Neublastin Challenge in Healthy Subjects and Migraine Patients

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON26663

Source
Nationaal Trial Register

Brief title
CHDR1755

Health condition

Migraine

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals, Inc
Source(s) of monetary or material Support: Regeneron Pharmaceuticals, Inc

Intervention

Outcome measures

Primary outcome

Primary Endpoints - Parts A and B
Assessment of pruritus
• The incidence of pruritus in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID) as measured by items 1 and 2 on the Pruritus Assessment questionnaire

• The severity of pruritus in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID) as measured by item 3 (Pruritus Average NRS) and item 4 (Peak Pruritus NRS) on the Pruritus Assessment questionnaire
• The duration of pruritus in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID) as measured by item 1 on the 5-D Pruritus Scale questionnaire
Assessment of rash
• The incidence of rash in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID) as measured by the Rash Assessment questionnaire
• The area and severity of rash in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID) as measured by the Eczema Area and Severity Index (EASI)
• The area and severity of rash in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID) as measured by patient-reported SCORing Atopic Dermatitis (PO-SCORAD) score
• Qualitative assessments of rash in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID) as observed from digital photography of rash
• The incidence and severity of erythema in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID) as measured by the Erythema index

Primary Endpoints - Part B
Assessment of headache in migraine patients
• The incidence of headache in migraine patients over a 28-day period after challenge with Neublastin or placebo (IV) as measured by the Headache Assessment questionnaire
• The severity (peak measurement) of headache in migraine patients over a 28-day period after challenge with Neublastin or placebo (IV) as measured by the Headache Assessment questionnaire
• The duration of headache in migraine patients over a 28-day period after challenge with Neublastin or placebo (IV) as measured by the Headache Assessment questionnaire
• The incidence of migraine-associated symptoms in migraine patients over a 28-day period after challenge with Neublastin or placebo (IV) as measured by the Headache Assessment questionnaire

Secondary outcome

Nociceptive thresholds
• The pain detection threshold (PDT) for heat-induced pain in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID)
• The PDT for cold-induced pain in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo (IV and ID)
• The PDT for pressure pain in healthy subjects and migraine patients over a 28-day period after challenge with Neublastin or placebo as measured by using a local algometer for the ID group and a pressure cuff for the IV group
• The pain tolerance threshold (PTT) for pressure pain in healthy subjects and migraine

patients over a 28-day period after challenge with Neublastin or placebo as measured by using a local algometer for the ID group and a pressure cuff for the IV group
• The area of secondary hyperalgesia in healthy subjects over a 28-day period after challenge with Neublastin or placebo, for ID administration only, as measured by the Von Frey test

Abnormal temperature perception

• The incidence of abnormal temperature perception in healthy subjects and migraine patients over a 28-day period after challenge with
Neublastin or placebo (IV and ID) as measured by the Abnormal Temperature Perception Assessment
• The severity of abnormal temperature perception in healthy subjects and migraine patients over a 28-day period after challenge with
Neublastin or placebo as measured by the Abnormal Temperature
Perception Assessment
• The duration of abnormal temperature perception in healthy subjects and migraine patients over a 28-day period after challenge with
Neublastin or placebo as measured by the Abnormal Temperature Perception Assessment

Pharmacokinetics

• The concentration of Neublastin in serum after a single IV dose of Neublastin in healthy subjects and migraine patients at each time
point that sample is collected

Safety

• The incidence of treatment-emergent serious adverse events throughout the duration of the study in healthy subjects and migraine
patients challenged with a single 50 µg/kg IV dose of Neublastin compared to placebo throughout the duration of the study.

Secondary Endpoints - Parts A

Headache assessment in healthy subjects

• The incidence of headache in healthy subjects over a 28-day period after challenge with Neublastin or placebo (IV and ID) as
measured by the Headache Assessment questionnaire
• The severity (peak measurement) of headache in healthy subjects over a 28-day period after challenge with Neublastin or placebo (IV
and ID) as measured by the Headache Assessment questionnaire
• The duration of headache in healthy subjects over a 28-day period after challenge with Neublastin or placebo (IV and ID) as measured
by the Headache Assessment questionnaire
• The incidence of migraine-associated symptoms in healthy subjects over a 28-day period after challenge with Neublastin or placebo
(IV and ID) as measured by the Headache Assessment questionnaire

Safety

• The incidence of treatment-emergent serious adverse events throughout the duration of the study in healthy subjects challenged with
Neublastin or placebo administered ID

Study description

Background summary

Glial cell-line derived neurotrophic factor receptor alpha-3 (GFRα3) is 1 of 4 members of the glial cell line-derived neurotrophic factor
(GDNF) receptor alpha family. These receptors are glycosylphosphatidylinositol (GPI)-linked proteins expressed in the central and peripheral nervous systems and are involved in the sensitization of pain-sensing neurons known as nociceptors (Baloh et al., 1998; Naveilhan et al., 1998; Worby et al., 1998). Artemin, the only known ligand for GFRα3 (Baloh et al., 1998), is a member of the family of GDNF ligands, which also includes GDNF, neurturin, and persephin (Baudet et al., 2000). In adults, GFRα3 receptors are localized in dorsal root, trigeminal and sympathetic ganglia, as well as peripheral nerves and gut (Bespalov & Saarma, 2007). Preclinical findings suggest that modulating the artemin-GFRα3 pathway may provide an analgesic effect in patients with chronic pain conditions. While the relevance of the GFRα3-artemin pathway outside of pain is poorly understood, the clinical experience from Neublastin (a recombinant human artemin protein of 102/103 amino acid homodimer; BG00010, Biogen, Inc.) provides clues to the supraphysiological effects of this pathway. Clinical studies in which Neublastin was administered intravenously (IV) and/or subcutaneously (SC) in healthy volunteers and patients with sciatica or painful lumbosacral radiculopathy resulted in reports of pruritus, headache, rash, and abnormal sensation of feeling hot in those who received Neublastin compared to placebo. Healthy volunteers who received systemically administered Neublastin also reported significantly higher incidence of headache compared to the placebo group (Okkerse et al., 2016; Rolan et al., 2015). These observations suggest a role for the GFRα3-artemin pathway in patients with intractable pruritus and headache states such as migraine. Stimulation of artemin-GFRα3 axis represents a potential model for inducing migraine. A GFRα3 antagonist can inhibit the effect of artemin and is therefore a potential therapeutic candidate for the treatment of migraine.
This study is a Neublastin challenge in healthy subjects and in patients suffering from episodic migraine to confirm and to quantify phenotypic effects associated with activation of the artermin/GFRα3 pathway with a focus on headache, hypoalgesia, pruritus, and rash. These results may improve the understanding of the mechanism of action and to identify pharmacodynamic biomarkers and potential indications for clinical follow-up studies with a GFRα3 antagonist.

Study objective

The GFRα3-artemin pathway plays a role in patients with intractable pruritus and headache states, such as migraine.

Study design

Day - 1 - EOS

Intervention

Investigational drug
Neublastin (also known as BG00010) acts as a selective ligand for the GFRa3 receptor. Neublastin is supplied as a liquid drug product in vials containing 5.0 mL of 1.6 mg/mL Neublastin. The formulation is as follows: 1.6 mg/mL Neublastin in 10 mM Succinate, 75 mM Sodium Chloride, 10 mM L-Arginine HCl, pH 5.5.

Comparator/placebo product
Placebo will consist of a 0.9% sodium chloride solution for IV infusion or ID administration. Placebo will not be visually distinguishable from the active investigational drug.

Contacts

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Eligibility criteria

Inclusion criteria

1. Male or female from 18 to 65 years of age (inclusive) at screening visit.
3. Body mass index (BMI) between 18 and 35 kg/m2, inclusive at screening, with a minimum weight of 50 kg at screening.
4. Subject is judged by the investigator to be in good health based on medical history (except for migraine in patients participating in Part B) based on all available data prior to administration of initial dose of study drug.
7. Able and willing to provide signed informed consent prior to any study-mandated procedure.

Additional inclusion criteria Part B (episodic migraine patients):
9. History of episodic migraine headaches with or without aura for ≥6 months as determined by a diagnosis provided by a neurologist.
10. Migraine headaches should either fulfil criteria A and B for migraine without aura or criterion C (“Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition,” 2018).

A. Headache has at least 2 of the following characteristics:
• unilateral location
• pulsating quality
• moderate or severe pain intensity (≥4 on headache questionnaire)
• aggravation by or causing avoidance of routine physical activity
B. Experiences at least 1 of the following during headache:
• nausea and/or vomiting
• photophobia and phonophobia
C. Headache described as mimicking usual migraine attack treated and responsive to treatment with triptan;
11. Migraine frequency an average of 1 to 7 migraine days per month in each of the 3 months prior to screening.
12. Migraine headaches should be responsive to treatment with non-steroidal anti-inflammatory agents (NSAIDs) and/or triptans.

Exclusion criteria

1. History of clinically significant cardiovascular, immunological, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, dermatologic, neurological (except for migraine for patients in Part B) or psychiatric disease, as assessed by the investigator that may confound the results of the study or pose an additional risk to the subject by participation in the study. Note: subjects with hay fever or childhood asthma can be enrolled in the study.
2. History of arterial or venous thrombotic or thromboembolic disease.
3. History of stroke or transient ischemic attack.
5. Recent history (within 1 year prior to screening) or presence of a clinically significant chronically painful condition or recent and unresolved acutely painful condition, except for migraine in Part B.
6. History of drug or alcohol abuse (>14 units of alcohol per week) within a year prior to the screening visit.
11. Use of anti-platelet or anti-coagulation therapy, including but not limited to daily aspirin (except for 81 mg daily doses), clopidogrel, prasugrel, ticagrelor, enoxaparin, apixaban, warfarin.
14. Presence of HIV (HIV Ab), hepatitis B (HBsAg, HBAb) or Hepatitis C (HCV Ab) seropositivity at screening.
15. Any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin or carcinoma in situ of the cervix or anus, that have been resected, with no evidence of metastatic disease for 3 years.
25. Use of concomitant medications, including non-prescription medication, nutritional and herbal supplements within 14 days or 5 and ½ half-lives (whichever is longer) prior to initial dose of study drug, except incidental use of paracetamol. Note: For part B: use of triptans, paracetamol, and NSAIDs are allowed for treatment of migraine headaches.

Additional key exclusion criteria Part B (migraine patients):
28. Greater than an average of 7 migraine days per month in each of the last 3 months prior

to screening.
29. Other headache disorders (except for episodic tension-type headache <5 days/month).
30. Greater than or equal to 5 headache days per month of any type/diagnosis (except migraine) in each of the last 3 months prior to screening.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-08-2019
Enrollment:	48
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	17-01-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 49543
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL8298
CCMO	NL69885.056.19
OMON	NL-OMON49543

Study results