Study No: NKI111364

Title : A 28-Day, Polysomnographic and subjective assessment of Vestipitant (15 mg/day) for the treatment of Primary Insomnia in adult Outpatients.

Rationale: It is not clear if the sleep improving effects of vestipitant observed in an acute dosing study will be maintained over a repeat dosing regimen. Therefore, the sleep promoting efficacy of 15mg/day of vestipitant compared to placebo, measured by two-night polysomnographic (PSG) sessions were evaluated at the beginning and end of a 4-week treatment period in subjects with primary insomnia. The principal aim of this study was to assess whether vestipitant has sustained efficacy in maintaining sleep (Wake-time after sleep onset [WASO]) after four weeks of daily dosing in subjects with primary insomnia.

Phase: IIa

Study Period: 11 MAY 2009-23 SEP 2009

Study Design: Multi-centre, randomised, double-blind, placebo-controlled, parallel-group, polysomnography (PSG) and subject-reported evaluation of bedtime oral doses of vestipitant (15 mg/day) in adult outpatients diagnosed with primary insomnia.

Centres: Eleven centres in Germany.

Indication: Primary Insomnia

Treatment: Subjects received single-blind placebo on three occasions: a) during the 2 PSG screening night (dosing 30 minutes prior to lights out); b) during the week preceding start of double-blind treatment (dosing at bedtime at home) and c) during the first post-treatment week (dosing at bedtime at home). Eligible subjects were randomly assigned to receive vestipitant 15 mg or placebo for four weeks. Subjects were assigned to study treatment in accordance with the randomisation schedule by using the central Interactive Voice Response System (RAMOS).

Objectives: The primary objective of this study was to compare the efficacy of oral vestipitant (15 mg/day) with placebo after 4 weeks of treatment in adult outpatients diagnosed with Primary Insomnia, as determined objectively by PSG.

Statistical Methods: The primary endpoint, WASO was recorded on 2 nights pre-dose and Nights 1 and 2 and at Nights 27 and 28. The mean of the pre-dose values were used as the baseline in the analysis and the means of nights 1/2 and 27/28 were derived and used in the analysis. WASO was fitted to a mixed model repeated measures at both time points. The primary analysis was performed on the log-e transformed scale. Ratios, 95% confidence intervals and p-values were derived for the difference in WASO at both Nights 1/2 and Nights 27/28 between vestipitant 15 mg day against placebo. Similar statistical models were applied to the other key PSG endpoints wake after the onset of persistent sleep (WASO1) obtained on Nights 27/28 allowing further assessment of the effect of vestipitant on sleep maintenance, LPS, TST as well as to the endpoints derived from the verbal learning memory test (VLMT) and the ISI (Insomnia Severity Index).

Study Population: Male and female outpatients, at least 18 to 64 years of age (inclusive) with body mass index (BMI) <34 kg/m^2 and with a diagnosis of Primary Insomnia (as defined by Diagnostic and Statistical Manual of Mental Disorders-Text Revision [DSM-IV-TR] criteria 307.42) were considered for entry. The subjects had a self-reported sleep history with at least three months of a usual TST of less than 6 hours (h), sleep onset latency (SOL) of at least 30 minutes (min), and WASO of more than 60 minutes. The sleep variables obtained on two PSG screening nights (single blinded placebo administration at each night), fell within the following range as determined by a central PSG reader:

- TST between 240 min and 420 min inclusive on both nigh
- Mean latency to persistent sleep (LPS) of 20 min or more, but not <15 min on either nigh
- Mean WASO of 60 min or more, with neither night <45 min

Number of Subjects:	**Placebo**	**Vestipitant 15 mg**	**Total**
Planned N	76	76	152
Dosed N	81	80	161
Completed n (%)	78 (96)	71 (89)	149 (92)
Total number subjects withdrawn N (%)	3 (4)	9 (11)	12 (7)
Withdrawn due to adverse events n (%)	0	0	0
Withdrawn due to lack of efficacy n (%)	0	0	0
Withdrawn for other reasons n (%)	3 (4)	9 (11)	12 (7)
Demographics			
N (ITT)	81	80	161
Females: Males	48:33	40:40	88:73
Mean age in years (sd)	45.2 (11.90)	44.9 (10.70)	45.0 (11.29)
Mean weight in kg (sd)	-	-	-

White n (%)	80 (99)	78 (98)	158 (98)

Pharmacokinetics (PK), Pharmacodynamic (PD), PK/PD Endpoints: Pharmacokinetic (PK) and Pharmacokinetic/Pharmacodynamic (PK/PD) assessments for the vestipitant group were performed to examine the correlation between clinical efficacy (WASO/WASO1, LPS, TST and other PSG variables) and next-day residual effects (e.g. DSST) and plasma levels of the drug.

Pharmacodynamic (PD) Endpoints: A summary of the primary statistical analysis of WASO (Wake after Sleep Onset) time for vestipitant compared to placebo for the means of Nights 1 and 2 and Nights 27 and 28, is shown in the table below.

Comparison	**Ratio**	**Geometric LS Means**		**95 % CI**	**p-value**
		Vestipitant	**Placebo**		
Vestipitant/Placebo: (Nights 1/2)	0.76	41.50	54.33	(0.65, 0.90)	0.0014
Vestipitant/Placebo: (Nights 27/28)	0.79	40.97	51.98	(0.65, 0.96)	0.0165

A summary of statistical analysis of WASO (Log-e transformed analysis) comparing within treatments across timepoints is presented in the Table below. The means from Nights 27 and 28 were directly compared against Nights 1 and 2 within each treatment arm in a mixed model for repeated measures analysis adjusting for the same covariates as in the main model. Lack of tolerance development to the sleep maintenance effect was evident from this within-treatment group comparison.

Treatment Comparison	**Ratio**	**Geometric LS Mean**		**95% CI**	**p-value**
		Nights 27/28	**Nights 1/2**		
Vestipitant	0.988	41.50	40.97	(0.860, 1.134)	0.8588
Placebo	0.957	54.33	51.98	(0.838, 1.093)	0.5133

A summary of statistical analyses of WASO1 (Wake after persistent Sleep Onset) (Log-e transformed analysis) adjusted for Baseline, Baseline visit, centre group, age & sex is presented in the table below. The mean reduction in WASO1 for Nights 1 and 2 was 19% for the vestipitant group compared to placebo, and this difference was statistically significant. However, the difference at Nights 27/28 was not statistically significant, although the reduction in WASO1 was still 16%.

Comparison	**Ratio**	**Geometric LS Means**		**95 % CI**	**p-value**
		Vestipitant	**Placebo**		
Vestipitant/Placebo: (Nights 1/2)	0.81	40.17	49.37	(0.681, 0.972)	0.0233
Vestipitant/Placebo: (Nights 27/28)	0.84	40.02	47.90	(0.690, 1.012)	0.0656

A summary of statistical analyses of WASO1 is presented in the table below. As was the case for WASO, there was also no evidence of tolerance to the effect on WASO1 based on a within-treatment group analysis (Table 18), supporting the lack of evidence of tolerance based on the WASO data.

Treatment comparison	Ratio	Geometric LS Means		95% CI	p-value
		Vestipitant	Placebo		
Vestipitant/Placebo (Day 1)	0.71	39.60	55.43	(0.583, 0.876)	0.0014
Vestipitant/Placebo (Day 2)	0.94	36.81	39.08	(0.764, 1.161)	0.5726
Vestipitant/Placebo (Day 27)	0.84	41.44	49.35	(0.674, 1.047)	0.1193
Vestipitant/Placebo (Day 28)	0.84	35.35	42.14	(0.674, 1.045)	0.1155

A summary of statistical analyses of LPS endpoint (Log-e transformed analysis) is presented in the table below.

Comparison	**Ratio**	**Geometric LS Means**		**95 % CI**	**p-value**
		Vestipitant	**Placebo**		
Vestipitant/Placebo (Nights 1/2)	0.72	26.94	37.63	(0.59, 0.86)	0.0006
Vestipitant/Placebo (Nights 27/28)	0.84	25.50	30.34	(0.68, 1.04)	0.1070

A summary of statistical analyses of TST endpoint (Un-transformed analysis) adjusted for Baseline, Baseline visit, centre group, age & sex is presented in the table below.

Treatment comparison	**Ratio**	**LS Means**		**95% CI**	**p-value**
		Vestipitant	**Placebo**		
Vestipitant/Placebo (Nights 1/2)	22.00	401.10	379.10	(11.30, 32.70)	<.0001

Vestipitant/Placebo (Nights 27/28)	14.50	402.80	388.30	(2.50, 26.49)	0.0182

Subjective Sleep Data:
A summary of statistical analyses of post-sleep questionnaire (PSQ) endpoints (Log-e transformed analysis) is presented in the table below.

Parameter	Comparison	Ratio	Geometric Means		95% CI	p-value
			Vestipitant	Placebo		
Total Time Spent Awake	Vestipitant/Placebo	0.85	49.24	57.74	(0.71, 1.03)	0.0909
Sleep Onset Latency	Vestipitant/Placebo	0.95	38.59	40.70	(0.82, 1.10)	0.4838
Number of Awakenings	Vestipitant/Placebo	0.94	1.87	1.99	(0.84, 1.05)	0.2609

A summary of statistical analysis of Insomnia Severity Index (ISI) is presented in the table below.

Treatment Comparison	Estimate	LS Mean		95% CI	p-value
		Vestipitant	Placebo		
Vestipitant/Placebo (Week 2)	-0.075	13.70	13.77	(-1.37, 1.22)	0.9094
Vestipitant/Placebo (Week 4)	-0.434	13.09	13.52	(-1.79, 0.92)	0.5264
Vestipitant/Placebo (Follow up)	0.326	14.03	13.70	(-0.96, 1.61)	0.6173

No statistically significant effect of vestipitant treatment was observed on the DSST scores.

Pharmacokinetics (PK) Endpoints: Descriptive statistics for Vestipitant plasma concentration data at each planned visit are presented by time in the table below.

Treatment	Visit (Day)	Time	N	Vestipitant Plasma Concentration (ng/mL)		
				Mean (SD)	Median	Range
Vestipitant 15 mg	1	10 h	79	14.6 (10.5)	13.3	BQL to 92.5
	2	10 h	77	17.4 (7.45)	17.1	BQL to 39.5
	15	-	72	12.2 (9.72)	10.7	BQL to 43.4
	27	Pre-dose	70	8.27 (21.3)	4.95	BQL to 179
	27	10 h	70	16.3 (12.9)	13.0	BQL to 102
	28	Pre-dose	69	6.58 (10.1)	4.70	BQL to 83.3
	28	10 h	71	14.8 (9.50)	12.7	BQL to 71.2

BQL=Below quantifiable limit

PK/PD Endpoints: The effect on WASO was correlated with plasma exposures at days 1/2 when including placebo data (concentration equal to zero). No significant correlation was observed after repeated treatment. The WASO effect appeared to be slightly lower at the higher exposures after repeated dosing. Lastly, the data suggest that the WASO PK/PD relationship was mainly driven by the younger adult subjects.

Safety results: Adverse event (AE) and serious adverse event (SAE) data were collected starting on Day 1 and continuing until the end of the confinement period. Thirty-eight subjects (24%) experienced AEs during the treatment phase, irrespective of estimated causality. The majority of the AEs were mild to moderate in intensity. The most common AEs in the vestipitant treatment arm were headache (8%), fatigue (6%), and dry mouth (3%).
There were 2 AEs of severe intensity: arthropathy and fatigue reported by one subject in the placebo and vestipitant arms, respectively. The AE of fatigue occurred during the treatment phase of vestipitant 15 mg and was considered to be drug-related by the Investigator. Neither of the two subjects with an AE of severe intensity was withdrawn from the study. There were no other subject withdrawals reported due to AEs during the study. A summary of all AEs is presented in the following table.

Adverse Events:	Placebo	Vestipitant 15 mg	Total
	N=81	N=80	N=161
No. subjects with AEs n (%)	18 (22)	20 (25)	38 (24)
All AEs, n (%)			
Headache	7 (9)	6 (8)	13 (8)
Fatigue	3 (4)	5 (6)	8 (5)
Dry Mouth	1 (1)	2 (3)	3 (2)
Nasopharyngitis	3 (4)	0	3 (2)
Diarrhoea	1 (1)	1 (1)	2 (1)
Somnolence	1 (1)	1 (1)	2 (1)
Hyperaesthesia	1 (1)	0	1 (<1)

Abdominal discomfort	0	1 (1)	1 (<1)
Abdominal pain	0	1 (1)	1 (<1)
Dyspepsia	0	1 (1)	1 (<1)
Flatulence	0	1 (1)	1 (<1)
Nausea	1 (1)	0	1 (<1)
Tooth disorder	1 (1)	0	1 (<1)
Cystitis	0	1 (1)	1 (<1)
Diverticulitis	0	1 (1)	1 (<1)
Epicondylitis	0	1 (1)	1 (<1)
Atrioventricular block second degree	1 (1)	0	1 (<1)
Vertigo	0	1 (1)	1 (<1)
Eyelid oedema	1 (1)	0	1 (<1)
Electrocardiogram T wave inversion	0	1 (1)	1 (<1)
Hypoglycaemia	0	1 (1)	1 (<1)
Back pain	1 (1)	0	1 (<1)
Oropharyngeal pain	1 (1)	0	1 (<1)
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: No SAEs were reported during the study			