Study of Safety, Tolerability, and Pharmacokinetics of BG00010 (Neublastin) Intravenous and Subcutaneous Single Ascending Doses in Healthy Volunteers, and Subcutaneous Multiple Ascending Doses in Subjects with Painful Lumbar Radiculopathy

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON40320

Source
ToetsingOnline

Brief title
SC and IV doses SAD/MAD study BG00010

Condition

- Spinal cord and nerve root disorders

Synonym
low back pain, Painful Lumbar Radiculopathy

Research involving
Human

Sponsors and support

Primary sponsor: Biogen Idec
Source(s) of monetary or material Support: Biogen Idec

Intervention

Keyword: Glial cell line-derived neurotrophic factor (GDNF), Multiple-Dose, Neuropathic pain, Painful Lumbar Radiculopathy

Outcome measures

Primary outcome

Safety:

- AE and SAEs monitoring

- clinical laboratory safety tests (hematology, clinical chemistry, and

urinalysis)

- physical and neurological examinations

- vital signs

- ECG

- binding and neutralizing antibody assays.

Pharmacokinetics Assessments:

- BG00010 concentrations in serum

Efficacy Assessments:

- Numeric rating Scale

- Visual Analogue Scale.

Secondary outcome

Pharmacodynamic (PD) Parameters:

- Blood, serum, and plasma samples will be collected for analyses to identify

potential biomarkers that may indicate BG00010 activity.

Study description

Background summary

BG00010 is a protein that interacts with sensory neurons in the peripheral nervous system to alleviate neuropathic pain.
BG00010 is being developed as a treatment for conditions like painful lumbar radiculopathy that are associated with neuropathic pain. This study expands on the safety, tolerability, and PK data obtained in initial IV SAD and IV MAD studies (103NS101 and 103NS102, respectively) for IV and SC administration of BG00010.

Study objective

The primary objective of the study is to evaluate the safety and tolerability of a range of single IV and SC doses of BG00010 in healthy volunteers, and a range of multiple SC doses of BG00010 in subjects with painful lumbar radiculopathy.
Secondary objectives of this study are:
-To determine the single IV and SC dose PK profile of BG00010 in healthy volunteers including assessment of bioavailability by comparing SC exposure to IV exposure in each subject.
-To determine the multiple SC dose PK profiles of BG00010 in subjects with painful lumbar radiculopathy.
-To assess the single IV and SC dose immunogenicity of BG00010 in healthy volunteers.
-To assess the multiple SC dose immunogenicity of BG00010 in subjects with painful lumbar radiculopathy.
-To assess the potential of BG00010 to reduce pain following multiple SC administrations in subjects with painful lumbar radiculopathy.
The exploratory objective of this study is the collection of blood samples for potential biomarker analysis, which may include potential future global and/or targeted transcriptional analysis and/or proteomics to identify biomarkers related to neuropathic disease.

Study design

This is a Phase 1 randomized, double-blinded, placebo-controlled study of BG00010 in 3 parts: Part I (SAD), Part II (Extended SAD), and Part III (MAD).
Part I: SAD

Single ascending IV and SC doses of BG00010 in healthy volunteers will be studied. Three cohorts of 6 unique healthy volunteers will be enrolled. Subjects will be randomized to receive a single IV dose of BG00010 or placebo (5:1 ratio) followed by a single SC dose of BG00010. IV and SC administration will occur at least 2 weeks apart (but not longer than 4 weeks). Doses will be the same for a given subject (i.e., subjects will receive either placebo IV followed by placebo SC, or BG00010 IV followed by BG00010 SC).
Doses of BG00010 are planned as follows:
Cohort A: 150 µg/kg or placebo Cohort B: 400 µg/kg or placebo Cohort C: 1200 µg/kg or placebo
Part II: Extended SAD
If the maximal tolerated and/or projected therapeutic dose is not reached in Part I (SAD), 6 healthy volunteers may be enrolled in each of the additional cohorts, Cohorts D1 and D2.
Subjects in Cohort D1 will receive a single IV dose of BG00010 2400 µg/kg or placebo (5:1 ratio). Subjects in Cohort D2 will receive a single IV dose of BG00010 3600µg/kg or placebo (5:1 ratio).
Within each of the SAD and Extended SAD cohorts, up to 2 subjects may be dosed on the first day. The remaining 4 subjects may be dosed at least 10 days after the first 2 subjects. In all cases, subjects will be dosed at least 2 hours apart.

Part III: MAD
Multiple ascending SC doses of BG00010 in subjects with painful lumbar radiculopathy will be studied following a randomized, double blinded, placebo controlled approach. Five planned cohorts of 8 unique subjects and the possibility of an additional cohort of 8 unique subjects will be enrolled. Subjects will be randomized to receive 3 SC doses of BG00010 or placebo (6:2 ratio); for Cohorts E and F, administration will occur every 48 hours; for Cohorts G1, G2, G3, and G4 (if applicable) administration will occur once per week. Doses of BG00010 are planned as follows:
Cohort E: BG00010 SC 150 µg/kg or placebo
Cohort F: BG00010 SC 400 µg/kg or placebo
Cohort G1: BG00010 150 µg/kg or placebo (once per week for 3 weeks)
Cohort G2: BG00010 400 µg/kg or placebo (once per week for 3 weeks)
Cohort G3: BG00010 600 to 800 µg/kg or placebo (dosage to be determined by the Drug Safety Review Committee [DSRC]; once per week for 3 weeks)
Cohort G4 (if applicable): BG00010 up to 1100 µg/kg or placebo (dosage to be determined by the DSRC; once per week for 3 weeks)

Intervention

Intravenous and/or subcutaneous administrations of BG00010 or placebo in ascending doses (150, 400 of 1200 µg/kg) in healthy volunteers and volunteers with painful lumbar radiculopathy, possible adjusted with IV and SC doses up to 3600 µg/kg in healthy volunteers and/or SC doses up to 1100 µg/kg in

volunteers with unilateral painful lumbar radiculopathy.

Study burden and risks

Side-effects that are reported after use of BG00010 are headache, ithciness, rash and feeling warm. An immune reaction to BG00010 is possible. Within animal studies, transient neuronal vacualation was observed at the highest dose levels. No exeptional severe adverse drug reactions are expected and burden/inconvenience for the subjects are considered relatively mild. Development of BG00010 could constitute an additional therapeuric tool for treatment of sciatica.

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

All subjects
-Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
-Must be 18 to 75 years old at the time of informed consent.
-Upper weight limits the number of SC injections per dose (maximum of 2 injections per dose.;Volunteers with Painful lumbar radiculopathy:
-Subjects must have a diagnosis of painful lumbar radiculopathy, determined by the Investigator, including pain radiating down the leg following a dermatome, suggesting L4, L5, or S1 nerve root involvement. Painful lumbar radiculopathy symptoms must be present for 3 or more months prior to the Screening Visit.
-Subjects must rate their pain at 40 mm and more on the 100 mm VAS of the SF-MPQ at the Screening and Baseline Visits.
-All male and all female subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 3 months after their last dose of study treatment.

Exclusion criteria

All Subjects:
-History of or positive screening test for hepatitis C infection (defined as positive for hepatitis C virus antibody), hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or positive for hepatitis B core antibody [HBcAb] at Screening), or positive for human immunodeficiency virus (HIV) antibody. Subjects who are HBsAg negative and HBcAb positive are allowed to participate if they are positive for HBsAb immunoglobulin G (see the Centers for Disease Control and Prevention's interpretation of the hepatitis B serology panel).
-History of malignancy or clinically relevant (as determined by the Investigator) allergies; cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic (not related to painful lumbar radiculopathy), dermatologic, rheumatic/joint, psychiatric, renal, and/or other major disease.
-Relevant history of illicit drug or alcohol abuse (as defined by the Investigator) within 1 year prior to the Screening Visit. Subjects must be willing to restrain from the use of illicit drug or consumption of alcoholic beverages within 24 hours prior to dosing on Day 1, and during the inpatient period.
-History of severe allergic or anaphylactic drug-related reactions.
-History of skin or systemic condition that predisposes to have pruritus, as determined by the Investigator.
-Clinically relevant abnormal electrocardiogram (12-lead ECG) at the Screening or Baseline Visits, as determined by the Investigator, or a marked prolongation of the QT corrected (QTc) interval (i.e., repeated demonstration of a QTc interval >450 msec for females or >430 msec for males) at the Screening or Baseline Visits.
-Female subjects who are pregnant or currently breastfeeding, or who have a positive

pregnancy test result at the Screening or Baseline Visits.
-Fever (body temperature >38°C) or symptomatic viral or bacterial infection within 2 weeks prior to the Baseline Visit.
-Any live or attenuated immunization/vaccination within 28 days prior to the Baseline Visit.
-Serum creatinine >1.5 x upper limit of normal (ULN).
-Treatment with any prescription medication and/or over the-counter products such as herbal supplements, unless the dose has been stable for 2 weeks prior to the Baseline Visit.
-Previous participation in a study with neurotrophic factors including BG00010.
-Smoke >5 cigarettes or the equivalent in tobacco per day. ;Subject with Painful lumbar radiculopathy:
-History of severe pain as judged by the Investigator, other than that caused by Painful lumbar radiculopathy, during the 3 months prior to the Screening Visit.
Signs or symptoms of peripheral neuropathy, other than symptoms of Painful lumbar radiculopathy, during the 3 months prior to the Screening Visit.
-Current generalized myalgia.
-Major or lumbar radiculopathy surgery within the 3 months prior to the Screening Visit or planned painful lumbar radiculopathy surgery within 3 months after the Screening Visit.
-Selective serotonin reuptake inhibitor (SSRI), serotonin noradrenaline reuptake inhibitor (SNRI), gabapentin, pregabalin, and tricyclic antidepressant (TCA) doses must be stable for 4 weeks prior to the Baseline Visit.

Study design

Design

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):	15-04-2013
Enrollment:	78
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Neublastin

Ethics review

Approved WMO Date:	19-03-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-03-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012-005224-15-NL
CCMO	NL43543.056.13