Trial number	KF6005/03
Title of trial	A randomized 4-week Phase IIa trial evaluating the efficacy, safety, and tolerability of GRT6005, a new centrally acting analgesic, in subjects with moderate to severe pain due to osteoarthritis (OA) of the knee
Trial design	Randomized, multi-center, double-blind, placebo-controlled, parallel-group, multiple-administrations, fixed-dose, 4-week treatment trial
Development phase	Phase IIa
EudraCT number	2010-022556-23
Publication number	116918 (ClinicalTrials.gov)
Indication	Moderate to severe pain due to OA of the knee
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Coordinating investigator	[redacted] Kraków, Poland
Trial sites	Austria (5 sites), Spain (10 sites), Poland (11 sites)
Trial period	First subject enrolled: 25 May 2011 Last subject completed: 15 Dec 2011

Objectives

The primary objective was to explore the analgesic efficacy of fixed doses of 75 µg, 200 µg, and 400 µg GRT6005 once daily compared to placebo in subjects with moderate to severe pain due to OA of the knee. Secondary objectives were to evaluate the safety and tolerability of fixed doses of 75 µg, 200 µg, and 400 µg GRT6005 once daily compared to placebo in subjects with moderate to severe pain due to OA of the knee, to investigate the relationship between exposure to GRT6005 and analgesic efficacy and tolerability, and to describe multiple-dose kinetics of GRT6005 over 4 weeks in subjects with pain due to OA of the knee.

Investigational medicinal products

The following batches of GRT6005 hard gelatin capsules (liquid filled with self-emulsifying drug delivery system [SEDDS]_0708) containing 25 µg, 50 µg, or 200 µg GRT6005 for oral administration and matching placebo capsules were used.

Substance	Strength	Batch no.	Retest date	Collective batch no.	Expiry date
GRT6005	25 µg	KGVY01	01/2012	011210	01/2012
		LGVY03	01/2013	250911	01/2013
	50 µg	KGWH01	02/2012	011210	01/2012
		LGWH02	01/2013	250911	01/2013
	200 µg	KLWA04	04/2012	011210	01/2012
		LGWA05	01/2013	250911	01/2013
Placebo	-	KGWB02	01/2012	011210	01/2012
	-	KGWB03	01/2012	011210	01/2012
	-	LGWB05	01/2013	250911	01/2013

Rescue medication

The following batches of paracetamol were used as rescue medication.

Substance	Strength	Batch no.	Retest date	Collective batch no.	Expiry date
Paracetamol	500 mg	629K101	09/2015	031210	09/2015
		612M091	11/2014	150911	11/2014

Treatments

The total daily doses of GRT6005 during the 4-week Treatment Period were 75 µg (1 x 25 µg capsule + 1 x 50 µg capsule), 200 µg (1 x 200 µg capsule + 1 placebo capsule), or 400 µg (2 x 200 µg capsules) in the first, second, and third treatment arm, respectively. Placebo was taken in the fourth treatment arm (2 capsules). The investigational medicinal products (IMPs) had to be taken starting on the day of the Baseline Visit (Visit 3), and the last dose was to be taken on the morning of the Final Visit (Visit 7) that was planned for Day 28. Since 2 capsules were required to achieve daily doses of 75 µg and 400 µg, all subjects took 2 IMP capsules orally once daily to maintain the blinding. On the visit days, subjects took their IMP at the trial site. The IMPs had to be taken orally with a glass of water after the intake of food and after the subjects had assessed and documented their pain intensity in an electronic diary. No dose adjustment of the IMPs was allowed. In case of intolerable adverse events (AEs) or lack of efficacy, the subjects had to discontinue their trial participation.

Subjects were allowed to take up to 1000 mg of paracetamol per day as rescue medication (tablets containing 500 mg paracetamol for oral administration) for the treatment of pain due to OA of the knee, except for the last 3 days before the Baseline Visit.

Trial population

Male or female subjects aged 40 years to 75 years inclusive were included who had a diagnosis of OA of the knee based on American College of Rheumatology criteria and functional capacity class of I-III and pain present for at least 3 months. Subjects had to be on stable analgesic medications for their condition with a regular intake of analgesics for at least 3 months prior to the Enrollment Visit according to their medical history, and had to be dissatisfied with their current analgesic treatment

in terms of efficacy and/or tolerability. During the last 3 days prior to treatment allocation, subjects had to complete at least 5 of 6 possible pain intensity assessments. After a washout of any previous analgesic treatment, their daily average pain intensity score had to be ≥4 on the 11-point numeric rating scale (NRS) without any intake of rescue medication.

Subjects with a joint surgery within 3 months of enrollment or any scheduled surgery or painful procedure during the course of the trial, with a need for treatment with prohibited medication, with a clinically relevant history of hypersensitivity, allergy, or contraindications to any of the IMPs' excipients as well as to opioids or paracetamol, were excluded. Furthermore subjects with the presence of conditions other than pain due to OA that could contribute to pain or confound the assessment of self-evaluation of pain, for instance rheumatoid arthritis, psoriatic arthritis, gout, lupus, fibromyalgia, or significant skin conditions such as abscesses could not participate.

Methodology

This was a randomized, multi-center, double-blind, placebo-controlled, parallel-group, multiple-administrations, fixed-dose, 4-week treatment, Phase IIa trial. It consisted of an Enrollment Period, a Treatment Period, and a Follow-up Period.

Subjects were asked to record their current pain intensity score and the average pain intensity during the last 12 hours (as rated on an 11-point NRS) in the morning and in the evening every day during the whole trial starting in the evening of the Enrollment Visit and ending in the morning of the Follow-up Visit.

The Enrollment Period lasted a minimum of 7 days and maximum of 13 days and comprised a Washout Phase (3 days to 7 days) and a Baseline Phase (4 days to 6 days). A washout of previous analgesic medication was performed as instructed in the respective Summary of Product Characteristics of the previous analgesic medication, and the baseline pain intensity score was assessed. The intake of rescue medication had to be documented in the electronic diary each evening during the Enrollment Period. The use of rescue medication was not permitted during the last 3 days prior to Baseline Visit.

The double-blind Treatment Period was the time span from the intake of the first dose of IMPs at the Baseline Visit (Visit 3) to the Final Visit (Visit 7) and was scheduled for 28 days of treatment. Blood samples for pharmacokinetic analyses were taken pre-dose and post-dose as planned and a blood sample for pharmacogenetic analyses was collected from subjects who had consented.

The Follow-up Period was the time span from the day after the Final Visit (Visit 7) to the Follow-up Visit (Visit 8). The Follow-up Visit at the site was scheduled within 3 days to 5 days following the last intake of the IMPs. At the Follow-up Visit, *a single blood sample was taken for pharmacokinetic analysis.*

Data collected

Efficacy

Subject-documented pain intensity assessed on an 11-point NRS: (0 = no pain, 10 = pain as bad as you can imagine). Current pain intensity and average pain intensity over the last 12 hours were assessed and recorded in an electronic diary twice daily in the morning and in the evening.

Scores of the Western Ontario McMaster Questionnaire (WOMAC), Short Form-12 Health Survey (SF-12), EuroQol-5 Dimension (EQ-5D) quality of life, Leeds Sleep Evaluation Questionnaire

(LSEQ), Patient's Global Impression of Change (PGIC), and Clinician's Global Impression of Change (CGIC).

Rescue medication intake.

Pharmacokinetics

Plasma concentrations of GRT6005.

Population pharmacokinetics/pharmacodynamics

Data on the correlation between drug exposure and therapeutic effect, concerned tolerability, and safety aspects of GRT6005.

Pharmacogenetics

DNA polymorphisms in genes associated with absorption, distribution, metabolism, and excretion of drugs.

Safety

Physical examination, clinical laboratory (biochemistry and hematology) and urinalysis, 12-lead electrocardiogram (ECG), vital signs (pulse rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation), pregnancy tests, drug abuse testing, Clinical Opiate Withdrawal Scale (COWS), and AEs.

Statistical methods

Descriptive statistics

All data collected in this trial were presented by summary statistics given by descriptive measures of location and variability for continuous variables (N, mean, standard deviation, minimum, first quartile, median, third quartile, maximum), and absolute and relative frequencies for categorical variables, as appropriate. The mixed-model repeated measures analysis (MMRM, the primary analysis method) does not require an explicit imputation of missing values. The MMRM, being a likelihood-based method rather uses all information from the observed values to provide statistical inference about the effects of interest (i.e., the treatment effect).

Efficacy

The primary efficacy analysis was performed for the Full Analysis Set, i.e., a subset of the Safety Set that includes all subjects who had at least 1 pain intensity assessment after IMP intake. The primary efficacy endpoint was summarized by descriptive statistics. The primary evaluation was done by means of a MMRM assuming a normal distribution. The longitudinal mixed effect model included fixed effects of baseline, treatment, day, and treatment-by-day interactions. A first order autoregressive AR(1) structure was envisaged for the covariance matrix. 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 includes all subjects taking any amount of IMP. For all comparisons of the safety laboratory parameters, vital signs, and ECG, the last values available before the first intake of IMP served as baseline. Adverse events were coded using Version 14.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

Summary of results

Subject disposition

This trial enrolled 207 subjects with chronic moderate to severe pain due to OA of the knee. About half of the subjects were enrolled in trial sites in Poland (n = 106), the remaining subjects in Spain (n = 58) and Austria (n = 43). A total of 79 subjects were not allocated to treatment. Overall, the subjects allocated to treatment (n = 128) were equally distributed among the treatment arms with 32 subjects per arm. One subject in the treatment arm taking 400 µg GRT6005 was excluded from the Safety Set. This subject was allocated by mistake (although the subject took rescue medication during the last 3 days before Visit 3) and did not receive any IMP. The subject's trial participation was discontinued.

Because all subjects of the Safety Set had at least 1 pain intensity assessment after IMP intake, no subject was excluded from the Full Analysis Set. In total, 68.8% of all subjects were included into the Per Protocol Set.

A total of 96 subjects completed the trial. Premature discontinuation in the double-blind Treatment Period was highest in the treatment arm taking 400 µg GRT6005. Overall, the main reason for early discontinuation was treatment emergent adverse event (TEAE), followed by lack of efficacy.

Parameter	Placebo N	Placebo %	GRT6005 75 µg N	GRT6005 75 µg %	GRT6005 200 µg N	GRT6005 200 µg %	GRT6005 400 µg N	GRT6005 400 µg %	GRT6005 Overall N	GRT6005 Overall %	Overall N	Overall %
Subjects enrolled											207	
Subjects allocated to treatment	32	(100)	32	(100)	32	(100)	32	(100)	96	(100)	128	(100)
Subjects evaluated												
Safety Set	32	(100)	32	(100)	32	(100)	31	(96.9)	95	(99.0)	---	
Full Analysis Set	32	(100)	32	(100)	32	(100)	31	(96.9)	95	(99.0)	---	
Per Protocol Set	24	(75.0)	26	(81.3)	25	(78.1)	15	(46.9)	66	(68.8)	---	
Subjects completing the trial	27	(84.4)	25	(78.1)	29	(90.6)	15	(46.9)	69	(71.9)	96	(75.0)
Subjects prematurely discontinued	5	(15.6)	7	(21.9)	3	(9.4)	17	(53.1)	27	(28.1)	32	(25.0)
Reason for discontinuation												
Adverse event	0		3	(9.4)	2	(6.3)	13	(40.6)	18	(18.8)	18	(14.1)
Lack of efficacy	3	(9.4)	3	(9.4)	0		0		3	(3.1)	6	(4.7)
Protocol deviation	0		1	(3.1)	0		2	(6.3)	3	(3.1)	3	(2.3)
Lost to follow up	1	(3.1)	0		0		0		0		1	(0.8)
Withdrawal by subject [a]	0		0		0		2	(6.3)	2	(2.1)	2	(1.6)
Other reasons	1	(3.1)	0		1	(3.1)	0		1	(1.0)	2	(1.6)

a) Withdrawal of informed consent

Demographics and baseline characteristics

A total of 127 subjects (36 men and 91 women) aged 40 to 75 years were treated in the trial (Full Analysis Set).

The treatment arms were largely similar concerning the demographic data: mean age ranged from 60.3 years to 63.1 years, mean height ranged from 1.625 m to 1.663 m, mean weight ranged from 83.4 kg to 90.3 kg, and mean body mass index ranged from 31.42 kg/m^2 to 33.24 kg/m^2. There were more women than men in all treatment arms (56.3% [200 µg GRT6005] to 84.4% [100 µg]). About one third of subjects was >65 years in each treatment arm except for the arm taking 400 µg GRT6005 where the elderly accounted for 54.8%.

The average 12-hour average pain intensity at baseline for all subjects in the Full Analysis Set was 6.8 (range 4.0 to 10.0), the mean duration of pain in the joints(s) was 92.8 months (range 6 months to 398 months); the mean time since diagnosis of OA was 75.8 months (range 0 months to 335 months). In 101 of 127 subjects (79.5%) both knees were affected. With respect to the most painful knee, the frequencies were similar with 53.5% (68 subjects) for the right knee in and 46.5% (59 subjects) for the left knee.

The majority of subjects (117 subjects, 92.1%) took non-opioid analgesics during the last 3 months prior to enrollment, but only 28.3% (36 subjects) received opioids (including tramadol) as stand-alone or combined therapy with non-opioids. All subjects were dissatisfied with their current analgesic treatment, 97.6% (124 subjects) due to inadequate analgesia, and 2.4% (3 subjects) due to poor tolerability.

Efficacy

Statistically significant and clinically relevant improvement in average pain intensity compared to placebo was demonstrated for subjects in the Full Analysis Set who took 400 µg of GRT6005 per day (-1.1988 points on NRS, p = 0.0145) as shown by the primary evaluation by means of an MMRM analysis using the pain average 12-hour pain scores of the last week of treatment. Pain reduction in subjects who took 200 µg of GRT6005 per day was also numerically larger than in subjects who took placebo (-0.5383), but without reaching statistical significance. The analysis of the primary endpoint revealed a dose-response trend for the 3 active treatment arms, with 75 µg of GRT6005 performing numerically worse than placebo, 200 µg of GRT6005 performing numerically better than placebo, and 400 µg of GRT6005 performing significantly better than placebo. A dose-response trend was also seen in the Per Protocol Set.

Results of the MMRM analysis for the entire 4 weeks of treatment indicate that numerically there was a better pain reduction in the treatment arms taking 200 µg or 400 µg GRT6005 per day when compared to placebo. Reduction of the 12-hour average pain was statistically significantly different to placebo after the entire 4 weeks of treatment for a treatment with 400 µg GRT6005 (p = 0.0013).

The overall picture obtained from the MMRM analyses for the 12-hour average pain intensity for the first, second, and third week of treatment matches the results obtained for the fourth week and the overall Treatment Period. Changes from baseline for the average 12-hour average pain intensity, the morning, and the evening pain in the last 24 hours before the Follow-up Visit generally indicate an increase in subjects' pain again during the Follow-up Period.

The results of the MMRM analyses for the current pain intensity in the morning and in the evening in the first, second, third, and the last week of treatment showed a dose-response trend for the 3 active treatment arms as observed for the primary endpoint.

In the Full Analysis Set, the responder rates after 4 weeks of treatment were lowest in subjects who took placebo and highest in subjects who took 200 µg GRT6005 per day. The responder rates were lower in the 400 µg arm due to the higher discontinuation rate of subjects in this arm (subjects who

prematurely discontinued their trial participation were regarded as non-responders). At Visit 7, 25.0% of subjects taking placebo, 34.4% of subjects taking 75 µg, 56.3% of subjects taking 200 µg, and 38.7% of subjects taking 400 µg GRT6005 per day reported a pain reduction of at least 30%. A pain reduction of at least 50% was reported in 21.9% of subjects taking placebo, 15.6% of subjects taking 75 µg, 40.6% of subjects taking 200 µg, and 22.6% of subjects taking 400 µg GRT6005 per day.

The evaluation of the secondary and other endpoints (e.g., responder rates, WOMAC, PGIC, CGIC, and use of rescue medication) showed a clear differentiation of the 200 µg GRT6005 treatment arm from placebo indicating analgesic efficacy of a daily dose of 200 µg GRT6005 as well. In general, in subjects who completed the trial as planned, the active treatment arms of GRT6005 showed a dose-response trend, with 400 µg GRT6005 per day performing numerically better than 200 µg, and 200 µg performing numerically better than 75 µg.

- WOMAC index score, pain subscale, and physical functioning sub-score reductions indicated an improvement which was numerically more prominent in treatment arms taking 200 µg or 400 µg GRT6005 per day than in the placebo arm. Changes to baseline were dose dependent at Visit 5 and – in trial completers – also at Visit 7 as follows:
    - The index score (baseline mean for all subjects 53.9 to 60.3 on a 0-96 points scale) was reduced at Visit 7 in trial completers who took 200 µg GRT6005 and 400 µg GRT6005 per day by -22.2 and by -29.9 compared to -12.5 for the placebo arm.
    - The pain subscale scores (baseline mean for all subjects 11.4 to 12.5 on a 0-20 points scale) were reduced at Visit 7 in trial completers who took 200 µg GRT6005 and 400 µg GRT6005 per day by -5.3 and -6.4 compared to -2.2 for placebo.
    - The physical functioning subscale scores (baseline mean for all subjects 38.1 and 42.7 on a 0-68 points scale) were reduced at Visit 7 in trial completers who took 200 µg GRT6005 and 400 µg GRT6005 per day by -15.7 and by -22.1 compared to -9.0 for placebo.
    - Changes from baseline for the stiffness subscale in the GRT6005 treatment arms did not differentiate from placebo.
- The PGIC indicated a dose-dependent improvement of the subject's condition ("very much and much improved") at Visit 5 and – in trial completers – also at Visit 7. When the evaluation at Visit 7 was restricted to subjects completing the trial according to protocol, 25.9% of subjects who took placebo, 36.0% of subjects who took 75 µg GRT6005 per day, 58.6% of subjects who took 200 µg GRT6005 per day, and 60.0% of subjects who took 400 µg GRT6005 per day reported that their impression of change was "very much improved and much improved" compared to baseline.
- The assessment of the investigators (CGIC) was similar to the PGIC results: after 4 weeks of treatment, the clinicians of subjects who completed the trial stated that 25.9% of subjects taking placebo, 44.0% of those taking 75 µg, 62.1% of those taking 200 µg, and 73.3% of those taking 400 µg GRT6005 per day had "very much improved and much improved".
- For the SF-12 sub-scores role physical, bodily pain, general health, vitality, role emotional, and social functioning, for all treatment arms of GRT6005 a similar improvement at Visit 5 and Visit 7 was seen when compared to baseline; the improvement was better than a treatment with placebo. For the sub-scores physical functioning and mental health, improvements under treatment with GRT6005 were less clear.

- The mean changes in the weighted EQ–5 D health score index (range 0-1) from baseline to Visit 7 indicated improvement and were higher for a treatment with GRT6005 than for a treatment with placebo (0.003 for placebo, 0.026 for 75 µg GRT6005, 0.189 for 200 µg GRT6005, and 0.128 for 400 µg GRT6005) and were highest in subjects completing the trial (0.032 for placebo, 0.085 for 75 µg GRT6005, 0.166 for 200 µg GRT6005, and 0.243 for 400 µg GRT6005 per day). Mean changes from baseline in the general health state (scale 0-100) were similar for placebo and for treatment with GRT6005 (14.5 for a treatment with placebo, 3.9 for 75 µg, 14.8 for 200 µg, and 11.2 for 400 µg GRT6005 per day).
- In the LSEQ, numerically higher improvement for the ease of getting to sleep, the perceived quality of sleep, and the ease of awakening from sleep was seen at Visit 7 for all subjects treated with 200 µg or 400 µg GRT6005 per day when compared to placebo. Changes were more pronounced at Visit 7 when only data of trial completers were analyzed. The results obtained for the low-dose treatment arm of 75 g of GRT6005 per day were similar to those for placebo treatment.
- The amount of paracetamol used during the entire Treatment Period and for the last week of treatment decreased with increasing daily doses of GRT6005. Subjects allocated to placebo treatment needed a higher amount of paracetamol (mean total amount of 10065.3 mg over 28 days of treatment and of 3711.6 mg during the fourth week of treatment) when compared to those who took GRT6005. Subjects taking 200 µg GRT6005 per day needed a mean total of 6197.4 mg paracetamol over 28 days of treatment and 2198.3 mg during the last week of treatment, those taking 400 µg GRT6005 per day additionally took 1834.9 mg paracetamol over 28 days of treatment and 1298.0 mg during the last week of treatment.

Pharmacokinetics

A descriptive analysis of GRT6005 plasma concentrations showed that the GRT6005 exposure was in line with previous predictions. The exposure increased with dose, steady state seemed to be reached after 2 weeks, and an approximately 2-fold accumulation was observed. Apparent deviations from dose proportionality and predicted accumulation after administration of 400 µg GRT6005 per day were caused by the absence of sufficient data from trial completers with higher exposure at the end of the trial owing to the high number of premature discontinuations in this treatment arm.

The results of the population pharmacokinetics/pharmacodynamics analysis will be presented in a separate report.

Exposure

Overall, the mean IMP intake was 16.6 to 26.7 doses within 4 weeks of the double-blind Treatment Period; the mean compliance (defined as actual exposure to IMP to planned intake of IMP) was 76.9% to 98.7%. Mean intake and compliance were reduced in subjects taking 400 µg GRT6005 due to the high premature discontinuation rate of subjects in this arm. For subjects discontinuing prematurely, the day of the last intake of IMP mostly was before the day of the investigator’s decision to exclude the subject; the latter, however, was used for the compliance calculations.

Safety and tolerability

The use of GRT6005 over a period of 4 weeks was safe within the tested dose range of 75 µg, 200 µg, and 400 µg of GRT6005 per day for the treatment of pain due to OA of the knee.

The tolerability of fixed daily doses of GRT6005 was good for the tested doses up to 200 µg.

Overall, 57 of 95 subjects (60.0%) taking GRT6005 reported 117 TEAEs. The frequencies of TEAE were similar in subjects taking placebo (40.6%), those taking 75 µg GRT6005 (46.9%), or 200 µg GRT6005 (50.0%), and were approximately twice as high in subjects taking 400 µg GRT6005 per day (83.9%) when compared to placebo. No serious TEAE occurred. The most frequent TEAEs (occurring in at least 5% of subjects in any treatment arm, i.e., GRT6005 or placebo) were vomiting, nausea, dizziness, somnolence, headache, constipation, dry mouth, fatigue, decreased appetite, vertigo central nervous system origin, nasopharyngitis, abdominal pain, diarrhea, and atrioventricular (AV) block first degree.

No subject of the placebo arm, 9.4% of subjects taking 75 µg GRT6005, 6.3% of subjects taking 200 µg GRT6005, and 41.9% of subjects in the Safety Set taking 400 µg GRT6005 discontinued due to TEAEs. In addition, more subjects taking 200 µg or 400 µg GRT6005 experienced TEAEs of moderate or severe intensity compared to subjects taking 75 µg GRT6005.

The TEAEs vomiting, nausea, and dizziness were the main reasons for premature trial discontinuations. These TEAEs mainly started within the first 24 hours after first IMP intake and lead predominately to premature trial discontinuation within a period of 7 days.

Based on the percentage of subjects who prematurely discontinued the trial due to TEAEs and based on the percentages of TEAEs of moderate and severe intensity, there was a reduced tolerability in particular for the fixed daily dose of 400 µg.

There were no clinically relevant changes in the mean values or shifts of any safety laboratory parameter. Individual outliers of safety laboratory parameters did not reveal evidence indicative for GRT6005 related effects.

No clinically relevant changes of vital signs and ECG, or systemic changes of safety laboratory parameters were observed.

There were no deaths and no pregnancies in this trial.

The abrupt cessation of the 4-week treatment with GRT6005 led to only mild opioid withdrawal symptoms in a low number of subjects (in 2 of 31 subjects taking 200 µg and 1 of 20 subjects taking 400 µg GRT6005 per day as assessed by the use of the COWS score).

Conclusion

GRT6005 was found to be safe in the dose range tested. The tolerability of fixed oral doses up to and including 200 µg of GRT6005 per day was very good. A reduced tolerability at the beginning of treatment with GRT6005 in subjects treated with a fixed oral daily dose of 400 µg GRT6005 indicate the need for a dose titration in order to reach daily oral doses of 400 µg GRT6005 or above for prolonged/chronic use/multiple dose administration.

A statistically significant and clinically relevant pain reduction in the primary endpoint was obtained for the highest dose of 400 µg GRT6005 but not for the lower doses. A dose-response trend for the 3 active groups was shown after 4 weeks of treatment. In addition, the evaluation of all secondary endpoints also indicated an analgesic efficacy of the dose of 200 µg GRT6005.

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SDR-CTR-SUP-01

KF6005/03
ICTR SYNOPSIS SUPPLEMENT

Original ICTR date / DMS version:	04 Sep 2012	DMS-ver. 2.0
ICTR synopsis supplement date / DMS version:	20 Jul 2015	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 was 1 amendment to the protocol.

Amendment 01 signed 13 May 2011 was prepared to document the change of the international coordinating investigator. Furthermore, the clinical opiate withdrawal scale (COWS) questionnaire version dated 27 Oct 2006 attached to the original protocol version was replaced by the version dated 24 Mar 2011. Because of a change in the standard operating procedures at the sponsor, the signature pages were adapted and the sponsor's medically qualified person was now defined in Section 6.2.1 of the protocol.

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.

Investigator	Site
(Name not given, since no consent given)	Toruń Poland
(Name not given, since no consent given)	Elbląg Poland
(Name not given, since no consent given)	Białystok Poland
(Name not given, since no consent given)	Warszawa Poland
(Name not given, since no consent given)	Wrocław Poland
(Name not given, since no consent given)	Kraków Poland
(Name not given, since no consent given)	Lublin Poland
(Name not given, since no consent given)	Gdynia Poland
(Name not given, since no consent given)	Szczecin Poland
(Name not given, since no consent given)	Warszawa Poland
(Name not given, since no consent given)	Włoszczowa Poland
(Name not given, since no consent given)	Barcelona Spain
(Name not given, since no consent given)	A Coruña Spain

Investigator	Site
(Name not given, since no consent given)	Santiago de Compostela Spain
(Name not given, since no consent given)	Barcelona Spain
(Name not given, since no consent given)	Sevilla Spain
(Name not given, since no consent given)	Mérida Badajoz Spain
(Name not given, since no consent given)	Oviedo (Asturias) Spain
(Name not given, since no consent given)	Petrer (Alicante) Spain
(Name not given, since no consent given)	Málaga Spain
(Name not given, since no consent given)	Torrelavega (Cantabria) Spain
(Name not given, since no consent given)	Vienna Austria
(Name not given, since no consent given)	Vienna Austria
(Name not given, since no consent given)	Vienna Austria
(Name not given, since no consent given)	Linz Austria
(Name not given, since no consent given)	Senftenberg Austria