If you are a volunteer who took part in the clinical trial, thank you for your time and commitment.
You made the clinical trial possible.
Thank you for helping us on our way to bringing medicines to patients.

1 TRIAL NAME

Brief trial name: Safety and tolerability of a dose escalation of neosaxitoxin alone and in combination with bupivacaine (with and without epinephrine) for brachial plexus blockade in healthy subjects

Protocol number: HP7020-02

Universal trial number: U1111-1189-1950

2 WHO SPONSORED THIS TRIAL?

Grünenthal GmbH.

3 GENERAL INFORMATION ABOUT THE CLINICAL TRIAL

3.1 When was the trial?

The clinical trial began on 30 Jan 2018 and ended on 21 Sep 2018.

The sponsor stopped the clinical trial early because they thought the doses of neosaxitoxin they had tested so far provided enough anesthesia to start clinical trials in patients.

3.2 What was the main objective of the trial?

The aim of the trial was to find out how safe it is to use increasing doses of neosaxitoxin to anaesthetize the volunteer's arm from the shoulder to the fingertips. The following treatments were administered:

- Neosaxitoxin, bupivacaine, and epinephrine (adrenaline).
- Neosaxitoxin and bupivacaine.

- Bupivacaine and epinephrine.
- Bupivacaine.

4 WHICH VOLUNTEERS WERE INCLUDED IN THIS TRIAL?

4.1 Where did the volunteers take part in the trial?

The clinical trial took place in the Netherlands.

242 volunteers were included in the trial. 42 of these volunteers were treated.

4.2 How old were the treated volunteers?

The youngest volunteer was 18 years old and the oldest volunteer was 54 years old. The average age was 30 years.

4.3 Were the treated volunteers men or women?

All volunteers were men.

4.4 Which volunteers were able to take part in the trial?

Volunteers were only able to take part in the clinical trial if they met certain criteria. This was important to make sure that it was safe for each volunteer to take part in the clinical trial, that the results of the clinical trial were valid, and that the laws and regulations were followed.

Only healthy men aged between 18 years and 55 years could take part in the trial.

5 WHICH MEDICINES WERE STUDIED?

Neosaxitoxin, bupivacaine, and epinephrine were the treatments tested in the trial. Neosaxitoxin was the new treatment. Bupivacaine and epinephrine are normally used for local anesthesia. Each volunteer received one injection above the collarbone on one side of their body with a liquid

containing some or all of these treatments. The injection was meant to anaesthetize the volunteer's arm on that side of the body, from the shoulder to the fingertips.

Volunteers were mainly treated in groups of 5. After one group had been treated, experts looked at how safe the injections had been for the volunteers in that group. If the injections had been safe, the next group of volunteers was treated. Group 1 was treated first, then Group 2, then Group 3, and so on. The dose of neosaxitoxin received in one group was higher than in the group before.

In Part A of the trial, volunteers received one injection with liquid containing all 3 treatments or just bupivacaine and epinephrine. Table 1 shows how many volunteers received which doses of which treatments in each group.

The red and yellow men show which volunteers had certain unwanted effects. These are explained in Section 6. The dark blue men show which volunteers had no unwanted effects.

Table 1: How many volunteers received which treatments in Part A

	New treatment combination	Normally used treatment combinations	
Group 1	 1.25 µg neosaxitoxin + 40 mg bupivacaine + 100 µg epinephrine	 40 mg bupivacaine + 100 µg epinephrine	 100 mg bupivacaine + 100 µg epinephrine
Group 2	 2.5 µg neosaxitoxin + 40 mg bupivacaine + 100 µg epinephrine	 40 mg bupivacaine + 100 µg epinephrine	 100 mg bupivacaine + 100 µg epinephrine
Group 3	 5 µg neosaxitoxin + 40 mg bupivacaine + 100 µg epinephrine	 40 mg bupivacaine + 100 µg epinephrine	 100 mg bupivacaine + 100 µg epinephrine

Group 4	 10 µg neosaxitoxin + 40 mg bupivacaine + 100 µg epinephrine	 40 mg bupivacaine + 100 µg epinephrine	 100 mg bupivacaine + 100 µg epinephrine
Group 5	 20 µg neosaxitoxin + 40 mg bupivacaine + 100 µg epinephrine	 40 mg bupivacaine + 100 µg epinephrine	 100 mg bupivacaine + 100 µg epinephrine
Group 6/7	 25 µg neosaxitoxin + 40 mg bupivacaine + 100 µg epinephrine	 40 mg bupivacaine + 100 µg epinephrine	 100 mg bupivacaine + 100 µg epinephrine

In Part B of the trial, volunteers received one injection with a liquid containing neosaxitoxin and bupivacaine, or just bupivacaine. Table 2 shows how many volunteers received which doses of which treatments in each group. The light blue men show which volunteers had no unwanted effects.

Table 2: How many volunteers received which treatments in Part B

	New treatment combination	Normally used treatments	
Group 8	 5 µg neosaxitoxin + 80 mg bupivacaine	 80 mg bupivacaine	 100 mg bupivacaine
Group 9	 10 µg neosaxitoxin + 80 mg bupivacaine	 80 mg bupivacaine	 100 mg bupivacaine

In Part A and Part B, neither the doctors nor the volunteers knew which volunteers in each group were given which treatments. This was to make sure that the results of the clinical trial were fair.

6 WHAT WERE THE OVERALL RESULTS OF THE TRIAL?

Before the start of the trial, some potential unwanted effects were identified which could indicate that too much of the trial medicine was in the blood stream. These unwanted effects were identified based on results from a previous trial. Volunteers that had these unwanted effects are shown as red men in Table 1 and Table 2. The volunteer who received neosaxitoxin, bupivacaine, and epinephrine felt sick and was sick. One volunteer who received bupivacaine and epinephrine and one volunteer who received neosaxitoxin and bupivacaine were not able to breathe in as strongly as usual. However, the trial doctor did not think that any of these unwanted effects were due to the treatments the volunteers had received.

During the trial, other volunteers had effects which the trial doctor thought could be side effects of the treatment they had received.

- Some volunteers who received neosaxitoxin, bupivacaine, and epinephrine reported swelling where the injection was, shortness of breath, general discomfort, feeling dizzy, feeling sick, and sweating lots.
- Some volunteers who received neosaxitoxin and bupivacaine reported numb tongue and mouth, and tingly tongue and mouth.
- Some volunteers who received bupivacaine and epinephrine reported higher blood pressure than usual, faster heartbeat than usual, and pain where the injection was.

These volunteers are shown as yellow men in Table 1 and Table 2.

The results of the trial found that the safety of the new treatment combinations with neosaxitoxin was similar to the safety of the normally used treatments without neosaxitoxin at the doses tested to anaesthetize volunteers' arms.

The results described in this report are for one clinical trial. The findings of other clinical trials might be different. How safe neosaxitoxin, bupivacaine, and epinephrine are to use must not be judged on the results of one clinical trial alone.

If you have any questions, please contact your doctor.

You can find out more about this clinical trial by searching for NCT03399435 in the US clinical trials register.