Efficacy, Safety, and tolerability of GRT6005 in subjects with moderate to severe chronic low back pain

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To assess the analgesic efficacy, safety, and tolerability of once daily orally administered GRT6005 in a total of 3 fixed doses (i.e., 200 µg, 400 µg, and 600 µg GRT6005) compared to placebo in subjects with moderate to severe chronic LBP.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)
Study type	Interventional

Summary

ID

NL-OMON39632

Source
ToetsingOnline

Brief title
GRT6005 in subjects with chronic low back pain

Condition

- Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)

Synonym
low back pain

Research involving
Human

Sponsors and support

Primary sponsor: Grunenthal
Source(s) of monetary or material Support: Grunenthal GmbH

Intervention

Keyword: chronic low back pain, GRT6005 and tapentadol, multiple dose, phase II study

Outcome measures

Primary outcome

In support of a marketing authorization in the European Union and other non-US countries worldwide, the primary endpoint will be the change from baseline pain to the weekly average 24-hour pain during the entire 12 weeks of the maintenance phase of the double-blind Treatment Period.

The 24-hour pain will be assessed once daily using an 11-point numeric rating scale (NRS) and a 24-hour recall period. For the US regulatory authority, the primary endpoint will be the change from baseline pain to the average 24-hour pain during Week 12 of the maintenance phase. The 24-hour pain will be assessed once daily using an 11-point NRS and a 24-hour recall period.

The baseline pain will be calculated as the average over the three 24-hour pain assessments of the last 3 days prior to the Baseline Visit.

Secondary outcome

Additional endpoints will be:

* The primary endpoint for a region will be considered as an additional endpoint for the other region.

* Response rate (%) defined in several ways: response (Yes/No) defined as *10%, *20%, up to 100% improvement in 24-hour pain during Week 12 of the maintenance phase compared to baseline.

* Change from baseline in current pain assessed twice daily on an 11-point NRS.

* Change from baseline in worst pain assessed once daily on an 11-point NRS.

* Change from baseline in the weekly averages of the 24-hour pain during the entire 12 weeks of the maintenance phase per identified painDETECT subgroup.

* Change from baseline in the average of the 24-hour pain during Week 12 of the maintenance phase per identified painDETECT subgroup.

* Use of rescue medication during the Treatment Period.

* Changes from baseline of the EuroQol-5 Dimension (EQ-5D) scores and the Short Form 12 Health Survey (SF-12®) scores.

* Change from baseline in the Brief Pain Inventory (Short Form, SF-BPI) score.

* Change from baseline in the scores of the Oswestry Disability Index (ODI) score.

* Scores of the newly developed patient reported outcome questionnaires Pain Assessment for Low Back Pain (PAL) (Impact) and PAL (Symptom).

* Change from baseline in the score of the CHRONIC PAIN SLEEP INVENTORY© (CPSI).

* Change from baseline of the anxiety and depression subscale scores of the Hospital Anxiety and Depression Scale (HADS).

* Patient*s Global Impression of Change (PGIC) using a 7-point scale.

* Safety related endpoints will be:

* Frequency of adverse events (AEs) and percentage of subjects discontinuing the trial due to AEs and drug-related AEs.

* Changes from baseline in vital signs, clinical laboratory values, and

12-lead ECG.

* Changes from baseline on the Columbia Suicide Severity Rating Scale (C-SSRS).

* Frequency of potential withdrawal symptoms using the Clinical Opioid

Withdrawal Scale (COWS).

Study description

Background summary

Low back pain (LBP) in general, regardless of the reason, is widely distributed, has a high incidence and represents one of the most significant socio-economic health-related problems in the developed countries. The estimated lifetime prevalence of low back pain for at least 3 months is about 9% in Europe and 10.1% in the United States. The rising cost of repeated diagnostic procedures, treatments (incl complications) are considerable. Also indirect costs due to loss of work represent the largest portion of overall costs releateerd with LRP.

Opioid analgesics, including tapentadol have been shown to be efficacious in chronic non-malignant pain including chronic LBP and can be an important asset in the therapeutic armamentarium . Although opioids have relieved human suffering for millennia, their long-term use in chronic LBP remains controversial . Nevertheless, despite the available analgesic medications, up to 60% to 80% of patients suffering from chronic pain are at times treated inadequately.
Nociceptive and neuropathic components can both contribute to LBP. Since each of these components requires a different pain management strategy, correct pain diagnosis before and during treatment is highly desirable. Screening tools can serve to identify patients with neuropathic back pain. The painDETECT® Pain Questionnaire, among other scales, has been used worldwide and has been validated in a patient population with LBP (Freynhagen et al. 2006). Subjects with a final score between 0 and 12 (painDETECT *negative*) show a small likelihood of a neuropathic pain component, those with a final score between 13 and 18 (painDETECT *unclear*) an unclear likelihood, and those with a final score between 19 and 38 (painDETECT *positive*) a defined likelihood of a neuropathic pain component.

In an unselected cohort of chronic LBP patients, 37% were found to have predominantly neuropathic pain and 35% were found to suffer from a predominately nociceptive type of pain. Patients with neuropathic pain showed higher ratings of pain intensity, with more (and more severe) co-morbidities

such as depression, panic/anxiety and sleep disorders. This also affected functionality and use of health-care resources.

Chronic LBP is a complex pain entity with neuropathic and nociceptive components. Subgroups of patients suffering from pain with and without a neuropathic pain component can be identified with the painDETECT (screening tool) questionnaire. As GRT6005 might be effective at different dose levels in nociceptive and neuropathic pain, the dose-response relationship in sub-populations with chronic LBP classified by the use of the painDETECT questionnaire will be explored.

Study objective

To assess the analgesic efficacy, safety, and tolerability of once daily orally administered GRT6005 in a total of 3 fixed doses (i.e., 200 µg, 400 µg, and 600 µg GRT6005) compared to placebo in subjects with moderate to severe chronic LBP.

Study design

Randomized, multi-center, double-blind, double-dummy, placebo- and active* controlled, parallel-group, multiple oral dose Phase II trial in approximately 600 allocated subjects with moderate to severe chronic low back pain (LBP) .

Intervention

During the course of this trial, a total of approximately 65 mL blood will be collected from each subject, including safety laboratory and blood samples for pharmacokinetic (PK) analyses and pharmacogenetic testing. The trial consists of an Enrollment Period (with a washout phase and a baseline phase), a double-blind Treatment Period (with a titration phase and a maintenance phase), and a Follow-up Period.

Enrollment Period:
Washout of previous analgesic medication will last at least 3 days or 5 half-lives of this medication (depending on information available in the Summary of Product Characteristics of the used analgesic) whichever is longer with a maximum of 21 days. The baseline phase will last 3 days (Day -3 to Day -1).

Double-blind Treatment Period:
The double-blind Treatment Period is the time between first IMP intake and the last IMP intake as documented in the electronic case report form (eCRF). The first dose will be taken at the investigational site at the end of Visit 3. The last dose will be taken on the morning of Visit 11 (End-of-treatment Visit). Subjects with a documented clinical diagnosis of chronic LBP, who comply with

all inclusion criteria and do not meet any of the exclusion criteria will be randomly assigned to 1 of 5 treatment arms at Visit 3:
* Placebo (Arm 1) * Subjects will receive placebo twice daily.
* Tapentadol HCl PR (Arm 2) * Subjects will be titrated in increments of 50 mg tapentadol twice daily every 3 days starting with 50 mg twice daily and increasing to the target dose of 200 mg twice daily on Day 10. Subjects will remain on a stable dose of 200 mg twice daily for the remainder of the titration phase and the 12-week maintenance phase.
* GRT6005 (Arm 3 to Arm 5) There are 3 target doses of GRT6005 in total.
Subjects assigned to Arm 3 will receive a fixed dose of 200 µg of GRT6005 and will be kept on this dose during the whole Treatment Period.
Subjects assigned to Arm 4 will be titrated in increments of 200 µg of GRT6005 starting with 200 µg for 3 days and increasing to the target doses of 400 µg on Day 4.
Subjects assigned to Arm 5 will be titrated in increments of 200 µg of GRT6005 starting with 200 µg for 3 days and increasing to the target doses of 400 µg on Day 4 and to 600 µg on Day 7. They will then be kept on these target doses during the remainder of the 14-day titration phase and the 12-week maintenance phase.
* Arm 3: subjects will receive 200 µg GRT6005 once daily.
* Arm 4: subjects will receive a target dose of 400 µg GRT6005 once daily.
* Arm 5: subjects will receive a target dose of 600 µg GRT6005 once daily.
In order to ensure the blinding, all IMPs will be administered in a double-dummy design in the morning and the evening. During the entire Treatment Period, all subjects will receive 3 film-coated tablets in the morning and 1 film-coated tablet in the evening, 2 of these being placebo tablets.

Follow-up Period:
The Follow-up Period comprises the time span from the day after Visit 11 up to and including Visit 13 (Follow-up Telephone Call or Visit). A Follow-up Visit (Visit 12) will be scheduled within 3 days to 5 days following the last intake of the IMP and a Follow-up Telephone Call or Visit (Visit 13) within 10 days to 14 days after the last IMP intake to follow up on AEs and document AEs newly occurring since the last visit.

Study burden and risks

Burden for the subject
Subjects who participate in this study will visit the hospital or research center a total of 12 times and will have one telephone visit.
The duration of these visits will be about 1.5 hours. During 4 of these visits, the subject undergoes a physical examination and an ECG. During 10 of these visits the vital functions of the subjectsare inspected.
During 9 of these visits blood samples will be taken. During 3 of these visits, a urine sample taken for further research. During 11 of these visits one or more questionnaires will be filled out by the subject.

All female subjects of childbearing potential should use acceptable methods of birth control during the trial to avoid pregnancy. All male subjects should use adequate birth control during the trial to avoid pregnancy of their partners.

Medication-related risks
- All patients will have a wash-out period of their current pain medication and this my cause an increase in their pain; for this they are allowed to use rescue medicaiton.
- 20% of the subjects will receive a placebo after their washout period. It is possible that these patients will experience more pain and for this they may need rescue medication
- 60% of the subjects will receive one of three dosages of GRT6005. Although GRT6005 was safe and well tolerated in previous studie, not all possible risks and side effects are known. The known side effects of GRT6005 are nausea, vomiting, dizziness, somnolence and fatigue.
- 20% of the subjects will receive Tapentadol . Common known side effects of this medicine include dizziness, somnolence, headache, nausea and constipation.

Blood sampling-related risks
The insertion of the needle can be painful or cause bruises may at the injection site. In addition, the subject may suffer from dizziness, light-headedness or fainting. In addition, rare complications such as local blood clotting, infection, inflammation of the vein, scarring of the vein, nerve damage and accidental puncture of an artery may occur.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Informed consent signed.
2. Male or female subject 18 years to 80 years of age at Visit 1.
3. Women of childbearing potential must have a negative urine * human chorionic gonadotropin
(*-hCG) pregnancy test at Visit 1 and at Visit 3.
4. Subjects must be using medically acceptable and highly effective methods of birth control as defined in protocol page 35 and 36. Women of non-childbearing potential may be included if surgically sterile (i.e., after hysterectomy) or post-menopausal for at least 2 years.
5. Subjects must be able to communicate meaningfully and able to differentiate with regard to location and intensity of the pain, and to complete the questionnaires used in this trial.
6. Documented clinical diagnosis of chronic LBP of non-malignant origin and pain present for at least 3 months.
7. Average 24-hour pain *5 on an 11-point NRS during the 3 days prior to Visit 3 without the use of rescue medication. Subjects must have 3 out of three 24-hour pain assessments during this 3-day period.
8. Subjects must be on stable analgesic medications (non-opioid and/or opioid medications) for their chronic LBP with regular intake (i.e., at least 4 days per week) for at least 3 months prior to Visit 1 according to their medical history and dissatisfied with current analgesic treatment.
9. Subjects requiring opioid treatment must be taking daily doses of opioid-based analgesic equivalent to*160 mg of oral morphine.

Exclusion criteria

1. Concurrent participation in another trial, or within 30 days before Visit 1 of this trial.
2. Previous participation in this or other trials with GRT6005 (unless enrollment failure due to technical reason). Exception: subjects who failed enrollment in this trial only because of the exclusion criteria that were changed in amendment 01 and 02, but for no other reason, and who may now be eligible may be re-enrolled.
3. Previous or current alcohol or drug abuse or opioid dependency according to the investigator*s judgment,based on subject*s history, physical examination, or the result of the

drug test at Visit 1 or at Visit 3.
4. Female subjects who are pregnant or are breastfeeding
5. Known or suspected of not being able to comply with the protocol and with the use of the IMPs or rescue medication.
6. Any clinically significant disease or laboratory findings that in the investigator's opinion may affect efficacy or safety assessments or may compromise the subject*s safety during trial participation, e.g., significant unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, metabolic, neurological, or psychiatric disorders.
7. Employees of the investigator, trial site, or sponsor, with direct involvement in the proposed trial or other trials under the direction of that investigator, trial site, or sponsor, as well as family members of employees or the investigator.
8. Subjects with moderate to severe functional hepatic impairment corresponding to Child-Pugh classification B and C. Subjects with impaired hepatic cellular integrity shown by ALT or ASAT values higher than 3 times ULN
9.History of acute hepatitis within 3 months of Visit 1or chronic hepatitis or a positive result on antihepatitis A IgM antibody within 6 months of visit 1, hepatitis B surface antigen, or anti*hepatitis C antibody. History of human immunodeficiency virus (HIV) infection.
10.Subjects with impaired renal function. Creatinine clearance less than 45 mL/min at Visit 1 (calculated from the Cockcroft Gault formula).
11. History of any major gastrointestinal prior procedures (e.g., gastric byepass) or gastrointestinal conditions (e.g., acute diarrhea, blind loop syndrome, gastric dumping syndrome, Whipple`s disease) that might affect the absorption or metabolism of GRT6005.
12.Presence of risk factors for Torsade de Pointes (e.g.,heart failure, hypokalemia, bradycardia, long QT syndrome)
13.Presence of QTcF >450 ms at Visit 1.
14. History of seizure disorder and/or epilepsy or any condition associated with a significant risk for seizure disorder or epilepsy at Visit 1 at the discretion of the investigator.
15.History or presence of malignancy, with the exception of curative treated subjects or subjects
being in remission of cancer for at least 2 years and not requiring treatment.
16. Subjects with chronic LBP potentially associated with a specific spinal cause (e.g., known high-grade spondylolisthesis [Grade 3 or 4], tumor, infection, vertebral compression fracture [history *1year], Paget*s disease, absolute spinal stenosis).
17. Subjects with >1 previous low back surgeries or recent low-back surgery (within the last 12 months) or scheduled low back surgery during the trial or any other scheduled surgery or painful procedure during the course of the trial that, in the opinion of the investigator, may affect efficacy or safety assessments.
18. Any invasive procedures aimed to reduce LBP (e.g. epidural injections, facet joint or sacroiliac joint blocks) within the past 3 months and throughout the trial
19. Subjects with any kind of neuromodulation (spinal cord stimulation therapy, peripheral neuromodulation, deep-brain stimulation).
20. Clinically relevant history of hypersensitivity, allergy or contraindications to any of the IMPs* excipients, paracetamol/acetaminophen, tapentadol HCl, or opioid analgesics (or excipients).
21. Presence of conditions other than LBP that could confound the assessment or self-evaluation of pain,such as but not limited to anatomical deformities, significant skin conditions such as infections (abscesses or ulcers), unilateral or bilateral lower limb pain

independent from the indication chronic LBP, painful venous insufficiency, painful post thrombotic syndrome, painful OA of the knee, distal lower limb inflammation, or diffuse widespread pain such as fibromyalgia.
22. Subjects with BMI *18 kg/m2 and *35 kg/m2.
23. Pending litigation or application for insurance/governmental benefits due to chronic pain or disability and, if granted, benefits that might be influenced by a participation in the trial.
24. Increased intracranial pressure, caused e.g., by severe traumatic brain injury or ischemic brain injury.
25. Subjects with significant respiratory depression, with acute or severe bronchial asthma or hypercapnia, and suspected or diagnosed sleep apnea.
26. Presence or suspicion of paralytic ileus.
27. Use of forbidden medication as specified in prohibited medications.
28. Rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose galactose malabsorption, lactose intolerance.
29. Conditions that require treatment with prohibited medication.
30. Subjects with a painDETECT score *19 and the maximum number of subjects for the "positive* painDETECT subgroup has been reached

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-07-2013
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GRT6005
Generic name:	GRT6005
Product type:	Medicine
Brand name:	palexia
Generic name:	tapentadol hydrochloride
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-01-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-02-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-08-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-001920-36-NL
CCMO	NL41830.060.12