TITLE OF TRIAL: A randomized Phase IIa trial evaluating the safety and efficacy of a new centrally acting analgesic in subjects with pain due to diabetic polyneuropathy.

SPONSOR/COMPANY: Grünenthal GmbH, 52099 Aachen, Germany

COORDINATING INVESTIGATOR: [redacted]
[redacted] 55116 Mainz, Germany

TRIAL CENTERS: 3 centers in Germany, 1 center in the United Kingdom

TRIAL PERIOD (YEARS):

First subject enrolled:	15 Apr 2009
Last subject completed:	25 May 2010
Data base lock:	02 Jul 2010

PHASE OF DEVELOPMENT: IIa

OBJECTIVES:

Primary objective:

- To evaluate the analgesic efficacy of GRT6005 in subjects with moderate to severe pain due to diabetic polyneuropathy (DPN).

Secondary objectives:

- To evaluate the safety and tolerability of GRT6005.
- To evaluate the relationship between plasma concentration and analgesic efficacy of GRT6005.

METHODOLOGY:

Randomized, multi-center, double-blind, placebo-controlled (Part A to Part D), active-controlled (Part D only), crossover, multiple-administration Phase IIa trial.

There were 4 sequential parts planned in the trial (Part A to Part D). Each part was a 3-way crossover. Subjects were only allowed to participate in 1 part. In Part A and Part B, only 3 randomized treatment sequences, which guaranteed that the lower dose of GRT6005 was given before the higher dose, were used in a balanced way. In Part D, 6 randomized treatment sequences were used in a balanced way. Part C was optional and to be performed only if the effective dose range would not have been established after the conduct of Part B. It was not deemed necessary to conduct Part C by the data review board based on the results of Part A and Part B.

The crossover sequences of Part A and Part B comprised placebo and 2 dose steps of GRT6005. The sequences for Part D comprised placebo, morphine sulfate controlled-release (CR) 60 mg, and 1 dose level of GRT6005. Thus, in Part D, the trial was conducted with an active control and double-dummy administration.

In Part A, the subjects received placebo, 40 µg, and 120 µg of GRT6005 in a predefined sequential order, once daily in the morning for 5 consecutive days. The subjects were randomly assigned to 1 of the sequences. The dose levels of GRT6005 to be administered in Part B and Part D were decided by a data review board (consisting of sponsor personnel not involved in the conduct of the

trial) after evaluation of pharmacokinetic and selected efficacy and tolerability data from the previous crossover part. In addition, on a subject level within each part of the trial, the higher doses of GRT6005 were only administered if plasma concentrations observed in individual subjects did not exceed a predefined level following the administration of the lower dose. The sponsor's pharmacokinetic expert checked the results and informed the relevant personnel at the sponsor who subsequently informed the site about the decision for each subject. The personnel directly involved in the conduct of the trial at the sponsor was not unblinded during this process. The doses administered in Part B were 80 µg and 200 µg of GRT6005; the dose administered in Part D was 100 µg GRT6005.

NUMBER OF SUBJECTS:

In total 91 subjects were randomized in 4 centers, 3 in Germany and 1 in the United Kingdom. In total, 89 subjects were allocated to 1 of the treatment sequences (Safety Set). Both in Part A and Part B, 1 subject was randomized, but remained untreated. In Part D, all randomized subjects were treated. The following table displays the number of subjects randomized and the number of subjects per analysis set by trial part and overall.

Parameter	Part A N (%)	Part B N (%)	Part D N (%)	Overall N (%)
Randomized subjects	27 (100)	24 (100)	40 (100)	91 (100)
Safety Set	26 (96.3)	23 (95.8)	40 (100)	89 (97.8)
Full Analysis Set	26 (96.3)	23 (95.8)	40 (100)	89 (97.8)
Per Protocol Set	17 (63.0)	21 (87.5)	33 (82.5)	71 (78.0)

N = number of subjects

NUMBER OF WITHDRAWALS:

The following table presents the number of subjects enrolled and randomized as well as the number of subjects who completed or prematurely discontinued the trial.

Parameter	Part A N	Part B N	Part D N	Overall N
Subjects enrolled	57	52	81	190
Subjects enrolled but not randomized	30	28	41	99
Enrollment failure [a]	22	27	36	85
Adverse event	1	0	0	1
Withdrawal of informed consent	2	1	3	6
Other reasons	5	0	2	7
	N (%)	**N (%)**	**N (%)**	**N (%)**
Randomized subjects	27 (100)	24 (100)	40 (100)	91 (100)
Subjects completing trial	25 (92.6)	22 (91.7)	33 (82.5)	80 (87.9)
Subjects randomized and prematurely discontinued [b]	2 (7.4)	2 (8.3)	7 (17.5)	11 (12.1)
Adverse event	0	0	4 (10.0)	4 (4.4)
Protocol deviation	0	2 (8.3)	1 (2.5)	3 (3.3)
Withdrawal of informed consent	2 (7.4)	0	1 (2.5)	3 (3.3)
Other reasons	0	0	1 (2.5)	1 (1.1)

a) Enrollment failures are subjects who did not qualify for the trial based on the inclusion and exclusion criteria and the pain intensity criteria during the Enrollment Pain Intensity Evaluation Period.

b) Including the 2 subjects who were randomized but no treated.

N = Number of subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male or female Caucasian or Hispanic subjects with type 1 or type 2 diabetes mellitus and a documented clinical diagnosis of painful DPN with symptoms and signs of DPN for at least 3 months, and pain present at the time of enrollment (pain intensity score of ≥4 on the 11-point numeric rating scale on at least 3 consecutive days), aged 18 years to 75 years (inclusive); blood glucose well controlled by a diet, oral hypoglycemics, or insulin for at least 3 months prior to enrolling in this trial.

INVESTIGATIONAL MEDICINAL PRODUCTS:

Test product	**GRT6005**
Dose	40 µg, 80 µg, 100 µg, 120 µg, and 200 µg of GRT6005 free base
Mode of administration	Oral
Batch number/expiration date	Batch no 180209/expiration date 06/2009 Batch no 140709/expiration date 12/2009 Batch no 150709/expiration date 12/2009 Batch no 281009/expiration date 10/2010 Batch no 291009/expiration date 10/2010
Duration of treatment	Once daily in the morning for 5 consecutive days

Comparator	**Morphine sulfate CR**
Dose	60 mg of morphine sulfate salt
Mode of administration	Oral
Batch number/expiration date	Batch no 281009/expiration date 10/2010 Batch no 291009/expiration date 10/2010
Duration of treatment	Once daily in the morning for 5 consecutive days

Placebo matching GRT6005

Dose	Not applicable
Mode of administration	Oral
Batch number/expiration date	Batch no 180209/expiration date 06/2009 Batch no 140709/expiration date 12/2009 Batch no 150709/expiration date 12/2009 Batch no 281009/expiration date 10/2010 Batch no 291009/expiration date 10/2010
Duration of treatment	Once daily in the morning for 5 consecutive days

Placebo matching morphine sulfate CR

Dose	Not applicable
Mode of administration	Oral
Batch number/expiration date	Batch no 281009/expiration date 10/2010 Batch no 291009/expiration date 10/2010
Duration of treatment	Once daily in the morning for 5 consecutive days

CRITERIA FOR EVALUATION:

Efficacy:

Primary endpoint criteria:

Reduction from baseline in average daily pain intensity score (over the last 24 h) measured with the 11-point numeric rating scale (NRS) at the final treatment day of each treatment period, in comparison to placebo.

On the basis of data from different doses, a dose response relationship will be assessed. When plasma levels are above the lower limit of quantification, the concentration response relationship will be assessed as well. The results of this analysis will be reported separately (see also Pharmacokinetics).

Secondary endpoint criteria

- Average daily pain intensity (11-point NRS): observed values from baseline to the final day of each treatment period.
- Neuropathic Pain Scale (NPS): change from baseline to the final day of each treatment period.
- Brief Pain Inventory (BPI) scores: change from baseline to the final day of each treatment period.
- Quantitative sensory testing (with a selection of tests, i.e., cotton swab testing, brush-evoked pain, and pinprick test): changes from baseline to the final day of each treatment period.

- Subject's and Physician's Global Evaluation of the investigational medicinal product, at the final day of each treatment period.
- Short Form 12 Health Survey (SF-12®): changes from baseline to the final day of each treatment period.
- Assessment of the Leeds Sleep Evaluation Questionnaire (LSEQ) on Day 2 and Day 6 of each treatment period.
- Time to overall withdrawal and time to withdrawal for specific reasons.
- Amount of rescue medication during each treatment period and time to first rescue medication in each treatment period.
- Assessment of different responder definitions (rates of 10% to 90% improvement of pain intensity score from baseline) at the final day of each treatment period.

Safety:

- Assessment of vital signs (including pulse oximetry) and physical examination.
- Assessment of adverse events.
- 12-lead electrocardiogram.
- Clinical laboratory parameters (biochemistry, hematology, and urinalysis).
- Clinical Opiate Withdrawal Scale.

Pharmacokinetics

In each of the 3 treatment periods, a total of 8 blood samples of 4 mL each were drawn from each subject to determine individual plasma concentrations.

Population pharmacokinetic and pharmacokinetic/pharmacodynamic modeling will be performed to evaluate the equi-analgesic dose of GRT6005 to morphine CR 60 mg. The results of these analyses will be reported separately.

Pharmacogenetics

A single venous blood sample of 10 mL was collected by venipuncture for the pharmacogenetic analysis of genes encoding subtypes of either the MOR and/or the ORL1 target receptors and/or subtypes of enzymes relevant for the metabolism of GRT6005. The exploratory pharmacogenetic analysis will be described separately and the results will be presented in a separate report.

STATISTICAL METHODS:

Descriptive statistics:

Measures of location and variance (e.g., mean, median, standard error, standard deviation, range, inter-quartile range, minimum, maximum, and quartiles, as appropriate to the analysis) were used to summarize continuous variables. Frequency counts and percentages were used to summarize categorical variables.

Efficacy:

The analysis of efficacy was performed in the Full Analysis Set, i.e., the subset of randomized subjects in the Safety Set who had at least 1 (non-missing) post-baseline pain intensity assessment. The primary efficacy endpoint was summarized by descriptive statistics grouped by treatment.

The primary endpoint was analyzed by means of an analysis of covariance (ANCOVA) accounting for the effects of the baseline value, treatment, period, and treatment sequence as fixed effects, and subject within sequence as random effect. Center and first order carry-over effects were included in the model as additional fixed effects. If their influence was not relevant ($p < 0.1$) they were removed from the model while estimating the treatment effects. For Part A and Part B, methods for estimating treatment differences described in Peace and Koch (1993) were applied.

The baseline value for all efficacy endpoints was the period baseline pain intensity (if not otherwise stated), i.e., the assessment performed at the Baseline Visit of the respective period. In addition, the primary endpoint analysis and the dose response analysis were performed using the overall baseline pain intensity instead of the period baseline pain intensity (both on numeric rating scale) to check the robustness of the results.

In addition, an analysis of variance was performed including all crossover parts to assess a dose response relationship.

Similar statistical models were used for the analysis of the secondary endpoints.

Safety:

The analysis of safety data was performed for the Safety Set. The Safety Set comprised all subjects who took at least 1 dose of investigational medicinal product. For all adverse events, clinical laboratory evaluations, vital signs, and 12-lead electrocardiogram measurements, baseline was defined as the last evaluation assessed before initial administration of the investigational medicinal product. Adverse events were coded using Version 13.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

Pharmacokinetics:

As the sparse PK samples were taken in wide time frames (2 samples on Day 1, 1 sample on Day 3 and 5 samples on Day 5) the concentrations of the individual PK samples taken in the same time window cannot be compared directly. Therefore, only a statistical analysis of t_{max} and C_{max} by treatment (as observed on Day 5) was performed.

Population pharmacokinetic modeling will be performed with a non linear mixed effects modeling approach. The models to be used for the population pharmacokinetic evaluation and the possible correlation of concentration with selected efficacy endpoints were described in a separate protocol. The results will be reported separately.

Data review board:

A data review board consisting of sponsor personnel not involved in the clinical trial conduct and operating according to its charter, reviewed the data from Part A to determine the dose levels in Part B, made decisions based on data from Part B to omit Part C and decided on the dose levels for Part D based on data from Part A and Part B. Decisions were made after the respective parts of the trial were clinically completed, the database was frozen and the unblinded data of pharmacokinetics and selected efficacy and tolerability data became available.

SUMMARY:

Demographics:

In total, 34 women and 55 men were treated in this trial aged 32 years to 76 years (based on the Full Analysis Set).

Subjects in the 3 parts of the trial had similar ages, height, weight, and body mass index. There were proportionally more men in Part B.

The body mass index was high (mean: 33.80 kg/m^2; standard deviation: 6.59) which was expected given that subjects with type II diabetes mellitus were included in this trial.

All subjects were White.

Pharmacokinetics:

A sparse sampling approach was used for the collection of samples, but within this limitation, C_{max} for GRT6005 increased linearly with dose. The obtained t_{max} was similar in each of the treatment periods of GRT6005, and also similar to that of morphine, at around 5 h. The observation of GRT6005 in predose samples of the next treatment period did not influence the pain evaluation because the concentrations were well below the concentrations observed after the lowest dose of GRT6005 (40 µg), which only tended to differentiate from placebo on Day 5.

Efficacy results:

The results of the primary and secondary endpoints were provided individually by trial part and also for the trial overall. The results presented overall have to be interpreted cautiously because different subjects were entered in the different parts and because the parts were conducted sequentially. The 3 parts were conducted as individual trials; thus, the overall presentation is comparable to an across-trial interpretation, although the same centers and logistics were used.

Overall

This trial compared in 89 treated subjects with painful diabetic neuropathy in a repeated triple cross-over design the efficacy of multiple doses of GRT6005 40 µg, 80 µg, 120 µg, and 200 µg with placebo (Part A and Part B); in Part D, GRT6005 was compared with placebo and morphine CR 60 mg and, additionally, morphine CR 60 mg was compared with placebo.

The treatment periods were well-balanced with respect to demographics and baseline characteristics within and between all 3 parts of the trial (Part A, Part B, and Part D). In all trial parts, a very low number of subjects used rescue medication. Adequate imputation strategies were used for the evaluation of the primary endpoint if subjects used rescue medication (e.g., last observation carried forward principle for pain assessments up to 4 h after intake of rescue medication). No such imputation strategies were used to the secondary endpoints. However, since only a small number of subjects used rescue mediation, the evaluation of the secondary efficacy endpoints was not influenced much by other analgesic medication than the investigational medicinal products.

The GRT6005 doses of 80 µg, 100 µg, and 120 µg, and morphine CR 60 mg once daily for 5 days showed clinically meaningful differences to placebo (as defined in Dworkin et al. 2007, Backonja and Glanzman 2003) on the primary endpoint parameter "average daily pain intensity change from period baseline" on Day 5. The difference reached statistical significance for the GRT6005 100 µg treatment period when compared to placebo in the ANCOVA analysis. GRT6005 100 µg

demonstrated analgesic effects similar to morphine CR 60 mg for the primary endpoint. The effect of the GRT6005 doses of 40 µg and 200 µg compared with placebo was less pronounced than the effect seen for the other GRT6005 doses. However, although the GRT6005 200 µg dose did not show a clinically meaningful difference to placebo for the change from period baseline, the change from overall baseline showed a clinically meaningful and statistically significant difference between GRT6005 and placebo. With this exception, all other findings relating to analgesic efficacy are supported by the sensitivity analyses performed such as change from overall baseline, worst observation carried forward and baseline observation carried forward instead of last observation carried forward, and the PPS instead of the FAS.

The GRT6005 doses showing clinically meaningful differences to placebo also started to separate in average daily pain intensity (pain reduction) from placebo on Day 1 with an increasing treatment effect over the 5 days.

Across all trial parts, women showed a numerically larger mean change in mean average daily pain intensity from period baseline than men. Similar results were seen for the change from overall baseline.

In the relevant questions of the NPS the active treatments showed a better reduction of the pain characteristics than the placebo treatment periods, with no major differences in the reduction of pain characteristics between the GRT6005 doses, and no clear indication of a dose-dependent effect of the GRT6005 doses across the parts.

In the BPI, all active treatments showed a better improvement than placebo, but there was no clear indication of a dose-dependent improvement for the GRT6005 doses across parts. The largest change of the GRT6005 doses was observed for the GRT6005 100 µg dose.

For all 3 quantitative sensory tests, no clear indication of a dose-dependent improvement for the GRT6005 doses across parts was seen. The GRT6005 40 µg and the GRT6005 100 µg treatment periods showed the largest mean change from baseline compared with the other GRT6005 treatment periods and morphine CR 60 mg. These results have to be interpreted with caution as only a small number of subjects showed positive results in the sensory tests at baseline as indicated by the low mean and median values.

A higher percentage of subjects and of physicians rated GRT6005 as excellent, very good, and good for the treatment of pain compared with placebo but there was no clear indication of a dose-dependent improvement for the GRT6005 doses across parts.

Overall across the trial parts, no clear pattern of change in the SF-12® was identified for the GRT6005 doses. All GRT6005 doses showed an improvement in the category social functioning compared with placebo, although not in a dose-dependent manner. In Part B and Part D, GRT6005 also showed an improvement in the categories physical functioning.

Across the trial parts, for the LSEQ, a pattern of change for the GRT6005 doses was only seen for the categories ease of getting to sleep and perceived quality of sleep: All GRT6005 doses showed a numerical improvement in these categories, but mainly without major differences to placebo, except for the GRT6005 200 µg dose. For the category ease of awakening from sleep, the GRT6005 doses showed similar results as placebo i.e., GRT6005 had no impact on the awakening of the subjects. For the category integrity of behavior following wakefulness, there was no consistent pattern of change between the active treatments and placebo, although in Part B and Part D, placebo showed numerically a slightly larger improvement than the active treatments.

Overall, the active treatments showed a higher response rate than placebo. With the exception of the GRT6005 200 µg dose, a dose-dependent pattern of pain reduction was seen for the GRT6005 doses for the responder categories 30% and 50% (Full Analysis Set). The GRT6005 40 µg and the GRT6005 100 µg treatment periods showed the lowest percentage of subjects with a pain reduction of ≥30% and the GRT6005 120 µg dose showed the highest percentage of subjects. Regarding the percentage of subjects with a pain reduction of ≥50%, the GRT6005 120 µg dose showed the highest responder rate of the GRT6005 doses and similar values as morphine CR 60 mg, while the GRT6005 40 µg and 200 µg doses showed the smallest responder rates.

The following table presents the reduction from period baseline in average daily pain intensity (Day 5) overall for Part A, Part B, and Part D (analysis of covariance, last observation carried forward; Full Analysis Set).

					p-value	
	N	**LSmean**	**SE**	**95% CI**	**Effect**	**Comparison**
GRT6005 40 µg	26	1.6	0.5258	[0.5; 2.6]	0.0036	
GRT6005 80 µg	23	1.8	0.5807	[0.6; 2.9]	0.0024	
GRT6005 100 µg	37	1.8	0.3495	[1.1; 2.5]	<0.0001	
GRT6005 120 µg	26	1.8	0.5335	[0.8; 2.9]	0.0008	
GRT6005 200 µg	22	0.9	0.5677	[-0.2; 2.0]	0.1164	
Morphine CR 60 mg	36	2.1	0.3390	[1.5; 2.8]	<0.0001	
Placebo	85	1.1	0.2104	[0.7; 1.5]	<0.0001	
GRT6005 40 µg - Placebo		0.5	0.4701	[-0.4; 1.4]		0.2983
GRT6005 80 µg - Placebo		0.7	0.5273	[-0.3; 1.8]		0.1711
GRT6005 100 µg - Placebo		0.7	0.3490	[0.1; 1.4]		0.0344
GRT6005 120 µg - Placebo		0.7	0.4853	[-0.2; 1.7]		0.1246
GRT6005 200 µg - Placebo		-0.2	0.5267	[-1.2; 0.9]		0.7470
Morphine CR 60 mg - Placebo		1.1	0.3413	[0.4; 1.8]		0.0019

The ANCOVA (analysis of covariance) model includes terms for baseline average daily pain intensity, first order carry-over, sequence, period, and treatment.

CI = confidence interval, LOCF = Last observation carried forward, LSmean = treatment effect means obtained using the method of least squares, N = number of subjects, SE = standard error.

Part A

The following conclusions can be made from Part A (n = 26):

- For the primary endpoint, the descriptive statistics indicated a treatment effect for the GRT6005 120 µg dose (Full Analysis Set; LOCF).
- The GRT6005 120 µg dose differentiated numerically from placebo from Day 1 onwards for the efficacy parameters change from baseline in average pain intensity and the NPS. This was not the case for the GRT6005 40 µg dose which only separated from placebo on Day 1 for the quantitative sensory testing assessments.

- On several other efficacy parameters assessed on Day 5 (NPS, BPI, responder rates, and the global impression of the investigational medicinal product), GRT6005 120 µg differentiated numerically from placebo and showed larger effects than GRT6005 40 µg, supporting the observed changes in mean daily pain intensity from baseline.

A period effect (ANCOVA) was identified during Part A that may have been caused by the fact that the low dose of GRT6005 or placebo had to be given before the high dose of GRT6005. Additionally, investigators may have communicated this scheme to the subjects. After re-training of the investigators on the importance of blindness to the treatment, no period effect was identified in Part B and Part D.

The center effect seen in Part A may have several reasons:

- Based on the descriptive statistics using the ANCOVA and the LOCF, subjects in all treatment periods in Center 11 have lower overall and period baselines as well as lower mean changes in mean average pain intensity on Day 5 than subjects in the other 3 centers.
- In Center 3, higher changes from period baseline were observed compared with the other centers.

Part B

The following conclusions can be made from Part B (n = 23):

- The GRT6005 80 µg and 200 µg doses differentiated numerically from placebo from Day 1 onwards in the change from period and overall baseline in average daily pain intensity. For the GRT6005 80 µg dose, this change was clinically meaningful.
- No period effect was seen in Part B.
- The ANCOVA showed a trend towards differentiation from placebo for the GRT6005 80 µg and GRT6005 200 µg treatment periods on Day 5 when compared to period baseline ($p \leq 0.0761$). When comparing to overall baseline, the difference to placebo for both doses was statistically significant.
- On several other efficacy parameters that were expected to correlate with the average daily pain intensity (NPS: pain intensity, BPI: pain severity and pain relief) the GRT6005 200 µg dose showed a clear numerical differentiation from placebo, larger than that observed for GRT6005 80 µg.

Part D

The following conclusions can be made from Part D (n = 40):

- The GRT6005 100 µg and morphine CR 60 mg treatment periods differentiated numerically from placebo in change in average daily pain intensity from baseline from Day 1 onwards. For both treatment periods, this change was clinically meaningful.
- No period effect was seen in Part D.
- The ANCOVA demonstrated that GRT6005 100 µg and morphine CR 60 mg statistically significantly differentiated from placebo when comparing to period baseline, and morphine CR 60 mg also when comparing to overall baseline.
- Other efficacy parameters that were expected to correlate with the average daily pain intensity (NPS: pain intensity, BPI) supported the results of the primary endpoint.

Safety results:

The SAF comprised 89 subjects and 86 subjects were exposed to GRT6005.

No deaths occurred during the trial.

No other serious adverse events were reported in a subject currently taking either GRT6005 or morphine CR 60 mg. However, 1 subject had vitreous hemorrhage of the right eye during the washout phase after receiving placebo and having taken GRT6005 100 µg in the previous period. This subject was hospitalized and discontinued the trial.

No subjects discontinued while taking GRT6005. There were 3 subjects who discontinued the trial due to adverse events while taking morphine CR 60 mg: 1 subject due to raised liver enzymes and 2 subjects due to vomiting.

Overall, the most commonly reported treatment emergent adverse events (TEAEs) for subjects on GRT6005 (>10% of these subjects) were dizziness, nausea, headache, fatigue, constipation, and vomiting.

There was no clear indication of an increase of TEAEs with increasing dose of GRT6005. However, the relative frequency of subjects with TEAEs was highest in the GRT6005 200 µ g treatment period. This includes TEAEs reported for >10% of the subjects receiving GRT6005 200 µg, such as blurred vision, dry mouth, nausea, vomiting, fatigue, dizziness, and headache. For the percentage of subjects with at least 1 TEAE there was an imbalance between the different treatment periods of GRT6005. Most subjects with at least 1 TEAE were observed in the highest GRT6005 dose, but the second largest percentage was recorded for the lowest GRT6005 dose. Thus, there was no dose dependency for the percentage of subjects with at least 1 TEAE in the GRT6005 treatment periods. In Part D, the percentage of subject with TEAEs was higher for morphine CR 60 mg than for GRT6005 100 µg (94.4% versus 73.0%).

Similar results were obtained when analyzing TEAEs by countermeasure (more TEAEs requiring countermeasures under morphine CR 60 mg), relationship to investigational medicinal product (higher percentage of subjects in the morphine CR 60 mg treatment period had TEAEs assessed as at least possibly related to the investigational medicinal product), and intensity (more TEAEs in the morphine CR 60 mg treatment period were assessed as moderate in intensity). Most TEAEs had resolved by the end of the trial. There was no consistent pattern for the GRT6005 doses regarding resolving or not resolved TEAEs that indicated a safety signal.

No severe events of dizziness or fatigue where reported, but for fatigue a trend for an increased intensity with increasing dose of GRT6005 was observed while for dizziness, clearly more events of moderate intensity were reported for the higher doses compared to the lower doses of GRT6005.

Based on the results of this trial, 2 new adverse drug reactions for GRT6005 were identified: dizziness and fatigue.

There were sporadic changes in laboratory parameters while subjects were taking either one of the active medications or placebo. The clinically relevant changes in liver enzymes seen with morphine CR 60 mg were not seen with GRT6005. There was no consistent change that could be attributed specifically to the intake of GRT6005. However, there was a more pronounced decrease in mean thrombocyte concentrations for the higher GRT6005 doses compared with morphine CR 60 mg, placebo and the lower GRT6005 doses. The clinical relevance of this finding is however, doubtful. The TEAEs and abnormal laboratory values relating to bacteriuria were unspecific and form a

common medical concept, which was found in similar frequencies in all treatment periods. All other laboratory parameters showed no clinically relevant differences in mean values between the treatment periods.

There were sporadic changes in ECG parameters while subjects were taking either one of the active medications or placebo. Overall, no evidence for a causal relationship between the administration of GRT6005 and the occurrence of QT prolongations, as might be indicated by the relevant categorical shifts or consistent patterns for those subjects with QT (borderline) prolongations was observed. No clinically relevant outliers or median shifts in any treatment period and no dose-dependent differences between the GRT6005 doses were observed for vital sign parameters.

The majority of the subjects did not show any opioid withdrawal according to the analysis of the Clinical Opiate Withdrawal Scale; <5% of the subjects in the GRT6005 treatment periods showed mild opioid withdrawal symptoms. No moderate, moderate to severe, or severe withdrawal symptoms were reported.

In summary, following once daily oral administration for 5 consecutive days, the 5 doses of GRT6005 (40 µg, 80 µg, 100 µg, 120 µg, and 200 µg) are assessed to be safe and well tolerated.

CONCLUSION:

- The GRT6005 doses of 80 µg, 100 µg, and 120 µg, and morphine CR 60 mg once daily for 5 days showed clinically meaningful differences to placebo on the primary endpoint parameter "mean daily pain intensity change from period baseline" on Day 5. The difference reached statistical significance for the GRT6005 100 µg dose when compared to placebo. The effect of the GRT6005 doses of 40 µg and 200 µg compared with placebo was less pronounced than the effect seen for the other GRT6005 doses.
- The analgesic effects in terms of "mean daily pain intensity change from baseline" for GRT6005 100 µg were similar to those of morphine sulfate CR 60 mg.
- For GRT6005 doses showing clinically meaningful differences to placebo, numerical separation from placebo started in Day 1, and the treatment effect increased over the 5 days of treatment for the efficacy parameters change from baseline in average pain intensity and the NPS.
- Secondary parameters (BPI, NPS, and responder rates) supported the results seen for the primary efficacy parameter. Evidence for efficacy was also seen for GRT6005 40 µg in these secondary parameters.
- Within the limitation of the sparse sampling procedure used in this trial, C_{max} of GRT6005 increased linearly with dose.
- All doses of GRT6005 (40 µg, 80 µg, 100 µg, 120 µg, and 200 µg once daily for 5 days) were safe and well tolerated. The definition of expected adverse drug reactions for GRT6005 was adapted based on the results of this trial to include dizziness and fatigue.

References

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