Synopsis – Study 10402

Title of Study A 12-month phase III safety study of gaboxadol 10 mg daily consisting of a 6-month double-blind, randomised, placebo-controlled, parallel-group period followed by a 6-month open-label period in elderly outpatients with primary insomnia
Investigators 53 investigators in 8 countries *Signatory investigator* – Jan Hedner, Professor, MD, University of Gothenburg, Gothenburg, Sweden
Study Centres 53 centres – 4 in Belgium, 9 in Canada, 6 in Finland, 5 in France, 11 in Germany, 6 in Norway, 5 in Sweden, and 7 in the United Kingdom
Publication Hedner J, Loft H, Hajak G, Lundahl J, Hedegaard K, Knoth Sorensen H, Torstenson R. Efficacy and tolerability of gaboxadol in elderly patients with chronic primary insomnia: a 6-month double-blind, placebo-controlled outpatient study. Associated Professional Sleep Societies (APSS), 2007.
Study Period *First patient first visit* – 5 August 2004 *Last patient last visit* – 14 November 2006
Objectives • *Primary objective*: – to obtain 12 months of safety data in elderly patients treated with 10 mg gaboxadol (GBX10) • *Secondary objectives*: – to evaluate the efficacy of long-term GBX10 treatment – to evaluate the occurrence of withdrawal symptoms after long-term GBX10 treatment – to evaluate rebound insomnia after long-term GBX10 treatment
Methodology • Multinational, multi-centre, fixed-dose study in elderly patients with primary insomnia • Patients were recruited into this extension study from Study 10403. • The study consisted of the following phases/periods: – *Core Phase* – 24-week, randomised, double-blind, placebo (PBO)-controlled period with either PBO or GBX10 – *Run-out Phase* – 1-week, double-blind run-out period. Patients who had received GBX10 in the Core Phase received either GBX10 or PBO (GBX10-GBX10 or GBX10-PBO) and patients who had received PBO in the Core Phase continued on PBO (PBO-PBO) – *Open-label Phase* – 27-week, open-label period with GBX10. Although all patients received GBX10, patients were divided into two groups based on the treatment they had received in the Core Phase: patients on GBX10 were designated GBX10 (GBX) and patients on PBO were designated GBX10 (PBO). – *Safety Follow-up Phase* – 4-week safety follow-up period after the last dose of investigational medicinal product (IMP) • Efficacy and safety data were collected at 4-week intervals throughout the Core Phase and Open-label Phase; safety data were also collected during the other phases of the study.

Number of Patients Planned and Analysed

- 320 patients were planned for enrolment: 240 in the GBX10 group and 80 in the PBO group
- Patient disposition in the Core Phase is tabulated below:

	PBO		GBX10		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	76		253		329	
Patients treated (all-patients-treated set [APTS]):	76		252		328	
Patients completed	47	(61.8)	185	(73.4)	232	(70.7)
Patients withdrawn	29	(38.2)	67	(26.6)	96	(29.3)
Primary reason for withdrawal:						
Adverse event(s)	9	(11.8)	24	(9.5)	33	(10.1)
Lack of efficacy	14	(18.4)	32	(12.7)	46	(14.0)
Analysis sets:						
APTS	76		252		328	
Full-analysis set (FAS)	73		251		324	
Per-protocol set (PPS)	72		246		318	

- Patient disposition in the Open-label Phase is tabulated below:

	GBX10 (PBO)		GBX10 (GBX)		Total	
	n	(%)	n	(%)	n	(%)
Patients treated (all-patients-treated set [APTS_OL]):	47		185		232	
Patients completed	40	(85.1)	160	(86.5)	200	(86.2)
Patients withdrawn	7	(14.9)	25	(13.5)	32	(13.8)
Primary reason for withdrawal:						
Adverse event(s)	2	(4.3)	7	(3.8)	9	(3.9)
Lack of efficacy	4	(8.5)	9	(4.9)	13	(5.6)
Analysis sets:						
APTS_OL	47		185			
Full-analysis set (FAS_OL)	47		185			

Diagnosis and Main Inclusion Criteria

Female and male outpatients with a primary diagnosis of primary insomnia according to DSM-IV-TR™ criteria, who:

- had completed Study 10403 (until Visit 7) and who entered Study 10402 within 3 days after completion of Study 10403
- had a subjective time to sleep onset (sTSO) ≥45 minutes and a subjective total sleep time (sTST) <6.0 hours during the run-in period in Study 10403
- were aged ≥65 years at the time of entry into Study 10403
- were otherwise healthy in the opinion of the investigator

Investigational Product, Dose and Mode of Administration, Batch Number

Gaboxadol – 10 mg/day before bedtime; encapsulated tablets or hard gelatin capsules, orally; batch Nos. PD1495/R875 (hydrochloride formulation), 0928DFC002C001 (monohydrate formulation)

Duration of Treatment

24 weeks of double-blind, placebo-controlled treatment in the Core Phase, followed by 1 week of double-blind, placebo-controlled treatment in the Run-out Phase, followed by 27 weeks of open-label treatment in the Open-label Phase

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo – once daily before bedtime; encapsulated tablets or hard gelatin capsules, orally; batch Nos. PD1455/R874 (encapsulated tablets), 0928DFC001P001 (capsules)

Criteria for Evaluation – Efficacy

- Sleep parameters – subjective daily assessments made the week prior to each monthly visit and based on the morning questionnaire (using an electronic diary):
  - total sleep time (sTST)
  - time to sleep onset (sTSO)
  - freshness upon awakening (sFRESH)
  - quality of sleep (sQUAL)
  - number of awakenings per night (sNAW)
  - wakefulness after sleep onset (sWASO)
  - presence or absence of premature awakening (sPAWK)
  - estimated amount of premature awakening (sEAWK; how much earlier the premature awakening occurred)
- Global Clinical Impression – Severity of Illness (CGI-S) score
- Profile of Mood States (POMS) total and subscale scores
- Quality of life – Medical Outcomes Study (MOS) 36-item Short-form Health Survey (SF-36) subscale scores

Criteria for Evaluation – Safety

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), and physical examinations
- Withdrawal effects (based on the Withdrawal Symptom Questionnaire [WSQ])
- Rebound insomnia (based on sTST and sTSO)

Statistical Methods

- In the efficacy and safety analyses, the baseline data were those obtained at Week -5.
- Analyses without multiplicity control were performed on an exploratory basis; for these analyses, *statistical significance* implies nominal p-values <0.05.

Efficacy:

- Weekly means of sleep parameters were based on daily assessments. Based on the individual weekly means (sTSTm, sTSOm, and so on), mean values for the treatment groups were calculated.
- For efficacy analyses, the Core Phase was further devided into two periods:
  - Period 1 – first 3 months with efficacy evaluations (Weeks 4 to 12)
  - Period 2 – last 3 months with efficacy evaluations (Weeks 16 to 24)
- The analyses of change from baseline in efficacy parameters were based on the FAS and observed cases (OC). A longitudinal data analysis (LDA) model was applied over Weeks 4 to 24 with an unstructured covariance matrix and the baseline value as a covariate, and with Period, CCentres (grouped centres), and Treatment as factors; the interaction term Treatment*Period was included. Based on the estimates obtained from the LDA model, the hypotheses in the testing strategy (described in the following) were tested.
- A formal testing strategy was established for efficacy to adjust for multiplicity:
  - Stage 1 – the following hypothesis (primary) was considered:
    - H11: sTSTm – no difference between GBX10 and PBO in Period 2
  - Stage 2 – if the above-mentioned primary hypothesis was rejected, then the Stage 2 hypotheses (secondary) were evaluated at the 5% level of significance, applying Hochberg's procedure:
    - H21: sTSOm – no difference between GBX10 and PBO in Period 2
    - H22: sFRESHm – no difference between GBX10 and PBO in Period 2
    - H23: sQUALm – no difference between GBX10 and PBO in Period 2
- Hypotheses that were rejected for Period 2 (after multiplicity adjustment) were tested at the 5% level of significance for Period 1, using a closed-test procedure. Secondary hypotheses for Period 1 were not evaluated if the primary hypothesis was negative.

Statistical Methods – continued

Quality of Life:

- The analysis of quality of life was a standard ANCOVA of the mean change from baseline to Week 24 based on the FAS and OC. The three primary dimensions were analysed in accordance with the testing strategy (described below); the five remaining dimensions (*physical functioning*, *bodily pain*, *general health*, *mental health*, and *social functioning*) were analysed in the same manner without adjusting for multiplicity.
- The following hypotheses were evaluated at the 5% level of significance, applying Hochberg's procedure:
  - H31: *role – physical* – no difference between GBX10 and PBO in the Core Phase
  - H32: *vitality* – no difference between GBX10 and PBO in the Core Phase
  - H33: *role – emotional* – no difference between GBX10 and PBO in the Core Phase

Safety:

- The incidences of adverse events were compared between treatment groups using Fisher's exact test and the time to first occurrence of certain adverse events was analysed using Kaplan-Meier plots, log-rank tests, and the Cox model.
- Absolute values and changes from baseline to the last assessment in clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameters were summarised using descriptive techniques. Values outside the reference range, as well as potentially clinically significant (PCS) values, were flagged and tabulated.
- Withdrawal symptoms and rebound insomnia were analysed in the double-blind Run-out Phase using a $\chi 2$ test and pairwise comparisons of treatment groups.

Demography of Study Population

- The ratio of men to women was 1:1 in the PBO group and approximately 2:3 in the GBX10 group. This sex imbalance was addressed in covariate and subgroup analyses. The mean age was approximately 71 years in both treatment groups, and the vast majority of patients were Caucasian (>97%). There were no clinically relevant differences in height, weight, or BMI between the two treatment groups.
- At baseline, the patients slept approximately 4½ hours per night (sTST) and had a time to sleep onset (sTSO) of approximately 106 minutes (approximately 94 minutes based on geometric mean). The patients had on average 2.3 awakenings per night (sNAW), with a total duration (sWASO) of approximately 111 minutes (approximately 85 minutes based on geometric mean). The patients rated their sleep quality (sQUAL) and their freshness upon awakening (sFRESH) as approximately 40 points on the 100-point visual analogue scale (VAS).

Efficacy Results

- Based on the testing strategy (focusing on efficacy in Weeks 16 to 24 [Period 2] and Weeks 4 to 12 [Period 1]), there was a statistically significantly ($p < 0.05$) greater improvement from baseline in the GBX10 group versus the PBO group in sTSTm, sFRESHm, and sQUALm in Period 2, as well as in Period 1.
- The mean baseline value and the mean changes from baseline (FAS, OC, LDA) for each of the sleeping parameters and for the CGI-S in Period 1 and Period 2 are summarised below:

Efficacy Variable	Treatment Group	Baseline	Mean Change from Baseline	
			Period 1 (Weeks 4 to 12)	Period 2 (Weeks 16 to 24)
Multiplicity controlled:				
sTSTm (min)	PBO	277	57.2	50.5
	GBX10	270	73.5*	74.5**
sTSOm (min)[a]	PBO	105	-43.0	-45.7
	GBX10	107	-48.3	-51.8
sFRESHm (points)	PBO	43	11.5	9.3
	GBX10	42	16.7**	16.6***
sQUALm (points)	PBO	40	13.7	11.9
	GBX10	38	19.6**	19.3***
Not multiplicity controlled:				
sNAWm	PBO	2.4	-0.7	-0.6
	GBX10	2.3	-0.8	-0.8
sWASOm[a] (min)	PBO	112	-46.0	-44.2
	GBX10	111	-50.8	-52.6
CGI-S	PBO	3.9	-1.0	-0.8
	GBX10	3.8	-1.2	-1.2**

* p<0.05, ** p<0.01, and *** p<0.001 compared to placebo

a Baseline values and mean changes from baseline are based on non-transformed values (FAS, OC, LDA); statistical significance is based on log-transformed values (FAS, OC, LDA).

Sleep Parameters:

- During the 6-month Core Phase, sTSTm increased from baseline by 71 to 76 minutes in the GBX10 group. There was a statistically significant ($p < 0.01$) difference between the GBX10 and PBO groups in Period 2 (24 minutes), as well as in Period 1 (16 minutes).
- During the 6-month Core Phase, there were no statistically significant differences between the two treatment groups in mean change from baseline in mean number of awakenings (sNAWm).
- On average, patients in the GBX10 group had 4 to 11 minutes less wakefulness after sleep onset (sWASOm) than patients in the PBO group. The difference between the two treatment groups was not statistically significant.
- In the GBX10 group, the mean time to sleep onset (sTSOm) decreased by 48 to 53 minutes during the 6-month Core Phase; sTSOm also decreased in the PBO group, although to a lesser extent than that in the GBX10 group (39 to 49 minutes). The difference between the two treatment groups ranged from 1 to 12 minutes; this difference was not statistically significant.
- During the 6-month Core Phase, patients felt more refreshed (sFRESHm) upon awakening in the GBX10 group than in the PBO group: on average, the improvements in sFRESHm in the GBX10 group relative to the PBO group were 5 points in Period 1 and 7 points in Period 2. These improvements were statistically significant.

Efficacy Results – continued

- Patients also had a higher subjective quality of sleep (sQUALm) in the GBX10 group than in the PBO group: on average, the improvements in sQUALm in the GBX10 group relative to the PBO group were 6 points in Period 1 and 7 points in Period 2.

CGI-S Scores:

- The investigators rated the patients as *mildly ill* to *moderately ill* at baseline: the CGI-S score was 3.8 in the GBX10 group and 3.9 in the PBO group. During the 6-month Core Phase, the CGI-S scores improved in both treatment groups, but the improvement was more pronounced in the GBX10 group (1.1 to 1.3 points) in both periods and statistically significant ($p < 0.01$) in Period 2. The improvement from baseline in CGI-S score was maintained in the 6-month Open-label Phase, indicating sustained improvement during a 1-year period.

POMS Total and Subscale Scores:

- The improvements from baseline in the POMS total and subscale scores, all of which were in favour of GBX10, were not statistically significantly different between the two treatment groups in Period 1 or Period 2, except for *fatigue* ($p < 0.05$ in Period 2). Over the One-year Period, the numerical improvements from baseline in POMS total and subscale scores were maintained.

Quality of Life (SF-36):

- Based on the testing strategy, there was a statistically significantly ($p < 0.05$) greater improvement from baseline in the GBX10 group than in the PBO group in SF-36 subscale scores for *role – physical*, *role – emotional*, and *vitality* at Week 24. In addition, there was a statistically significantly greater improvement in the GBX10 group than in the PBO group in *social functioning* and *bodily pain* at Week 24. The improvements in SF-36 subscale scores (all dimensions) were maintained in the 6-month Open-label Phase.
- The data from patients who received GBX10 during the Core Phase and Open-label Phase indicated sustained improvement in the primary dimensions *role – physical*, *role – emotional*, and *vitality*, as well as in the remaining five SF-36 subscales during the One-year Period.

Safety Results

Death:

- One patient (a [redacted] man in the PBO group) died of pancreatic cancer during the study. After 14 days on PBO, he was hospitalised for 15 days and died 8 days later. He had been treated with GBX05 in Study 10403.

Serious Adverse Events (SAEs):

- In the Core Phase, a total of 19 patients (including the one who died) had SAEs: 13 (5%) in the GBX 10 group and 6 (8%) in the PBO group. Three SAEs (abdominal pain, cerebral infarction, and transient ischaemic attack) in the GBX10 group and 2 SAEs (dysarthria and lacunar infarction) in the PBO group were considered *possibly related* to IMP. There were no trends with respect to SAEs between or within treatment groups. One patient had an SAE (subileus) in the Run-out Phase. In the Open-label Phase, 10 patients had SAEs: 6 (3%) in the GBX10 (GBX) group and 4 (9%) in the GBX10 (PBO) group); in the Safety Follow-up Phase, 4 patients had SAEs.

Adverse Events – Core Phase:

- The adverse event incidence in the Core Phase is summarised below:

	PBO		GBX10	
	n	(%)	n	(%)
Patients who died	1		0	
Patients with serious AEs (SAEs)	5	6.6	13	5.2
Patients with AEs	47	61.8	168	66.7
Total number of AEs	113		490	

n = number of patients; % = percentage of patients within treatment group

Safety Results – continued

- In the Core Phase, approximately two-thirds of the patients in each of the two treatment groups had one or more adverse events. The proportion of patients who had adverse events considered *related* to treatment was 40% in the GBX10 group and 32% in the PBO. Most of the adverse events were *mild* or *moderate*. The incidence of *severe* adverse events was 4% in both treatment groups.
- In the Core Phase, the proportion of patients who withdrew due to adverse events was similar in the PBO group (12%) and in the GBX10 group (10%).
- In the Core Phase, there was a difference in the distribution and nature of adverse events in the GBX10 group compared to those in the PBO group. Adverse events in the *eye disorders* and *nervous system disorders* SOCs had a statistically significantly higher incidence in the GBX10 group than in the PBO group; the difference in the incidence of *nervous system disorders* was driven by the high incidences of dizziness and headache in the GBX10 group, while that of *eye disorders* was mainly driven by the incidences of conjunctivitis and vision blurred. A statistically significantly higher incidence of *nervous system disorders* was also seen in women, but not in men. Adverse events in the remaining SOCs were essentially equally distributed in the two treatment groups.
- In the Core Phase, in the GBX10 group, dizziness (11%), headache (8%), nasopharyngitis (7%), and arthralgia (6%) were the four adverse events with highest incidences. In the PBO group, back pain (8%), nasopharyngitis (7%), pain in the extremities (5%), dizziness (4%), and nausea (4%) were the adverse events with the highest incidences. None of the adverse events had a statistically significantly higher incidence in the GBX10 group than in the PBO group; gastroenteritis had a statistically significantly ($p < 0.05$) higher incidence in the PBO group (3.9%) than in the GBX10 group (0.4%).
- Exploratory analyses revealed no effect of covariates (sex, age, weight, LBM, and CrCL) on the incidences of adverse events of particular interest.
- In the Core Phase, 7 patients (3%) in the GBX10 group had hypertension; in 2 of them, the blood pressure had increased from screening to the time the event was reported.
- In the Core Phase, depression was reported in 3 patients (1.2%) in the GBX10 group and 1 patient (1.3%) in the PBO group. The incidence of falls was 1.6% (4 patients) in the GBX10 group and 1.3% (1 patient) in the PBO group. In none of the cases was dizziness reported prior to or around the time of the fall.

Adverse Events – Run-out Phase:

- In the Run-out Phase, the overall incidence of adverse events was equal (13%) in the GBX10-PBO group and in the GBX10-GBX10 group; there was no indication of any specific adverse event related to run-out in the GBX10-PBO group.

Adverse Events – Open-label Phase:

- In the Open-label Phase, a little more than half of the patients in each treatment group had one or more adverse events. Six patients (3%) in the GBX10 (GBX) group and 2 patients (4%) in the GBX10 (PBO) group withdrew due to adverse events that had started in the Open-label Phase.

Adverse Events – Safety Follow-up Phase:

- In the Safety Follow-up Phase, less than 11% of the patients in any treatment group had adverse events.

Adverse Events – One-year Period:

- In general, no new or unexpected adverse events were seen in the second 6-month period in patients who received GBX10 in both the Core Phase and the Open-label Phase. Thus, there was no evidence of any adverse events unique to long-term treatment.
- The overall incidence of adverse events was highest within the first 90 days (56%) and decreased over time; particularly, the incidences of dizziness, fatigue, and nausea decreased markedly over time.

Safety Results – continued

Symptoms Possibly Relevant for Abuse:

- In the Core Phase, the incidence of symptoms possibly relevant for abuse was higher in the GBX10 group (7%) than in the PBO group (0%). The lowest level terms possibly relevant for abuse with the highest incidence in the GBX10 group were *anxiety* and *irritability* (3 patients each plus 1 patient who had both symptoms). In the Open-label Phase, the incidence of symptoms possibly relevant for abuse was 4.3% in the GBX10 (PBO) group and 3.8% in the GBX10 (GBX) group. The lowest level terms possibly relevant for abuse with the highest incidence were *overdose* (2 patients in the GBX10 (PBO) group) and *anxiety* (3 patients in the GBX10 (GBX) group).

Laboratory Tests, Vital Signs, Weight, Physical Examination Findings, and ECGs:

- There were no clinically relevant changes within or differences between treatment groups in clinical laboratory values, vital signs, weight changes, physical examination findings, or ECGs

Withdrawal Symptoms and Rebound Insomnia:

- Neither the pooled nor the day-by-day analysis of data from the WSQ indicated a statistically significantly higher proportion of patients with withdrawal signals in the GBX10-PBO group than in the GBX10-GBX10 group.
- The frequency of rebound insomnia, based on either sTST or sTSO, after discontinuation of treatment was similar in the two treatment groups.

Conclusions

- GBX10 is more effective than PBO in the treatment of primary insomnia in the elderly, as demonstrated using the pre-defined testing strategy focusing on efficacy in Weeks 16 to 24 (Period 2): patients have a greater increase in total sleep time (sTSTm); patients also feel more refreshed upon awakening (sFRESHm) and have a better quality of sleep (sQUALm). There is insufficient evidence to suggest a beneficial effect of GBX10 on the time to sleep onset (sTSOm).
- Based on exploratory analyses, patients on GBX10 have an improvement in the CGI-S scores with no evidence of tolerance development during 1 year of treatment with GBX10.
- Patients on GBX10 have an improvement in the multiplicity controlled dimensions of the SF-36: *role – physical*, *role – emotional*, and *vitality*, as well as in *social functioning* and *bodily pain*, with no evidence of tolerance development during 1 year of treatment with GBX10.
- Treatment with GBX10 for 6 months and 12 months is generally safe and well tolerated in this elderly population with primary insomnia.
- The adverse events with the highest incidence during gaboxadol treatment are dizziness and headache.
- There is no evidence of any adverse event unique to long-term treatment with GBX10 and there are no clinically relevant mean changes in the clinical laboratory values, vital signs, or ECG values.
- There is insufficient evidence to suggest an abuse potential with GBX10 treatment when specifically analysing symptoms possibly relevant for abuse.
- No evidence of withdrawal symptoms is found after discontinuation of GBX10 treatment, and no new adverse events are observed after discontinuation of 6 months of GBX10 treatment.
- Relative to PBO treatment, no overall rebound effect is seen after discontinuation of 6 months of GBX10 treatment.

Date of the Report

15 June 2007

This study was conducted in compliance with the principles of *Good Clinical Practice*.