The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: NKI110334

Title: A multi-centre, randomised, double-blind, placebo-controlled, cross-over study to evaluate the effects of GW597599 (vestipitant) and GR205171 (vofopitant) on sleep continuity, polysomnography (PSG) sleep recordings, subjective sleep assessment and daytime cognitive function in subjects with primary insomnia.

Rationale: Vestipitant and vofopitant are piperidine derivatives that have been shown to be potent antagonists of the human neurokinin-1 (NK1) receptor, the primary receptor for Substance P. Based on their novel modes of action and suitable developability characteristics, both compounds were selected for clinical development for the treatment of primary insomnia. The aim of the study was to evaluate the efficacy and safety / tolerability of vestipitant and vofopitant in the acute treatment of primary insomnia in adult subjects.

Phase: 2

Study Period: 19 Dec 2007 to 07 May 2008.

Study Design: A multi-centre, randomised, double-blind, placebo-controlled, 3-period cross-over study.

Centres: This study was conducted at 10 centres in Germany.

Indication: Insomnia

Treatment: Subjects received single-blind placebo during the 2 nights-PSG screening. Eligible subjects were then randomised to receive placebo, vofopitant or vestipitant: one treatment for each PSG session in a balanced order.

Treatment	Drug	Form/Route	Frequency/Duration
A	placebo	capsule/ oral	Once/ single dose
C	GW597599 (vestipitant) 15 mg	capsule/ oral	Once/ single dose
D	GR205171 (vofopitant) 10 mg	capsule/ oral	Once/ single dose

Objectives: The primary objectives were 1) to evaluate the acute effects of vestipitant 15 mg on sleep in adults with primary insomnia as determined objectively by PSG and 2) to evaluate the acute effects of vofopitant 10 mg on sleep in adults with primary insomnia as determined objectively by PSG.

Statistical Methods:

PSG key endpoints (Total sleep time[TST], wake time after sleep onset[WASO1],latency to persistent sleep[LPS]): Summary statistics (median, minimum, maximum, arithmetic mean, Standard deviation (SD) were produced by treatment for each key PSG endpoint by night and as an average of the two nights. Statistical analysis of PSG endpoints (TST, WASO1, LPS) were performed on the average of the 2 nights values. A mixed effect model was applied, with period and treatment as fixed effects and subject as random effect. Estimates for mean treatment differences were calculated together with corresponding 95% confidence intervals. Additional analyses were performed to investigate the carry-over effect (effect of the treatment received in the previous period), the treatment by period interaction, the centre effect and the treatment by centre interaction. For each of these analyses a specific additional term was added to the original model. Model assumptions of homogeneity of variance and normality of the distribution underlying the analysis of variance were assessed by visual inspection of residual plots. The presence of a first night effect was investigated: By means of plots of mean values (±SD) by treatment and night and fitting a model on TST, WASO1, LPS single night values including a term for 'night' and a term for the interaction between night and treatment. Estimated treatment effects on Night 1 and Night 2 were reported. The same analysis was repeated, for WASO1 and LPS on $\log_e$ transformed values.

Other relevant PSG endpoints of sleep continuity (number of awakenings after sleep onset 1 [NAW1], sleep efficiency percentage [SEP]): Summary statistics (median, minimum, maximum, arithmetic mean, SD) were produced by treatment for each PSG endpoint by night and as an average of the two nights. The statistical analysis was performed using the same model for mean values (untransformed) over the two nights described before.

PSG endpoints of sleep structure (stage 1[ST1] / ST1 percentage [ST1P], stage 2[ST2] / ST2 percentage [ST2P], slow wave sleep[SWS] / SWS percentage [SWSP], rapid eye movement [REM] / percent REM [REMP], non-rapid eye movement [NREM] / percent NREM [NREMP]): Summary statistics (median, minimum, maximum, arithmetic mean, SD) were produced by treatment for each PSG endpoint by night and as an average of the two nights. The statistical analysis was performed using the same model for mean values (untransformed) over the two nights described before. Estimates of sleep structure were plotted by treatment. This plot represented the TST percentually distributed according to four categories: ST1P, ST2P, SWSP and REMP.

Other PSG endpoints (exploratory): The remaining PSG endpoints (number of REM/non REM cycles, micro arousal index, mean duration of REM/non REM cycles, number of stage shifts, duration of all the 3 thirds of REM sleep, REM activity, REM density, gravity centre for REM, REM latency, REM sleep latency from lights off, REM sleep latency from persistent sleep, sleep onset latency, sleep period time, total stage 3 duration, total stage 4 duration, duration of all the

3 thirds of SWS, gravity centre for SWS, time in bed, total time awake, wake prior to sleep onset, wake after last sleep epoch, duration awake after sleep onset) were summarised by treatment.
Other pharmacodynamics (PD) measurements: For each treatment, mean values over the two consecutive nights and, where applicable, over the 3 nights spent at home documented in the diary card, were obtained and analysed. Summary statistics and statistical comparisons were produced mirroring the methods described for PSG analysis.

Study Population: Male and female outpatients, at least 18 years of age and <65 years with body mass index (BMI) <34 kg/m^2 and with the 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 this study.

Number of Subjects:	Total
Planned N	48
Dosed N	51
Completed n (%)	48 (94)
Total Number Subjects Withdrawn N (%)	3 (6)
Withdrawn due to Adverse Events n (%)	1 (2)
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons n (%)	2 (4)
Demographics	
N (ITT)	51
Females: Males	33: 18
Mean Age in Years (range)	49.2 (21 – 64)
Mean Weight in kg (range)	73.17 (51.0 – 103.0)
Caucasian, n (%)	50 (98)

Pharmacodynamics Endpoints: The primary endpoints analysed were: TST, LPS and WASO1 derived from PSG recording. The secondary endpoints assessed were: 1) Objective PSG measures of sleep continuity including: wake during sleep (WDS), wake after sleep (WAS), and number of awakenings during sleep. 2) Objective PSG measures of sleep structure: NREM sleep time, SWS time (stage 3 and 4), stage 2 NREM sleep time; REM sleep time, REM activity, REM density. 3)Subjective post-sleep questionnaire: TST, WASO, sleep onset latency (SOL), number of awakenings, and sleep quality (SQ) to be applied on each morning following PSG recording and at home during the 3-day period following each 2-night PSG sessions. 4)Daytime cognitive function data on the morning following dosing, including tests of alertness, memory, attention and fine motor control (i.e. Romberg, digit symbol substitution test (DSST), and immediate and delayed word recall using modified verbal learning memory test (VLMT).
Summary of results of the statistical analysis of post-treatment key PSG data (untransformed – mean over the two nights) is given in the table below.

Parameter.	Comparison	LS mean Test treatment	LS mean Reference treatment	Difference.	95% CI	p-value
TST (min)	vestipitant - placebo	402.6	374.6	28.0	(19.2 , 36.7)	<0.001
	vofopitant - placebo	410.9	374.6	36.2	(27.5 , 45.0)	<0.001
	vestipitant - vofopitant	402.6	410.9	-8.3	(-16.9 , 0.4)	0.061
LPS (min)	vestipitant - placebo	28.1	39.3	-11.2	(-16.5 , -5.8)	<0.001
	vofopitant - placebo	23.7	39.3	-15.6	(-21.0 , -10.2)	<0.001
	vestipitant - vofopitant	28.1	23.7	4.5	(-0.9 , 9.8)	0.099
WASO1 (min)	vestipitant - placebo	54.2	72.3	-18.1	(-25.5 , -10.7)	<0.001
	vofopitant - placebo	50.8	72.3	-21.6	(-29.0 ,-14.2)	<0.001
	vestipitant - vofopitant	54.2	50.8	3.4	(-3.9 , 10.7)	0.354

LS= least square, CI= Confidence interval

Summary of results of the statistical analysis of post-treatment LPS and WASO1 PSG data (log$_e$ transformed – mean over the two nights) is given in the table below.

Parameter.	Comparison	LS geometric mean Test treatment	LS geometric mean Reference treatment	Ratio.	95% CI	p-value
LPS (min)	vestipitant / placebo	21.5	32.7	0.66	(0.53 , 0.82)	<0.001
	vofopitant / placebo	18.9	32.7	0.58	(0.46 , 0.72)	<0.001
	vestipitant / vofopitant	21.5	18.9	1.14	(0.92 , 1.42)	0.229

WASO1 (min)	vestipitant / placebo	44.2	62.3	0.71	(0.62 , 0.82)	<0.001
	vofopitant / placebo	44.1	62.3	0.71	(0.61 , 0.82)	<0.001
	vestipitant / vofopitant	44.2	44.1	1.00	(0.87 , 1.15)	0.986

Summary of results of the statistical analysis of post-treatment key PSG data (untransformed– analysis by night) is given in the table below

Parameter	Occasion	Comparison.	LS mean Test treatment	LS mean Reference treatment.	Difference.	95% CI	p-value
TST (min)	Night 1	vestipitant – placebo	396.0	365.1	30.8	(15.3 , 46.4)	<0.001
		vofopitant - placebo	405.7	365.1	40.6	(25.0 , 56.2)	<0.001
		vestipitant - vofopitant	396.0	405.7	-9.8	(-25.2 , 5.7)	0.214
	Night 2	vestipitant – placebo	408.5	384.1	24.4	(15.1 , 33.7)	<0.001
		vofopitant - placebo	415.6	384.1	31.5	(22.2 , 40.8)	<0.001
		vestipitant - vofopitant	408.5	415.6	-7.0	(-16.2 , 2.2)	0.133
LPS (min)	Night 1	vestipitant – placebo	34.0	44.3	-10.3	(-19.0 , -1.6)	0.021
		vofopitant - placebo	28.3	44.3	-16.0	(-24.7 , -7.3)	<0.001
		vestipitant - vofopitant	34.0	28.3	5.7	(-3.0 , 14.4)	0.196
	Night 2	vestipitant – placebo	22.3	34.3	-12.0	(-19.2 , -4.8)	0.001
		vofopitant - placebo	19.4	34.3	-14.9	(-22.0 , -7.7)	<0.001
		vestipitant - vofopitant	22.3	19.4	2.9	(-4.2, 10.0)	0.425
WASO1 (min)	Night 1	vestipitant – placebo	55.7	77.2	-21.5	(-33.6 , -9.4)	0.001
		vofopitant - placebo	52.5	77.2	-24.7	(-36.8 ,-12.5)	<0.001
		vestipitant - vofopitant	55.7	52.5	3.2	(-8.8 , 15.2)	0.601
	Night 2	vestipitant – placebo	53.1	67.4	-14.3	(-22.9 , -5.7)	0.001
		vofopitant - placebo	49.1	67.4	-18.3	(-26.9 , -9.7)	<0.001
		vestipitant - vofopitant	53.1	49.1	4.0	(-4.5 , 12.5)	0.354

Summary of results of the statistical analysis of post-treatment LPS and WASO1 PSG data ($\log_e$ transformed – analysis by night) is given in the table below.

Parameter	Occasion	Comparison	LS Geometric mean Test treatment	LS Geometric. mean Reference treatment	Ratio	95% C.I.	p-value
LPS (min)	Night 1	vestipitant / placebo	24.5	32.5	0.75	(0.56 , 1.01)	0.060
		vofopitant / placebo	20.9	32.5	0.64	(0.48 , 0.86)	0.004
		vestipitant / vofopitant	24.5	20.9	1.17	(0.87 , 1.58)	0.287
	Night 2	vestipitant / placebo	13.8	25.2	0.55	(0.39 , 0.77)	0.001
		vofopitant / placebo	13.0	25.2	0.52	(0.37 , 0.72)	<0.001
		vestipitant / vofopitant	13.8	13.0	1.06	(0.76 , 1.49)	0.720
WASO1 (min)	Night 1	vestipitant / placebo	42.3	62.9	0.67	(0.55 , 0.82)	<0.001
		vofopitant / placebo	42.7	62.9	0.68	(0.56 , 0.83)	<0.001
		vestipitant / vofopitant	42.3	42.7	0.99	(0.81 ,1.21)	0.928
	Night 2	vestipitant / placebo	43.0	55.5	0.78	(0.65 , 0.92)	0.005
		vofopitant / placebo	41.9	55.5	0.75	(0.63 , 0.90)	0.002
		vestipitant / vofopitant	43.0	41.9	1.03	(0.86 , 1.22)	0.763

Both compounds were able to increase the sleep efficiency, based on PSG, in a statistically significant way. The number of awakenings after sleep onset, also based on PSG, was reduced for both compounds, but the difference from placebo reached statistical significance only for vofopitant. The time spent in stage 1, when expressed in relative time (% of TST), was decreased with the two compounds respect to placebo while no evident difference was observed when the time in stage 1 was expressed as absolute values (minutes). Both the compounds increased the time spent in stage 2 and reduced the time spent in SWS both in absolute and relative (% of TST) times. Both compounds increased the total sleep time spent in the REM stage and in the NREM stage, however no significant differences were observed for either stage when values were expressed as percentage of the total sleep time. Post sleep (i.e. next day) questionnaire data followed the same trend shown by PSG data but, as expected, the variability was higher and the only statistically significant effects versus placebo were observed for vofopitant (for TST and SOL). No effect was observed on the mean values obtained over the 3 nights spent at home following dosing (treatment was administered

only during the 2 PSG nights). A significant improvement was observed in the Getting to Sleep domain (LSEQ Scale) for both vestipitant and vofopitant and a trend in the same direction was also noted for the Quality of Sleep domain for vofopitant only. No clear effect was detected for the other 2 domains (awakening following sleep and behaviour following wakefulness) and on data collected over the 3 nights spent at home.
No statistically significant effect was observed in Stanford sleepiness scale (SSS), DSST and VLMT. No formal statistical analyses was carried-out on the numerous (28) exploratory PSG endpoints.

Pharmacokinetics (PK) endpoints: Plasma concentration of vestipitant and vofopitant were analysed.

Treatment	Day	Time (h)	n	Mean (ng/mL)	SD	Median (ng/mL)	Minimum (ng/mL)	Maximum (ng/mL)
Vofopitant 10 mg	1	pre-dose	49	0.016	0.0785	0	0	0.52
		10 h	50	0.765	0.8764	0.374	0	3.83
	2	pre-dose	49	0.318	0.4659	0.155	0	2.05
		10 h	49	1.003	1.2308	0.52	0	5.57
Vestipitant 15 mg	1	pre-dose	49	0	0	0	0	0
		10 h	50	16.867	8.0523	15.85	0	39.23
	2	pre-dose	50	5.797	4.0631	4.97	0	21.49
		10 h	50	22.183	12.6986	21.315	0	67.76

PK/PD results: Exploratory analyses of the change from placebo for the three key PSG endpoints revealed a relevant and similar effect at all the explored vestipitant and vofopitant exposure levels as depicted by the statistically significant intercepts ($p<0.05$), while no evidence of exposure-response was detected (slopes were not statistically different from 0). Summary results of descriptive analysis of key PSG data (untransformed – mean over the two nights) by class of exposures* is given in the table below.

Parameter (Change from placebo)	Treatment	Class of exposure	N	Mean	Maximum	Median	Minimum
LPS (min)	vofopitant	Low	16	-11.92	10.5	-8.25	-33.75
		Medium	15	-18.27	13	-19.75	-47.5
		High	15	-16.65	36.25	-16.5	-70
	vestipitant	Low	16	-11.75	18.25	-9.5	-52.5
		Medium	15	-17.08	8.25	-7.25	-63.5
		High	15	-5.55	36.25	-9.75	-43
TST (min)	vofopitant	Low	16	29.75	131.5	29.12	-19.75
		Medium	15	44.62	89.5	45.5	-10.25
		High	15	35.67	72.5	35.5	-19
	vestipitant	Low	16	35.38	80.5	42.25	-20.5
		Medium	15	28.5	102.5	24.25	-20.5
		High	15	22.9	77.25	25.5	-25.25
WASO1 (min)	vofopitant	Low	16	-18.62	24.25	-14.38	-111
		Medium	15	-27.98	27.75	-28	-91.75
		High	15	-20	7	-17.5	-56.5
	vestipitant	Low	16	-24.67	26.75	-23.12	-91.5
		Medium	15	-14.53	32.25	-25.75	-59.75
		High	15	-17.23	22.75	-11.25	-59

*Class of Exposure (mean of 10 hrs post dose): vestipitant plasma concentrations (ng/mL): low [8.87, 13.5], medium [13.5, 22.5], high [22.5, 53.5]. Vofopitant plasma concentrations (ng/mL): low [0.102, 0.273], medium [0.273, 0.849], high [0.849, 4.42].

Safety results: From the time a subject received their first dose until he or she completed the study (including any Follow-up period), all adverse events (AEs) were recorded. Any serious adverse event (SAE) reported after a subject consented to participate in the study but before receiving their first dose and also after the final Follow-up visit and considered related to the investigational product by the Investigator would also be reported. Both vestipitant and vofopitant were generally well-tolerated in this study. The number of subjects reporting AEs are summarised in the table below.

Adverse Events:	placebo	vestipitant 15 mg	vofopitant 10 mg	Total
N (ITT)	49	50	50	51
No. subjects with AEs n (%)	18 (37)	13 (26)	10 (20)	30 (59)
Most Frequent AEs				

Headache	6 (12)	6 (12)	4 (8)	11 (22)
Nasopharyngitis	6 (12)	1 (2)	3 (6)	10 (20)
Fatigue	1 (2)	3 (6)	0	4 (8)
Dry mouth	0	0	2 (4)	2 (4)

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: There were no deaths or pregnancies reported in this study. A single SAE of moderate abdominal pain was reported during the course of the study. This event developed during the screening phase of the study, prior to randomisation and administration of study drug. The subject was hospitalised and underwent abdominal sonography which revealed no abnormalities. The Investigator confirmed that the subject had not received study drug prior to the onset of the abdominal pain.

Publications: None