TITLE OF TRIAL: **Crossover multiple-dose trial assessing the analgesic efficacy and safety of oral GRT9906 PR compared to active comparator and placebo in subjects with painful polyneuropathy of mixed origin**

SPONSOR/COMPANY: Grünenthal GmbH, 52099 Aachen, Germany

COORDINATING INVESTIGATOR: [redacted]
20249 Hamburg, Germany
[redacted]

TRIAL CENTERS: 8 Centers: 2 in Denmark, 6 in Germany

PUBLICATION (REF.): None

TRIAL PERIOD:

First subject enrolled:	08 Nov 2005
Last subject completed:	09 Aug 2006
Database lock:	13 Oct 2006

PHASE OF DEVELOPMENT: Phase II

OBJECTIVES:

- To assess the multiple-dose analgesic efficacy and safety of oral GRT9906 PR at 120 mg to 240 mg daily in comparison with placebo in subjects with painful polyneuropathy.
- To compare the multiple-dose analgesic efficacy and safety of oral GRT9906 PR at 120 mg to 240 mg per day with tramadol PR 200 mg to 400 mg per day in subjects with painful polyneuropathy.
- To evaluate population pharmacokinetic (PK)/ pharmacodynamic (PD) relationship for GRT9906 PR.

METHODOLOGY: Randomized, multicenter, double-blind, placebo- and active comparator-controlled, 3-way crossover, dose-titration, Phase II trial.

NUMBER OF SUBJECTS:

In this 3-way crossover trial 60 subjects were originally planned, 64 were randomized and treated. The full-analysis set comprised 64 subjects, the per-protocol population 47 subjects.

NUMBER OF DROPOUTS:

Treatment	Number of subjects	Reason for withdrawal*		
		Adverse events	Unsatisfactory response	Other reasons
GRT9906 PR	6	4	1	5
Tramadol PR	7	4	0	5
Placebo	3	2	0	1

* More than 1 reason for withdrawal was possible.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Medically stable subjects were included according to the following criteria:

1) Written informed consent given, 2) male or female between 18 and 75 years of age, 3) Painful polyneuropathy of mixed origin (diabetic, idiopathic, alcoholic or drug-induced neuropathy) with symptoms present for more than 6 months, 4) distal and symmetric pain in the extremities and reduced or absent tendon reflexes, 5) no pain increase on activity, 6) altered sensation distally on examination (touch; pin-prick; temperature), 7) abnormal conduction (motor nerve conduction velocity, distal motor latency, motor action potential amplitude, sensory nerve conduction velocity or sensory action potential amplitude) in at least 2 nerves, one of them being a leg nerve, 8) average pain intensity of neuropathic pain over the last 3 days before randomization visit must be at least 4 points, on an 11-point NRS, 9) negative urine test for drugs of abuse at enrolment and at Day 1 visit of each treatment period, 10) compliance with use and completion of assessments by means of electronic diaries (eDiaries).

INVESTIGATIONAL MEDICINAL PRODUCTS:

	Test product GRT9906 PR	**Comparator product tramadol PR**	**Placebo to test and comparator product**
Dose	60 mg	100 mg	
Batch number	EFLP15	CHKS02	AKKRP1
Mode of administration	Oral	Oral	Oral
Duration of treatment	Up to 4 weeks	Up to 4 weeks	Up to 4 weeks

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy endpoint was the average pain intensity (API) determined by an 11-point NRS over the last 3 days prior to the last visit per treatment period. The primary efficacy endpoint was assessed in the “per-protocol” (PP) population (primary analysis) and in the full-analysis set (FAS). Secondary endpoints were the API including changes from overall and period baseline, API for each treatment week, subjects’ global evaluation on Day 28, 30% and 50% reduction in pain based on the API prior to the last visit in each treatment period, the number needed to treat (NNT) for 30% and 50% reduction in pain, quality of sleep using the Sleep Problem Scale (SPS), assessment of anti-depressive effects using the Major Depression Inventory (MDI), assessment of allodynia using the Neuropathic Pain Symptom Inventory (NPSI), ratings of evoked pain, subject’s and Investigator’s Global Assessment of the investigational medicinal product (IMP) on a 5-point Verbal Rating Scale (VRS), Patient’s Global Impression of Change (PGIC) on a 7-point VRS, and an assessment of the individual optimal dosage of the IMP and the amount of rescue medication taken. Secondary endpoints were analyzed for the FAS and PP population.

Safety: The safety population comprised all subjects who ingested at least one dose of trial or rescue medication.

STATISTICAL METHODS:

The primary analysis was performed within the PP population. An ANOVA model was used to determine whether there was a statistically significant treatment effect. It was to be concluded that the treatment with GRT9906PR was efficacious only if a statistically significant main effect of

treatment was observed, together with a statistically significant pair-wise effect that supported a decline in pain under GRT9906 PR compared to placebo. The evaluation of the primary endpoint was performed by means of ANOVA, accounting for the effects of sequence, period, first order carryover, center, treatment, and the 2-way interaction for center-by-treatment. There was no statistically significant carryover effect and no statistically significant center-by-treatment interaction effect. Therefore, the first order carryover effect and the center-by-treatment interaction were removed from the final ANOVA model due to a pre-specified model selection procedure.

In addition to the primary analysis, the primary endpoint was analyzed using the FAS and different imputation strategies for imputing missing values to test the robustness of results from the primary analysis.

In addition to the analysis of the primary endpoint, the secondary endpoints, API change from baseline/period baseline, API over Weeks 1, 2 , 3, and 4 as change from baseline, SPS, MDI, NPSI, subjects/physicians global assessment of the IMP and Patient's Global Impression of Change were analyzed using the final ANOVA model selected for the analysis of the primary efficacy endpoint (for API over Weeks 1, 2, 3 and 4, the model was adapted to include a time effect and interaction terms for sequence by time, period by time and treatment by time).

Fisher's exact test was used to compare frequencies between treatments (overall and pair-wise) for the 30% reduction and 50% reduction of API. The NNT were calculated for GRT9906 PR and tramadol PR using the 30% and 50% reduction of the API.

Further descriptive analyses were given for individual optimal dosage of the IMP, mean daily numbers of rescue medication, and for the categorical variables regarding evoked pain.

Using appropriate variations of the analyses described above, a separate analysis of the first treatment period for the efficacy data was performed to stand alone.

Standard descriptive analyses were performed for all safety parameters (adverse events [AEs], laboratory values, vital signs, ECG parameters, and the Clinical Opiate Withdrawal Scale).

SUMMARY:

Efficacy results:

Efficacy of GRT9906 PR 120 mg to 240 mg was demonstrated in subjects with painful polyneuropathy of mixed origin. Analyses were performed using both the PP population (N = 47) and the FAS (N = 64).

Primary endpoint:

GRT9906 PR was superior to placebo regarding the reduction of the API. In the PP population, the least square mean (LS Mean) API on the 11-point NRS scale, as an average of the 3 days prior to the last visit of the treatment period, was significantly lower in subjects treated with GRT9906 PR (3.98 [0.421]) compared with placebo (5.55 [0.420]). The LS Mean of the difference (-1.57 [0.350]) was statistically significant ($p < 0.0001$). No statistically significant period or sequence effects could be identified. Also, changes to the overall baseline API values were significantly greater for GRT9906 PR (-2.14 [0.360]) compared with placebo (-0.57 [0.359]) ($p < 0.0001$).

Superiority of GRT9906 PR to placebo was also seen using the FAS regardless the imputation strategy used.

The model sensitivity was validated by comparing tramadol PR 200 mg to 400 mg daily with placebo. Pain reduction during tramadol PR treatment (3.75 [0.420]) was significantly better compared with placebo ($p < 0.0001$), and API changes to overall baseline were greater for tramadol PR (-2.37 [0.359]) ($p < 0.0001$) than for placebo in the PP population.

Secondary endpoints (PP population):

Compared to placebo, a significant decrease in the API was observed when displayed by treatment week (LS Mean -1.66 to -2.36 for GRT9906 PR vs. -0.75 to -0.94 for placebo).

More than 50% of subjects treated with either GRT9906 PR (25 of 47, 53.2%) or with tramadol (32 of 47, 68.1%) but only 23.4% (11 of 47) of subjects treated with placebo experienced a 30% reduction in pain based on API as average pain over the 3 days prior to the last visit compared to overall baseline. Compared to overall baseline data, a 50% reduction in API was achieved in 18 of 47 (38.3%) subjects treated with GRT9906 PR, 18 of 47 (38.3%) subjects treated with tramadol PR and 6 of 47 (12.8%) subjects treated with placebo.

Treatment with GRT9906 PR resulted in a NNT of 3.4 and 3.9, respectively to achieve 30% and 50% reduction in pain.

A LS Mean change from baseline of the absolute SPS and NPSI scores of -0.7 [0.69] and -17.1 [3.83], respectively, were statistically significant for GRT9906 PR treatment compared to placebo.

Reductions in Brush-, cold-, or Frey hair-evoked pain were similar in all treatments.

The treatment of subjects with GRT9906 PR resulted in a LS Mean (SE) change of the absolute MDI scores of -1.0 (1.85) from Day 28 to baseline. Scores for tramadol were changed on average by -1.4 (1.85), scores for placebo by -0.2 (1.85). No statistically significant difference between active drugs and placebo could be observed. However, 87.2% of subjects treated with GRT9906 PR, 83.0% with tramadol PR, and 85.1% treated with placebo had no sign of depression at baseline according to the MDI.

A higher proportion of subjects (20 of 47 [42.6%]) and of Investigators (18 subjects of 47 [38.3%]) rated GRT9906 PR as excellent or very good for the treatment of pain when compared to placebo (4 of 47 subjects, 8.5%; 7 of 47 Investigators, 14.9%). For tramadol PR, excellent or very good ratings were obtained from 13 of 47 (27.7%) of subjects and from 17 of 47 (36.2%) of Investigators. Both active treatments were assessed as being almost equal by the Investigators, but the perception by subjects differed by 14.9% in favor of GRT9906 PR compared with tramadol PR.

Approximately half of the subjects treated with GRT9906 PR (22 of 47, 46.8%) or tramadol PR (26 of 47, 55.3%) rated the improvement in pain as “much” and “very much” after 4 weeks of treatment. For placebo, 12 of 47 subjects (25.5%) rated changes in pain as “much” or “very much” improved and 19 of 47 subjects (40.4%) reported “no change”. No subject on GRT9906 PR reported worsening of pain.

The optimal daily dosage of GRT9906 PR was 4 tablets (240 mg) for most subjects (33 of 47, 70.2%). For 8 of 47 subjects (17.0%) it was 2 tablets (120 mg). The optimal daily tramadol PR dosage was 4 tablets (400 mg) for 36 (76.6%) and 2 tablets (200 mg) for 6 (12.8) of 47 subjects.

The mean (SD) daily number of paracetamol tablets (rescue medication) taken by subjects treated with GRT9906 PR was 0.36 (0.615) (range 0 to 2.2) which was considerably lower than for placebo

(0.90 [1.046], range 0 to 3.9). For tramadol PR, similar data to GRT9906 PR were reported (0.39 [0.695], range 0 to 2.6).

Safety results:

GRT9906 PR appeared to be safe and was well tolerated by subjects in the trial. Most AEs reported by subjects were largely consistent with the opioid agonist mode of action of the compound. Other adverse events such as, tremor (12.1% of subjects), nightmare (13.8%), and dysuria (8.6%), based on the small sample size, should be interpreted with care and further experience from clinical trials is needed to judge their importance for the safety profile of GRT9906 PR.

No or only very mild withdrawal symptoms were observed and they were similar between the 2 active treatments. The dose range of 120-240 mg daily is considered safe. No compound-specific risks have been identified that would lead to additional exclusion criteria or more intense monitoring in future trials. The overall safety profile appears favorable of further clinical trials to evaluate the benefit of the triple mode of action of GRT9906 PR.

CONCLUSION:

The analgesic efficacy of GRT9906 PR in subjects with neuropathic pain of mixed origin has clearly been demonstrated. As in this trial most of the subjects had no symptoms of depression according to the MDI, the observed analgesic effect appears to be explained mainly by other effects than an anti-depressive component. The AE profile was in line with the known opioid agonist mode of action and GRT9906 PR appeared to be safe and well tolerated by subjects in the trial. Therefore, in future trials, doses exceeding 240 mg may be administered. Unexpected AEs observed in this trial may be associated with other well described mode of actions of GRT9906 PR. The overall benefit/risk profile justifies further development of GRT9906 PR for the “neuropathic pain” indication.

Date of report: 24 Jul 2007

KF9906/02
ICTR SYNOPSIS SUPPLEMENT

Original ICTR date / DMS version:	24 Jul 2007	DMS-ver. 2.0
ICTR synopsis supplement date / DMS version:	17 Apr 2014	DMS-ver. 1.0

1 SUPPLEMENT CONTENT

This document contains information about the trial that is not already covered in the synopsis of the corresponding clinical trial report.

2 INFORMATION ABOUT PROTOCOL AMENDMENTS

There 2 amendments to the protocol.

Amendment 1 of the protocol dated 16 Aug 2005:

- The exclusion criterion related to QT/QTc values was modified to record at trial enrolment in order be consistent in the protocol.
- For operational reasons, subjects were allowed to have a positive drug screening for the possible pre-treatment medications.
- Procedures for handling case report forms were adjusted in order to reflect planned operational changes in data management.
- Further changes were necessary for ensuring consistency with publications of the Neuropathic Pain Symptom Inventory (NPSI) and the tramadol medication data.

Amendment 2 of the protocol dated 08 May 2006:

- In addition to the analysis of GRT9906 and its metabolite, tramadol and its O-demethyl metabolite were planned to be measured.
- The wording regarding the adverse event sections was adapted as requested by Corporate Drug Safety for all clinical protocols.
- To ensure adequate supply with rescue medication during the washout periods between treatment periods in subjects who could not follow the weekly visits, the amount of rescue medication supplied was increased.

Inconsistencies within the protocol in time windows between visits regarding washout and treatment periods were eliminated.

3 INFORMATION REGARDING CLINICAL HOLD OR EARLY TERMINATION

This clinical trial was not subjected to a clinical hold or early termination.

4 NAMES AND ADDRESSES OF PRINCIPAL INVESTIGATORS

The names of principal investigators for all initiated sites are not here listed because consent for public disclosure was not obtained.

Site ID	Site
DE003	(Name not given, since no consent given), 24105 Kiel Germany
DE004	(Name not given, since no consent given), 20249 Hamburg Germany
DE005	(Name not given, since no consent given), 13125 Berlin Germany
DE006	(Name not given, since no consent given), 23538 Lübeck Germany
DE007	(Name not given, since no consent given), 19055 Schwerin Germany
DE008	(Name not given, since no consent given), 45355 Essen Germany
DK001	(Name not given, since no consent given), 5000 Odense C Denmark
DK002	(Name not given, since no consent given), 8000 Aarhus C Denmark