TITLE OF TRIAL:

A randomized, double-blind, parallel-group, multiple-dose study to assess the analgesic efficacy and safety of 3 different doses of GRT0151Y compared to placebo and an active comparator in adults following tonsillectomy.

SPONSOR/COMPANY: Grünenthal GmbH, Zieglerstrasse 6, 52078 Aachen, Germany

COORDINATING INVESTIGATOR: [redacted]
1777 Kuopio, Finland

TRIAL CENTER(S):

In total, 23 centers participated in this trial: 1 center in the Czech Republic, 1 center in Finland, 7 centers in Hungary, 3 centers in Poland, 4 centers in Romania, 5 centers in the Russian Federation, and 2 centers in the United Kingdom.

PUBLICATION (REFERENCE): Not applicable.

TRIAL PERIOD (YEARS):

First subject enrolled:	12 Aug 2005
Last subject completed:	17 Feb 2006
Database lock:	20 Apr 2006

PHASE OF DEVELOPMENT: Phase II

OBJECTIVES:

The main objective of this trial was to compare the oral multiple-dose analgesic safety and efficacy of 3 different doses of GRT0151Y to placebo in subjects with moderate to severe postoperative pain after tonsillectomy on Day 4 and Day 5. Further objectives of this trial were:

- To assess the dose-response of 3 different dose levels of GRT0151Y in multiple-dose application in subjects with moderate to severe postoperative pain after tonsillectomy from Day 1 to Day 5.
- To evaluate the oral multiple-dose analgesic efficacy of 3 different dose levels of GRT0151Y in comparison with tramadol IR in subjects with moderate to severe postoperative pain after tonsillectomy from Day 1 to Day 5.
- To evaluate the oral tolerability of multiple doses of 3 different dose levels of GRT0151Y in comparison with placebo in subjects with moderate to severe postoperative pain after tonsillectomy from Day 1 to Day 5.
- To evaluate the oral tolerability of multiple-dose of 3 different dose levels of GRT0151Y in comparison with tramadol IR in subjects with moderate to severe postoperative pain after tonsillectomy from Day 1 to Day 5.
- To assess the time to onset of the analgesic effect of 3 oral dose levels of GRT0151Y on Day 1.
- To describe the pharmacokinetics of GRT0151Y in the trial population from Day 1 to Day 5.

METHODOLOGY:

Randomized, multi-center, double-blind, placebo and active controlled, parallel group, multiple-dose, Phase II trial. Subjects with moderate to severe postoperative pain at rest on a 4-point VRS and a pain intensity at rest of a minimum of 4 on an 11-point NRS within 4 hours after the end of anesthesia were randomly allocated to one of the treatment groups: placebo, tramadol IR, GRT0151Y low dose, GRT0151Y medium dose or GRT0151Y high dose. On Day 1, subjects received a total daily dose of 150 mg GRT0151Y, 200 mg GRT0151Y, 250 mg GRT0151Y, 200 mg tramadol IR or placebo dispensed in two equal doses separated by 4 hours. On Days 2 to 5, subjects received a total daily dose of 150 mg GRT0151Y, 250 mg GRT0151Y, 300 mg GRT0151Y, 300 mg tramadol IR or placebo at four fixed dosing time points (6 a.m./2 p.m./6 p.m./10 p.m.). Therefore, tramadol IR 300 mg and GRT0151Y 300 mg were administered as a 3 times daily regimen (TID) and GRT0151Y 150 mg and 250 mg as a 2 times daily regimen (BID). If required, rescue medication (acetaminophen, diclofenac) was administered, however, subjects were encouraged not to take any rescue medication within 60 and 90 minutes after dosing on Day 1 and from Day 2 to Day 5, respectively. On Day 1, subjects had to assess the times to first perceptible, meaningful pain relief and the time to 50% pain reduction. Subjects were not

to be discharged for at least 12 hours after the last intake of investigational medicinal product and until they were considered medically stable by the Investigator. The subjects had to return for a follow-up visit 10 to 14 days after the last medication intake. During the entire treatment period, subjects had to assess pain intensity at rest and while swallowing, as well as the number of awakenings during the night due to pain.

NUMBER OF SUBJECTS:

Subjects enrolled:	603
Subjects randomized and treated:	493 (full analysis set: 493; per protocol set: 430; completer set: 467)
Subjects completed:	474
Subjects withdrawn:	19

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male and non-pregnant female subjects were included, aged 18 to 65 years (inclusive), with moderate to severe postoperative pain at rest on a 4-point VRS and a pain intensity at rest of a minimum of 4 on an 11-point NRS within 4 hours after the end of the anesthesia following bilateral tonsillectomy due to recurrent acute tonsillitis or chronic tonsillitis performed according to the anesthesiological and surgical procedures defined in the protocol.

INVESTIGATIONAL MEDICINAL PRODUCT(S):

Test product	**GRT0151Y**
Dose	84.8 mg HCl salt capsules (corresponds with 75 mg GRT0151Y free base) and 56.5 mg HCl salt capsules (corresponds with 50 mg GRT0151Y free base)
Mode of administration	Multiple oral doses
Batch number	GRT0151Y 50 mg – EDMD04 GRT0151Y 75 mg – EDLE06
Duration of treatment	5 days

Comparator product	**Tramadol IR**
Dose	50 mg tramadol HCl capsules
Mode of administration	Multiple oral doses
Batch number	604H
Duration of treatment	5 days

Placebo	**Microcrystalline cellulose, low - substituted hydroxypropylcellulose, colloidal anhydrous silica cellulose, magnesium stearate**
Mode of administration	Multiple oral doses
Batch number	EDRIP1
Duration of treatment	5 days

CRITERIA FOR EVALUATION:

Pharmacokinetics:

Blood samples were drawn to investigate population kinetics for GRT0151Y, its O-demethyl metabolite (GRT0643Y) and for the active comparator, tramadol IR, in the target population. The exact evaluation of the pharmacokinetic procedure was described separately in a separate evaluation protocol.

Efficacy:

The primary endpoint was the time averaged pain intensity (TAPI-48) while swallowing on trial Days 4 and 5. Secondary efficacy endpoints were pain intensity (PI) including changes from baseline while swallowing and at rest, time averaged daily pain intensity (TAPI-24) while swallowing and at rest, pain relief (PR) while swallowing and at rest rated on a 4-point VRS, total pain relief assessed daily (TAPR-24) and at Days 4 and 5 (TAPR-48) while swallowing and at rest, time averaged pain intensity difference, subject's global evaluation of the investigational medicinal product using a 5-point rating scale rated on Day 6, time to first perceptible pain relief on Day 1, time to meaningful pain relief on Day 1, time to 50% pain reduction on Day 1, time to first rescue medication on Day 1, amount and type of rescue medication, frequency of intake of rescue medication, time to withdrawal due to adverse events, time to withdrawal due to lack of efficacy, daily assessment of the number of awakenings due to postoperative pain, and responder rate.

Furthermore the following data were calculated using the pain intensity and pain relief values determined during the trial: time averaged pain intensity (TAPI-48) at rest for the evaluation Days 4 and 5; time averaged daily pain intensity (TAPI-24) while swallowing and at rest for each evaluation day; time averaged daily pain relief (TAPR-24) while swallowing and at rest rated daily and TAPR-48 for the evaluation Days 4 and 5; and time averaged pain intensity difference daily (TAPID-24) and for the evaluation Days 4 and 5 (TAPID-48).

Additionally, the secondary efficacy analysis of the TAPI-48 at rest (based on the NRS) was repeated for Days 3 and 4.

Safety:

Safety variables were adverse events, safety laboratory parameters, vital signs, ECG, SpO_2, and sedation scores.

STATISTICAL METHODS:

The primary analysis was performed within the full analysis set and within the per protocol set. The null-hypothesis of no difference between placebo and any of the GRT0151Y dose groups was tested against the alternative that at least one GRT0151Y group was different from placebo. The evaluation of the primary endpoint was done by means of many-to-one comparisons according to Dunnett. The number of active groups to be compared with placebo was 3 (the 3 different doses of GRT0151Y). Under these assumptions for α=5% (two-sided) and 90% power (β=0.1), a sample size of N=90 for each treatment group was planned to be necessary to show a difference of 1.75 on the TAPI-48 (based on NRS) between at least one treatment group of GRT0151Y and placebo. Assuming 5 treatment groups (3 dose levels of GRT0151Y, one active comparator and placebo group), a total of N=450 subjects had to be randomized for this trial. Evaluation of efficacy was performed for 3 populations: full analysis set, completer set and the per protocol set. Additional data sets and/or populations (e.g. completer) were analyzed to test the robustness of the results and of imputation methods. Evaluation of the primary endpoint was performed by means of ANOVA accounting for the effects of treatment, center and baseline pain intensity.

Additional analyses were performed on the effect of type of surgery and type of anesthesia on the primary and selected secondary endpoints. Furthermore, subgroup analyses by type of anesthesia were performed.

SUMMARY:

Pharmacokinetics results:

Plasma concentrations for the enantiomers of GRT0151Y base and its metabolite GRT0643Y base are provided in a separate bioanalytical report (PK820A), as are the tramadol plasma concentrations (PK820B).

The population pharmacokinetic evaluation of these data was also planned. However, after the decision was made to stop the development of this substance for the treatment of acute pain, this report was not produced.

Efficacy results:

For the primary endpoint (TAPI-48 while swallowing on Day 4 and Day 5), no statistically significant difference between any of the GRT0151Y dose groups (150 mg, 250 mg, and 300 mg) and placebo was demonstrated. All active treatment groups did, however, demonstrate a numerically lower mean TAPI-48 while swallowing compared with the placebo group. The largest difference to placebo was observed in the tramadol IR 300 mg group. There was no evidence of a dose response among the GRT0151Y treatment groups. In general, the magnitude of the observed effect of each GRT0151Y treatment on the pain intensity endpoints evaluated while swallowing compared with placebo was not considered to be clinically relevant and much lower than the expected effect size of a difference of 1.75 on the 11-point NRS on which the sample size determination of this trial was based.

For the secondary endpoints TAPI-48 at rest on Days 4 and 5, TAPI-48 at rest on Days 3 and 4, TAPI-24 at rest (each evaluation day), TAPID-48 at rest on Days 4 and 5, TAPID-24 at rest, TAPR-48 (while swallowing and at rest; for Days 4 and 5), and TAPR-24 (while swallowing and at rest), a statistically significant difference to placebo was demonstrated for the tramadol IR group. These results for the tramadol IR group confirm that the clinical model (tonsillectomy) applied in this trial allows differentiation of active treatment effects from placebo over a treatment period of 5 days. For the GRT0151Y 150 mg group, statistically significant differences to placebo were shown for the secondary endpoints TAPR-24 while swallowing (Days 3 and 4) and at rest (Days 1 to 3). For the GRT0151Y 250 mg group, a statistically significant difference to placebo was demonstrated for the TAPI-48 at rest on Days 3 and 4, the TAPI-24 and the TAPID-24 at rest on Days 2, 3, 4, and 5, the TAPR-24 while swallowing on Days 2 and 3, and for the TAPR-24 at rest on Days 1 to 4. For the GRT0151Y 300 mg group, a statistically significant difference to placebo was shown for the TAPI-24 and the TAPID-24 at rest on Days 1 and 2, the TAPR-48 at rest on Days 4 and 5, the TAPR-24 while swallowing on Days 2, 3, and 4, and the TAPR-24 at rest on Days 1 to 4. Regarding the onset of analgesia, the highest number of subjects with onset of analgesia was observed in the tramadol IR group, and there were no marked differences between the active treatment groups. None of the GRT0151Y treatment groups showed consistent results in any of the endpoint parameters and there was no evidence for a dose-response relationship.

The responder rates (subjects experiencing 30% and 50% reduction in TAPI-48 at rest) were similar in all active treatment groups and the active treatment groups showed a numerically higher reduction compared with placebo.

The number of subjects who assessed their IMP as *excellent*, *very good* and *good* was high in all active treatment groups with no remarkable differences between the active treatment groups; more subjects receiving active treatment assessed their treatment as *excellent, very good* and *good* than subjects receiving placebo.

In the additional analyses of the effect of the type of anesthesia (general or local) on the primary and secondary endpoint TAPI-48 at rest on Days 4 and 5, the local anesthesia subgroup showed larger differences relative to placebo for each active treatment group compared with the differences observed for the general anesthesia subgroup; these differences were statistically significant for the GRT0151Y 250 mg group and tramadol IR on TAPI-48 at rest under local anesthesia.

In both the GRT0151Y groups and the tramadol IR group considerably fewer subjects required rescue medication compared with placebo. The difference between tramadol IR and placebo in the percentage of subjects with rescue medication was approximately 25%, and ranged from 9.7% in the GRT0151Y 250 mg group to 20% in the GRT0151Y 300 mg group.

Safety results:

No death and no Suspected Serious Unexpected Adverse Reaction occurred during the course of this trial. A total of 17 subjects (3.4%) experienced serious adverse events (SAEs). Regarding the incidence of SAEs, no relevant differences were seen between the treatment groups. Most SAEs were mild or moderate in intensity. One SAE of mild intensity in the GRT0151Y 300 mg group was assessed as possible related to the IMP: vomiting in Subject [redacted].

A total of 303 subjects (61.5%) experienced at least 1 treatment-emergent adverse event (TEAE) during the course of this trial. In general, more TEAEs occurred in the active treatment groups than in the placebo group but there was no indication for a relationship between the incidence of TEAEs and the dose of GRT0151Y.

Overall, the most frequent TEAEs occurred in the SOC *gastrointestinal disorder* (208 subjects, 42.2%), *nervous system disorders* (40 subjects, 8.1%), *injury, poisoning and procedural complications* (39 subjects, 7.9%), and *skin and subcutaneous tissue disorders* (33 subjects, 6.7%).

Nausea, vomiting, constipation, and dizziness occurred most frequently after intake of GRT0151Y or tramadol IR. The incidence of these TEAEs was similar in all active treatment groups. Nausea, vomiting, constipation, and dizziness are expected adverse drug reactions for GRT0151Y (Investigator's Brochure, Version 7, 2005).Regarding gender differences, more female subjects experienced the TEAEs nausea and vomiting than male subjects (33.4% versus 7.7% and 30.4% versus 8.8%, respectively). Post-procedural hemorrhage (following the tonsillectomy), headache, pyrexia, and palatal edema occurred frequently (i.e. in > 5% of the subjects in any treatment group). However, apart from nausea, vomiting, constipation, and dizziness, no other frequent TEAEs occurred that were assessed as at least possibly related to the IMP. Post-procedural hemorrhage, pyrexia, and palatal edema are unexpected TEAEs. Most of the unexpected TEAEs can be attributed to the tonsillectomy; therefore, there is no indication of an influence of GRT0151Y on the occurrence of these events.

In general, there were no clinically meaningful changes in clinical laboratory parameters or sedation scores during the course of this trial nor were there any relevant differences between the treatment groups regarding these assessments. The same applies for vital signs. However, for the pulse rate measurements, a constant increase of the values from baseline to final examination was observed which was most prominent for the GRT0151Y groups (range: 3.7 bpm to 7.0 bpm). Therefore, a slight influence of GRT0151Y on the pulse rate in this setting cannot be excluded.

Regarding the parameters relating to the hepato-biliary system, the number of observed liver injuries according to the classification of the Consensus Committee was comparable between all treatment groups. No influence of the amount of daily dose or dose administered per individual was observed. Therefore no drug effect on the occurrence of liver injuries was seen in this trial. Nevertheless, an influence of GRT0151Y on the less specific abnormalities of liver injuries cannot be excluded, even though the results might be confounded by peri-operative procedures including general anesthesia.

Although the ECG readings revealed borderline and prolonged QTcB values that were not equally distributed among all treatment groups, there is no clear dose relationship to GRT0151Y and abnormal QTcB values were also found in the placebo group. It has to be noted that the present trial was not designed to investigate cardiac repolarization involvement of GRT0151Y in a comprehensive way. The limitations and design of this trial do not allow any firm conclusions about any minor repolarization influence of GRT0151Y.

Overall, the three doses of GRT0151Y (150 mg, 250 mg, and 300 mg) appeared to be safe. The overall tolerability was affected by opioid-specific adverse drug reactions such as nausea and vomiting. Only the incidence of nausea was between 20% and 30% of the subjects in each active treatment groups. The safety profile of GRT0151Y was as expected for a substance with μ-opioid activity.

CONCLUSION:

For the primary endpoint (TAPI-48 while swallowing on Day 4 and Day 5) no statistically significant difference between the three GRT0151Y dose groups (150 mg, 250 mg, and 300 mg) and placebo was observed. The difference between tramadol IR and placebo regarding TAPI-48 was larger than the difference between the GRT0151Y groups and placebo but also not statistically significant.

The results for tramadol IR, which showed a statistically significant difference to placebo for most secondary endpoints evaluated at rest, showed that the pain model used in this trial was sensitive for detecting differences in pain relief following tonsillectomy.

Because of the lack of a clear treatment effect and because of the fact that two GRT0151Y groups were dosed as twice daily and one group as three times daily, it was not possible to analyze a dose response relationship.

Overall, the three doses of GRT0151Y (150 mg, 250 mg, and 300 mg) given two to three times daily appeared to be safe. The results obtained in this trial were in line with a safety profile for a substance with μ-opioid activity and previous experiences with this compound, and did not constitute a change in the scientific knowledge of GRT0151Y.

Date of report: 07 May 2007

KF0151Y/06
ICTR SYNOPSIS SUPPLEMENT

Original ICTR date / DMS version:	23 May 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 was 1 amendment to the protocol.

Amendment No. I (dated 15 Jul 2005) was prepared according to the requests by authorities to include contraception for males as an additional requirement for this trial. This change affected the exclusion criteria which were extended by the criterion that males, who did not use satisfactory contraception (e.g. being sterilized, condom) from the first dose up to 7 days after the last dose of the IMP were to be excluded from the trial.

Furthermore, the protocol stated that the unique medication number was also used to identify the subject in lieu of the subject's name and was used to report adverse events and other trial related data. Instead the unique medication number was assigned to a unique subject number previously assigned to a subject. This subject number was used instead of the subject's name to report trial related data.

The protocol also stated that pain intensity at rest was assessed during the pre-baseline period, at baseline and during the entire treatment period, and that during the pre-baseline period and at baseline, the assessments were recorded in the "postoperative assessment booklet". The pain intensity assessments during the pre-baseline period were assessed but not collected for the statistical analysis.

In addition, it was planned according to protocol to have a clinician's global assessment of the IMP(s) at the final examination performed by the Investigator. As this was not provided for in the CRF, this assessment could not be performed.

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
CZ-001	(Name not given, since no consent given), 53203 Pardobice, Czech Republic
CZ-002	(Name not given, since no consent given), 65691 Brno, Czech Republic
FI-001	(Name not given, since no consent given), 70100 Kuopio, Finland
HU-001	(Name not given, since no consent given), 1704 Budapest, Hungary
HU-002	(Name not given, since no consent given), 1115 Budapest, Hungary
HU-003	(Name not given, since no consent given), 1096 Budapest, Hungary
HU-004	(Name not given, since no consent given), 2600 Vac, Hungary
HU-005	(Name not given, since no consent given), 4400 Nyiregyhaza, Hungary
HU-006	(Name not given, since no consent given), 6725 Szeged, Hungary
HU-007	(Name not given, since no consent given), 4012 Debrecen, Hungary
HU-008	(Name not given, since no consent given), 9024 Gyor, Hungary
HU-009	(Name not given, since no consent given), 9700 Szombathely, Hungary
PL-001	(Name not given, since no consent given), 51-124 Wroclaw, Poland
PL-002	(Name not given, since no consent given), 31-826 Krakow, Poland
PL-003	(Name not given, since no consent given), 00-908 Warsaw, Poland
RO-001	(Name not given, since no consent given), 400006 Cluj-Napoca, Romania
RO-002	(Name not given, since no consent given), 011172 Bucharest, Romania
RO-003	(Name not given, since no consent given), 022115 Bucharest, Romania
RO-004	(Name not given, since no consent given), 030171 Bucharest, Romania
RO-005	(Name not given, since no consent given), 300024 Timisoara, Romania
RO-006	(Name not given, since no consent given), 050751 Bucharest, Romania
RO-007	(Name not given, since no consent given), 310010 Arad, Romania
RU-001	(Name not given, since no consent given), Moscow, 119881, Russia
RU-002	(Name not given, since no consent given), Moscow, 111558, Russia
RU-003	(Name not given, since no consent given), Moscow, 123448, Russia
RU-004	(Name not given, since no consent given), Moscow, 125367, Russia
RU-005	(Name not given, since no consent given), 190013 Saint Petersburg, Russia
RU-006	(Name not given, since no consent given), 197022 Saint Petersburg, Russia
RU-007	(Name not given, since no consent given), Moscow, 119049, Russia
UK-001	(Name not given, since no consent given), London SW17 ORE, United Kingdom
UK-002	(Name not given, since no consent given), Surrey CR7 7YE United Kingdom