Neublastin Challenge in Healthy Subjects and Migraine Patients

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

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON26663

Bron
Nationaal Trial Register

Verkorte titel
CHDR1755

Aandoening

Migraine

Ondersteuning

Primaire sponsor: Regeneron Pharmaceuticals, Inc
Overige ondersteuning: Regeneron Pharmaceuticals, Inc

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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

Onderzoeksopzet

Day - 1 - EOS

Onderzoeksproduct en/of interventie

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.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-08-2019
Aantal proefpersonen:	48
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	17-01-2020
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 49543
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

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

Resultaten