Summary of clinical trial results for the public

Clinical Trial Information

Simple clinical trial name: A clinical trial performed in healthy subjects to examine whether the experimental medicine GRT6018 is able to reduce the response to a painful stimulus

Protocol number: HP6018-02

EudraCT identifier: 2021-002305-95

Clinical Trial Sponsor: Grünenthal GmbH

Thank you to the clinical trial participants

If you took part in the clinical trial, thank you for your time and commitment.

You made the clinical trial possible.

You helped us on our way to bringing new medicines to patients.

Important note: You should not use this summary to make decisions about the medical treatments you use. You should always see your doctor for advice about medical treatments.

About this summary

This summary is written to share the results of this clinical trial with the public. It is written in a way that will be easy for most people to understand. It describes why the clinical trial was needed, how it was done, and the results.

General information about the clinical trial

Why was this clinical trial needed?

GRT6018 is an experimental medicine being developed to treat chronic (long-lasting) nerve pain which can occur in patients following injury to a nerve as a result of illness, infection, surgery, or treatment with a chemotherapeutic agent.

For example, in some individuals with diabetes, the disease can damage the nerves that specialize in detecting and carrying pain signals. This can result in ongoing pain in some body regions, such as the limbs. This condition is called painful diabetic neuropathy.

Currently there are only a few medicines available for the treatment of painful diabetic neuropathy. These medicines are not completely effective for all patients and can cause unwanted side-effects.

There is, therefore, a need to develop better medicines for this painful condition.

GRT6018 has been developed to decrease the ongoing pain caused by nerve damage to these specialized pain nerves.

This clinical trial was designed to examine whether **GRT6018,** when dosed to healthy male subjects, was able to reduce the response to an evoked painful stimulus in an experimental pain model. The data from this clinical trial could be helpful in supporting further clinical studies with **GRT6018.**

Which medicines were studied?

GRT6018 is an experimental medicine that is being developed to treat chronic nerve pain. It was taken orally in capsules. **GRT6018** has not been approved as a treatment in humans.

In this clinical trial, **placebo** **(dummy medicine)** was used to help understand if any of the changes in the responses to the evoked pain stimulus may have happened as a result of the experimental procedure, rather than the experimental medicine being tested. The people who received the **placebo** were given an identical capsule to the participants who received **GRT6018,** but the **placebo** capsule did not contain any active ingredients.

Pregabalin is an approved medicine for the treatment of neuropathic pain in adults. In this clinical trial people were given **pregabalin** to test that the experimental model of evoked pain was working correctly. This is called an active comparator. **Pregabalin** was also given orally in capsules identical to those used for **GRT6018**.

The doctors who administered the capsules did not know which participants were receiving **GRT6018**, **pregabalin** or **placebo.** Also, the participants did not know which capsules they received at any time. This was to help make sure that the results of the clinical trial were fair. This is known as “blinding”. The code was kept secret until the trial was completed.

What was the main objective of the clinical trial?

The main objective of the clinical trial was to find out:

Is GRT6018 effective in reducing the response to an experimental pain stimulus in healthy, male subjects?

When and where did this clinical trial take place?

This clinical trial started on 24 September 2021 and ended on 22 November 2021.

The clinical trial took place at a single clinical trial site in Germany.

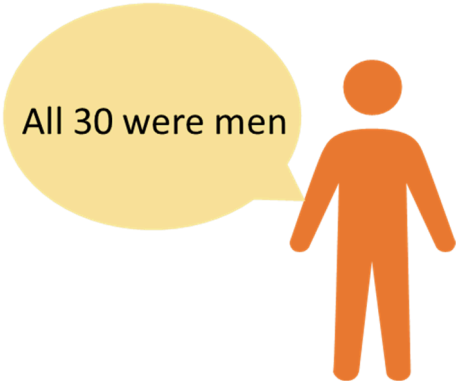
Which participants were included in this clinical trial?

A total of 30 healthy, male subjects took part in this clinical trial.

How old were the participants?

The average age of the participants was 44 years. The youngest participant was 23 years old, and the oldest participant was 60 years old.

Were the participants men or women?



Which participants were able to take part in the clinical trial?

Participants were only able to take part in the clinical trial if they met certain requirements. This was important to make sure that it was safe for each participant to take part in the clinical trial. It was also important to make sure that the results of the clinical trial were valid, and that all applicable laws and regulations were followed.

Subjects could take part in this trial if they:

- ✓ were healthy, male subjects and not on any medicines,
- ✓ were between 18 and 64 years of age, inclusive,
- ✓ had a body mass index (a measure of body weight based on height) between 18.5 and 29.9 kg/m^2, inclusive, and
- ✓ had a body weight of at least 60 kg.

What happened during this clinical trial?

This Phase 1 clinical trial was performed to help researchers understand:

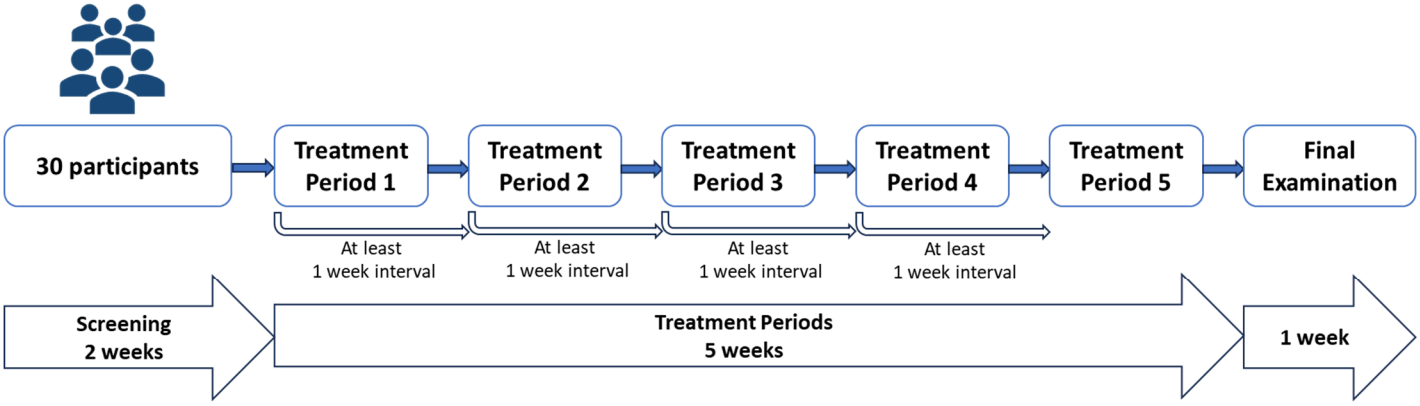
- the effectiveness of **GRT6018** in reducing the response to an experimental pain stimulus,
- whether there are any side-effects associated with **GRT6018**.

Thirty healthy participants took part in the clinical trial. At the start of the clinical trial, participants were randomly assigned into different sequence groups. All participants were planned to receive a single dose of 3 mg **GRT6018**, 15 mg **GRT6018**, 90 mg **GRT6018**, **placebo,** and 150 mg **pregabalin**. The order (or sequence) in which the participants received each treatment depended on which group they had been assigned to during the randomisation process (see diagram below).

This type of clinical trial is known as a crossover design and helps ensure that a minimal number of participants are used to test the effectiveness of an experimental medicine. In addition, the randomisation process helps reduce factors that could unintentionally influence the outcomes of the clinical trial.

There was at least a one-week period between participants receiving each treatment. Blood samples were taken from the participants at different times during the treatment periods to monitor the levels of **GRT6018** over time.

Researchers regularly monitored the health status of the participants throughout the clinical trial.



In each Treatment Period, participants received either a 3 mg, 15 mg, or 90 mg dose of **GRT6018**, **placebo** or 150 mg **pregabalin**.
All participants were planned to receive all 5 different treatments.
The order in which the treatments were taken was not the same for each participant.

Researchers assessed the effect of each treatment in modulating the response to an experimentally induced (evoked) painful stimulus on three, separate small areas of skin on each of the participant's back:

1) **Normal skin** – the skin had not been subjected any treatment.
2) **UV_B-treated skin** - skin that was pre-exposed to ultraviolet (UV_B) light causing a type of "sunburn".
3) **Capsaicin-treated skin** - skin that was treated by applying a solution of capsaicin to cause a localized, mild-burning sensation and redness. Capsaicin is a chemical found in chili peppers and causes a hot, spicey sensation when eaten.

In order to cause (or evoke) experimental pain, a laser beam pulse was applied to each of the three skin areas. On normal skin this might feel like a "pinprick", but on the other two conditions it might feel more painful because the UV_B-light and the capsaicin may have made the skin more sensitive.

The participant's response to the laser-evoked pain was assessed during the clinical trial using two methods:

1) by recording the electrical activity in the brain of participants using a test called an **electroencephalogram (EEG).** In this test, detectors, which can pick up electrical activity in the brain, are placed on the outside of the head.
2) by asking the participants how much pain they felt using a specialized and reliable **scoring system**.

This allowed **GRT6018** to be compared to **placebo** and to assess whether any changes detected were statistically significant.

What were the results of this clinical trial?

1) Effects of **GRT6018** on normal skin versus **placebo**
    - Both the 15 mg and 90 mg doses of **GRT6018** showed statistically significant increases in EEG activity.
    - None of the doses of **GRT6018** showed a statistically significant effect on pain scores reported by the participants.

2) Effects of **GRT6018** on UV_B-treated skin versus **placebo**
    - All doses of **GRT6018** showed statistically significant reductions in EEG activity.
    - Both the 3 mg and 15 mg doses of **GRT6018** showed statistically significant reductions in the pain scores reported by the participants.

3) Effects of **GRT6018** on capsaicin-treated skin versus **placebo**
    - None of the doses of **GRT6018** showed a statistically significant reduction in EEG-activity.
    - None of the doses of **GRT6018** showed a statistically significant effect on the pain scores reported by the participants.

4) Effects of **pregabalin** on the different skin areas versus **placebo**
    - **Pregabalin** showed a statistically significant reduction in EEG activity in UV_B- and capsaicin-treated skin but not in normal skin.
    - **Pregabalin** caused on normal skin, capsaicin-treated skin and UV_B-treated skin a statistically significant reduction in the pain scores reported by the participants.
    - The data with **pregabalin** indicates that the experiment was generally working correctly.

Analysis of the blood samples that were collected indicated that **GRT6018** levels were in the expected range for each dose.

Overall, these data show that **GRT6018** can reduce evoked pain in healthy, adult male participants in some, although not all situations tested. The clinical trial indicated that the effect of **GRT6018** on each of the skin conditions was different, with statistically significant reductions in both EEG activity and pain scores detected in the UV_B-treated skin but not in capsaicin-treated skin or in normal skin. This observation may be helpful in guiding future clinical trials in patients.

What side-effects did participants have in this clinical trial?

Side-effects, also known as adverse reactions related to treatment, occur with many medicines and are unwanted, undesirable effects that are observed or felt by people alongside beneficial effects. They can vary in seriousness, ranging from mild to severe, and with a few medicines could be life-threatening.

What serious side-effects did the participants have?

Serious side-effects are those that may cause death, disability, lasting problems, life-threatening conditions, or hospitalization.

No serious side-effects or deaths were reported during this clinical trial.

How many participants had other side-effects?

GRT6018: Five out of 27 of the participants who received this treatment had side-effects including tiredness, headache, and slow heart rate.

Placebo: Two out of 26 of the participants who received this treatment had side-effects including headache and slow heart rate.

Pregabalin: Four out of 25 of the participants who received this treatment had side-effects including tiredness and sleepiness.

How many participants stopped treatment because of side-effects?

No participants stopped trial treatment due to side-effects in this clinical trial.

How was this clinical trial useful for patients and researchers?

Thanks to the help of participants in this clinical trial, researchers were able to discover valuable information regarding the effects and safety of **GRT6018** in healthy, adult males.

GRT6018 produced effects on evoked pain and there were no concerning safety issues observed during the clinical trial.

These outcomes can be used to help design future clinical trials in patients with **GRT6018** in chronic pain.

The results described in this report are for one trial. The findings of other trials might be different. How **GRT6018** works and how safe it is to use must not be judged on the results of one clinical trial alone.

Where can I learn more about this clinical trial?

If you were a participant in the clinical trial and have any questions, please contact the trial doctor using the details you were provided with during the clinical trial.

Full clinical trial name: A Phase I, single-site, randomized, double-blind, double-dummy, placebo- and active reference-controlled, crossover trial to assess the effects of single oral doses of GRT6018 on laser-evoked potentials in healthy male subjects.

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