Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants With Spinal Muscular Atrophy

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The primary objectives of this study are to examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with spinal muscular atrophy (SMA), as measured by change in Children's Hospital of Philadelphia...

Ethical review	Approved WMO
Status	Pending
Health condition type	Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)
Study type	Interventional

Summary

ID

NL-OMON51427

Source
ToetsingOnline

Brief title
232SM203 (Devote)

Condition

- Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)

Synonym
SMA, spinal muscular atrophy

Research involving
Human

Sponsors and support

Primary sponsor: Biogen Idec Research Limited
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Nusinersen, SMA, Spinal Muscular Atrophy, Spinraza

Outcome measures

Primary outcome

Part B Infantile-onset SMA:

1) Change from Baseline in Children's Hospital of Philadelphia Infant Test of

Neuromuscular Disorders (CHOP INTEND)

Secondary outcome

Part B Infantile-onset SMA:

1) Percentage HINE Section 2 Motor Milestone Responders

2) Change from Baseline in HINE Section 2 Motor Milestones Total Score

3) Time to Death or Permanent Ventilation

4) Time to Death (Overall Survival)

15) Change from Baseline in Head Circumference

16) Change from Baseline in Chest Circumference

17) Change from Baseline in Arm Circumference

33) Percentage of Time on Ventilation

35) Change from Baseline in the Parent Assessment of Swallowing Ability (PASA)

Scale

Part B Later-onset SMA:

5) Change from Baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE) Score

6) Change from Baseline in Revised Upper Limb Module (RULM) Score

7) Total number of New WHO Motor Milestones

8) Change from Baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)

9) Change from Baseline in Pediatric Quality of Life Inventory* (PedsQL)

18) Change from baseline in Ulnar Length

Part B:

10) Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

11) Number of Participants with Clinically Significant Shifts from Baseline in Clinical Laboratory Parameters

12) Number of Participants with Clinically Significant Shifts from Baseline in Electrocardiograms (ECGs)

13) Number of Participants with Clinically Significant Shifts from Baseline in Vital Signs

14) Change from Baseline in Body Length/Height

19) Ratio of Weight for Age

20) Ratio of Weight for Length

21) Ratio of Head-to-chest Circumference

22) Change from Baseline in aPTT

23) Change from Baseline in PT

24) Change from Baseline in INR

25) Change in Urine Total Protein

26) Change from Baseline in Neurological Examination Outcomes

27) Percentage of Participants with a Postbaseline Platelet Count Below the

Lower Limit of Normal on at least 2 Consecutive Measurements

28) Percentage of Participants with a Postbaseline QTcF of > 500 millisecond

(msec) and an Increase from Baseline to Any Postbaseline

Timepoint in QTcF of > 60 msec

29) Number of Hospitalizations

30) Duration of Hospitalizations

31) Clinical Global Impression of Change (CGIC)

32) Number of Participants with Serious Respiratory Events

34) Ventilator Use

Study description

Background summary

SMA is an autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk. With an incidence of 8.5 to 10.3 per 100,000 live births, it is the most common monogenetic cause of infant mortality and a major cause of childhood morbidity due to weakness in the US.

Efficacy and safety results across the nusinersen clinical development program have demonstrated an overall positive benefit-risk profile of nusinersen across a broad range of SMA phenotypes and patient populations. Nusinersen is approved in the US, Europe, and other countries and regions for the treatment of SMA in pediatric and adult patients at a recommended dosage of 12 mg administered in 3 loading doses at 14-day intervals, a fourth loading dose 30 days after the third dose, and maintenance doses every 4 months thereafter.

Pharmacokinetic (PK) and pharmacodynamic (PD) analyses indicate that nusinersen drug exposure higher than that achieved with 12 mg in patients with SMA may produce an even greater benefit in motor function. Additionally, PK modeling and simulations identified dosing regimens that achieve higher drug exposure more rapidly. Therefore, this study is being conducted to investigate the efficacy, safety, tolerability, and PK of a 50/28-mg dose of nusinersen (50-mg loading dose/28-mg maintenance dose) and a dosing regimen targeted to achieve higher drug exposure more rapidly.

Study objective

The primary objectives of this study are to examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with spinal muscular atrophy (SMA), as measured by change in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) total score (Part B)

Study design

This is a global, phase II, escalating dose and randomized-controlled study of Nusinersen (BIIB058) in participants with Spinal Muscular Atrophy.

Intervention

Participants will be assigned to either a control group (1/3) or a higher dose group (2/3):
- Control Group: Children in this group receive the approved dose and dosing schedule of the study drug. Your child will receive 6 study drug injections. This will include 4 loading doses of 12 mg study drug, followed by 2 maintenance doses of 12 mg study drug once every 4 months.
- Higher Dose group: Children in this group receive 4 study drug injections. This will include 2 loading doses of 50 mg study drug followed by 2 maintenance doses of 28 mg study drug once every 4 months.
The study drug will be administered intrathecally.

Study burden and risks

Participation in the study will last up to 11-14 months: 21 days of screening, 279 days of treatment and 23-120 days of follow-up. Participants have to visits the study site up to 9-10 times.

In addition to section E6, subjects will be subjected to: questions regarding medical history, use of concomitant medications/procedures and adverse events; urine sampling; measurement of vital signs; physical examination; neurological examination; assessment of movement abilities; SARS CoV-2 test; record of ventilator use in a diary, parental assessment of swallowing and patient

reported outcomes questionnaires.

Subjects will be expected to not take part in other medical studies, keep their appointments for visits, follow instructions from the study team, keep a patient card with them at all times. Also, subjects and parents will be asked not to talk about which group they/their child might be in.

The study drug may have following side effects: constipation, upper respiratory tract infection, pneumonia (infection of the lungs), nasopharyngitis (common cold), teething and respiratory tract infection (infections of the nose, sinuses, throat, or lungs), pyrexia (fever), headache, vomiting (throwing up) and back pain.

The following side effects are rare and can be serious:
• Serious infection such as meningitis after a lumbar puncture (LP)
• Meningitis not caused by a bacterial infection
• Hydrocephalus (a build up of too much fluid around the brain)
• Hypersensitivity (an allergic or allergic-like reaction that may include swelling, rash, or itching)

Nusinersen (Spinraza) 12 mg has a positive benefit-risk profile, with more than 4 years of postmarketing experience and more than 11,000 patients treated. The safety profile to date does not preclude study of higher doses in any population.
Anticipating a potential enhancement of benefit with the dosing regimens proposed for Study 232SM203, substantiated by PK/PD modeling described in Section 3.1.2, the safety of the loading period for Study 232SM203 is supported by a nonclinical study conducted in monkeys (Study P058-17-03). In this study, the no-observed-adverse-effect level (NOAEL) was 15 mg (human equivalent dose of 150 mg). As such, dosing for Study 232SM203 has a safety margin of at least 4.5-fold for cumulative doses during the loading period and a 3-fold margin for a single loading dose of 50 mg.

The safety of long-term exposure during the Study 232SM203 maintenance period is supported by a 53-week monkey study (Study 396443-AS06). Monkeys received a cumulative dose of 3.9, 13, and 52 mg at each dose level (0.3, 1, and 4 mg per dose, respectively) during the 52-week treatment duration. The overall NOAEL was determined to be 4 mg. Tissue concentrations measured in monkeys from the 53-week toxicology study at the NOAEL (4 mg) were compared to the estimated tissue concentrations in patients with SMA. The exposure-based safety margin is at least 1.4-fold based on exposure in the spinal cord (safety margins are higher for other tissues).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

Part B
- Genetic documentation of 5q SMA (homozygous gene deletion, mutation, or compound heterozygote)
- Participants with SMA symptom onset <= 6 months (<= 180 days) of age (infantile onset) should have age > 1 week to <= 7 months (<= 210 days) at the time of informed consent
- Participants with SMA symptom onset > 6 months (> 180 days) of age (later onset):
- Age 2 to < 10 years at the time of informed consent
- Can sit independently but has never had the ability to walk independently
- HFMSE score >= 10 and <= 54 at Screening

Exclusion criteria

Part B:
- Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening period
- Presence of an implanted shunt for the drainage of CSF or of an implanted central nervous system (CNS) catheter
- Hospitalization for surgery, pulmonary event, or nutritional support within 2 months prior to Screening or planned within 12 months after the participant's first dose
- Treatment with an investigational drug including but not limited to the treatment of SMA, biological agent, or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening or anytime during the study; any prior or current treatment with any survival motor neuron-2 (SMN2)-splicing modifier or gene therapy; or prior antisense oligonucleotide treatment, or cell transplantation
- Participants with SMA symptom onset > 6 months (> 180 days) of age (later onset)
- Respiratory insufficiency, defined by the medical necessity for invasive or noninvasive ventilation for > 6 hours during a 24-hour period, at Screening
- Medical necessity for a gastric feeding tube
- Participants with SMA symptom onset <= 6 months (<= 180 days) of age (infantile onset): Signs or symptoms of SMA present at birth or within the first week after birth

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	16-05-2022
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Spinraza
Generic name:	Nusinersen
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	31-01-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-05-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2019-002663-10-NL
ClinicalTrials.gov	NCT04089566
CCMO	NL79273.000.22