with AE		
	Placebo (N=62)	Casopitant 10 mg (N=60)	Casopitant 30 mg (N=61)
Headache	4 (6)	6 (10)	6 (10)
Fatigue	2 (3)	4 (7)	5 (8)
Lethargy	1 (2)	0	2 (3)
Somnolence	2 (3)	1 (2)	0
QRS axis abnormal	0	2 (3)	0

The only AEs that occurred with either casopitant dose at an incidence >2% that was also at least 2-fold the placebo incidence were fatigue and QRS axis abnormal.

There were no severe AEs during the treatment phase and the majority were mild in intensity.

There were no deaths or serious adverse events during the study.

Adverse events leading to withdrawal

Seven subjects were withdrawn from the study as a result of an AE, 2 subjects in the placebo group and 5 subjects in the casopitant 10 mg group. The reasons for withdrawal after placebo treatment were hypoglycemia (duration 8 days) and QTc prolongation (duration 6 days); both events were deemed by the investigator to be treatment-related. The reasons for withdrawal after casopitant 10 mg were blood in stool (ongoing at time of reporting), QRS axis change in ECG (ongoing at time of reporting), low pepsinogen I (ongoing at time of reporting), ECG QRS axis abnormal value of 124 degrees (duration 14 days), and tiredness (duration 22 days). All events were deemed by the investigator to be treatment-related.

Other Safety Findings

There were no subjects with Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) values ≥2 or 3 times the upper limit of the reference range (ULRR) during the study. There were no subjects with Creatine Kinase (CK) values ≥5 times the ULRR during the study. There were no subjects with troponin I values greater than the threshold value of interest during the study.

There was no consistent effect of casopitant 10 mg and 30 mg treatment on the incidence of ECG abnormalities and specific ECG parameters. One notable exception was the incidence of a decrease in QRS axis of 30 degrees or more in the casopitant 10 mg and 30 mg groups being at least twice that of placebo (9% and 4% versus 2%).

Daytime cognitive function tests and tests for ataxia

Dosed over a 9-day period, casopitant 10 mg/day and 30 mg/day showed only minor neurocognitive effects at a few timepoints, but no clear evidence of overall impairment or benefit.

Pharmacokinetic and Pharmacodynamic Analysis:

Observed casopitant plasma concentrations at 10 mg and 30 mg were consistent with healthy volunteer studies conducted to date.

The population PK analysis using prior information did not reveal relevant differences from healthy volunteers' studies. A slightly higher CL/F (14.4 L/hrs) of approximately 20% was estimated compared with the phase I analysis (12.1 L/hrs). Moderate to high variability on clearance was observed in this study.

A flat concentration-effect relationship on LPS (EC50 <1 ng/mL) was observed after both acute and repeated dosing, suggesting similar effect at both doses. According to the Emax model results no tolerance was detected in the LPS effect.

A flat concentration-response in TST was observed after single and repeat dosing. In addition, a statistically significantly ($p<0.05$) greater effect was estimated after acute (Days 1 to 2) than repeated (Days 8 to 9) dosing.

A concentration-response relationship for WASO was observed only after acute dosing (Days 1 to 2). Evidence of tolerance on WASO was observed on Days 8 and 9 and the exploratory analysis showed an increased tolerance with increasing concentrations after repeated dosing.

Conclusions:

- This placebo-controlled study in primary insomnia demonstrated that morning administration of casopitant 10 mg and 30 mg for 9 days promotes sleep onset as measured objectively by PSG (LPS) when subjects retire at their normal bedtime.
- Neurocognitive effects, as assessed by a selection of tasks from a computerized cognitive assessment system administered at times of maximum plasma concentrations following dosing, showed only minor effects at a few timepoints, but no clear evidence of overall impairment or benefit.
- Although the 30 mg dose maintained sleep better than placebo on the first 2 days of administration, i.e. less WASO, this benefit was lost by the end of the 9-day treatment period. The reason for the loss of sleep maintenance effect may be due to tolerance, a phenomenon encountered with some marketed hypnotics.
- Fatigue and QRS axis abnormality were the only AEs in this study that occurred with an incidence >2% and at least 2 fold the placebo incidence during 9 days of casopitant 10 mg and 30 mg/day treatment.
- There were no notable laboratory, ECG, vital signs, or other safety findings with casopitant treatment, except for isolated cases of QRS axis abnormality which will require further scrutiny in future studies.
- In terms of PK/PD data, a flat concentration-effect relationship on LPS was observed after both acute and repeated dosing.

Date of Report: December 2007