A Randomized, Blinded, Placebo-Controlled, Phase 1 Single Ascending Dose Study in Healthy Adult Male Volunteers and an Open-Label Multiple Ascending Dose Study in Pediatric SMA Participants Previously Treated with Onasemnogene Abeparvovec (Zolgensma*) to Evaluate the Safety, Tolerability, and Pharmacokinetics of BIIB115

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This study has been transitioned to CTIS with ID 2023-505643-39-00 check the CTIS register for the current data. Part A: PrimaryTo evaluate the safety and tolerability of single ascending dose of BIIB115 administered via IT bolus injection to...

Ethical review	Approved WMO
Status	Pending
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON53796

Source
ToetsingOnline

Brief title
277HV101

Condition

- Neuromuscular 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: Sponsor

Intervention

Keyword: ASM, BIIB115, PK, Safety

Outcome measures

Primary outcome

Incidence of AEs/ SAEs

Secondary outcome

Part A:

• CSF BIIB115 concentration

• CSF PK Parameters: t*

• Serum BIIB115 concentration

• Serum PK parameters: t*, AUC0-last, AUC*, Cmax, Tmax

Part B:

1. Concentration of BIIB115 in Cerebral Spinal Fluid (CSF)

2. Concentration of BIIB115 in Serum

3. Terminal Elimination Half-Life (t*) of BIIB115 in Serum

4. Area Under the Concentration-Time Curve from Time 0 to Last

Measurable Concentration (AUC0-last) of BIIB115 in Serum

5. Area Under the Concentration-Time Curve from Time 0 to Infinity

(AUCinf) of BIIB115 in Serum

6. Maximum Observed Concentration (Cmax) of BIIB115 in Serum

7. Time to Reach Maximum Observed Concentration (Tmax) of BIIB115

in Serum

Study description

Background summary

Spinal muscular atrophy (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 1 in 10,000 live births globally, it was the most common monogenic cause of infant mortality and a major cause of childhood morbidity prior to approval of treatments.

Historically, the natural history of SMA includes 4 major recognized phenotypes that are dependent on age of onset and achieved motor abilities. Type I SMA has a disease onset within the first few months of life; these children are never able to sit or walk and usually die from respiratory failure by 2 years of age. Patients with Type II SMA are able to sit but never walk unaided, with symptoms presenting between 6 and 18 months of age. Patients with Type III SMA are able to sit and walk but have limited mobility as they grow and may become disabled. Patients with Type IV SMA typically have disease onset after the age of 18 years with mild motor impairment.

SMA is caused by a homozygous deletion or, infrequently, by mutations within the SMN1 gene leading to reduced levels of the SMN protein. The SMN1 gene lies in a region of the chromosome that includes a nearly identical copy of the SMN1 gene, the SMN2 gene. The majority of the transcripts produced from the SMN2 gene lack exon 7 (Δ7 transcript), resulting in a truncated protein product that is defective and unstable. Increasing the amount of full-length transcript from the SMN2 gene is predicted to result in an increase in SMN protein in patients with SMA. Humans have a variable number of copies of the SMN2 gene (0 to 8 copies). SMN2 copy number is an important predictor of SMA disease severity,

and patients with fewer copies generally have a more severe form of the disease.

Study objective

This study has been transitioned to CTIS with ID 2023-505643-39-00 check the CTIS register for the current data.

Part A:
Primary
To evaluate the safety and tolerability of single ascending dose of BIIB115 administered via IT bolus injection to HVs

Secondary
To evaluate the single dose PK of BIIB115 administered via IT bolus injection to HVs

Part B:
Primary
To evaluate the safety and tolerability of multiple ascending doses of BIIB115 administered via IT bolus injection to participants with SMA who previously received onasemnogene abeparvovec.

Secondary
To evaluate the PK of multiple ascending doses of BIIB115 administered via IT bolus injection to pediatric SMA participants who previously received onasemnogene abeparvovec.

Study design

This is a randomized study to evaluate the safety, tolerability, and PK of BIIB115 administered via IT bolus injection to healthy adult male volunteers and pediatric SMA participants previously treated with onasemnogene abeparvovec (Zolgensma*).

Intervention

Part A:
Approximately 38 participants will be assigned to receive a single dose of either BIIB115 (10 mg, 20 mg, 40 mg, or 80 mg) or placebo (6:2 ratio for Cohort 1; 8:2 ratio for Cohorts 2 to 4).
Part B:
Approximately 24 children will be assigned to receive two doses of BIIB115 (up to 40mg or up to 80 mg)

Study burden and risks

Part A: Participants are healthy adult volunteers and will not receive any health benefit (beyond that of an assessment of their medical status) from taking part in the study. Other benefits include the contribution to science and the potential that the results of this study may contribute to the clinical development of a therapy for SMA. The risks of participation are primarily those associated with the investigational medicinal product, lumbar puncture procedure, blood draws, and other study procedures. The study has been designed with appropriate safety monitoring and stopping. The results of this study will primarily offer key insights into the safety/tolerability and PK of BIIB115 and may contribute to the clinical development of a disease modifying drug for SMA.

Part B:
For SMA participants in Part B of the study, there is the potential for direct clinical benefit from BIIB115 treatment. Studies demonstrate that intravenous (IV) onasemnogene abeparvovec transduces only a subpopulation of motor neurons in neonatal mice and patient spinal cord tissue at autopsy. BIIB115 has the potential to increase SMN protein in non-transduced motor neurons and rescue these motor neurons, which may provide added clinical benefit.

Clinically, children with SMA who have been treated with onasemnogene abeparvovec have residual motor deficits (e.g., a necessity of nutritional and ventilatory support, inability to walk unassisted). Nusinersen and onasemnogene abeparvovec have been used sequentially in select cases. The hypothesis that nusinersen after onasemnogene abeparvovec leads to improved clinical outcomes is currently being studied in the RESPOND trial (NCT04488133). Because BIIB115 has a similar mechanism of action to nusinersen with a higher potency, it may provide additional
benefit in SMA patients who have received onasemnogene abeparvovec.

Together with anticipated higher dose (supported by nonclinical data), BIIB115 is predicted to be administered less frequently than nusinersen, with a target dosing regimen of once every 12 months. This dosing regimen is expected to lead to a significant reduction in patient burden. Furthermore, greater efficacy may be observed with BIIB115 given the potential for potency-normalized exposures to be higher than with nusinersen and the relationship between exposure and efficacy. Based on the non-clinical data, risk-benefit assessment supports continued development of BIIB115 for the treatment of SMA.

Contacts

Public
Biogen Idec Research Limited

Innovation House, Norden Road 70

Maidenhead SL6 4AY
GB
Scientific
Biogen Idec Research Limited

Innovation House, Norden Road 70
Maidenhead SL6 4AY
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Part A:
1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with applicable privacy regulations.
2. Males aged 18 to 55 years, inclusive, at the time of informed consent.
3. Have a body mass index of 18 to 30 kg/m2, inclusive.
4. All participants must practice highly effective contraception as described in Section 12.5 of the protocol.
5. Must be in good health as determined by the Investigator, based on medical history and Screening evaluations.

Part B:
- Age 0.5 to 12 years old, inclusive, at the time of informed consent
- Weight =7 kg at the time of informed consent
- Genetic diagnosis of SMA (5q SMA homozygous survival motor neuron 1 (SMN1)gene deletion or mutation or compound heterozygous

mutation)- Survival motor neuron 2 (SMN2) copy number =1
- Must have received IV onasemnogene abeparvovec per the approved label or per guidelines including the steroid regimen and monitoring specified therein
- Treatment with onasemnogene abeparvovec =180 days prior to first BIIB115 dose
- Potential for improvement due to suboptimal clinical status secondary to SMA, as determined by the Investigator

Exclusion criteria

Part A: 1. Any reason, anatomical or otherwise (including abnormal hematology/coagulation), that presents increase of risk of complication from multiple LP procedures required for dosing and CSF collection, per the investigator discretion. 2. History of any clinically significant cardiac, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, or renal disease, or other major disease, as determined by the Investigator. 3. History of severe allergic or anaphylactic reactions, or of any allergic reactions that in the opinion of the Investigator are likely to be exacerbated by any component of the study treatment, including LP procedures. 4. History of, or ongoing malignancy, carcinoma in situ, or high-grade dysplasia (with the exception of no more than 1 basal cell carcinoma or squamous cell carcinoma that was completely excised and cured at least 12 months prior to randomization). Participants with cancers in remission for greater than 5 years prior to Day -1 may be included after discussion with the Sponsor. 5. Systolic blood pressure > 150 mmHg or < 90 mmHg after resting in a sitting position for at least 5 minutes at screening or prior to dosing. If out of range, testing may be repeated once at screening and once prior to dosing. 6. Clinically significant (as determined by the Investigator) 12-lead ECG abnormalities. 7. Confirmed demonstration of corrected QT interval, using Fridericia*s correction method, of > 450 ms. 8. Plans to undergo elective procedures or surgeries at any time after signing the ICF through the follow-up visit. 9. History of a suicide attempt within 5 years prior to screening or suicidal ideation in the past 6 months as indicated by a positive response (*Yes*) to either Question 4 or Question 5 of the Screening/Baseline version of the C-SSRS at screening. Participants with a history of a suicide attempt spanning more than 5 years should be evaluated by a mental health care practitioner before enrollment in the study. 10. History of, or positive test result at Screening for, HIV. 11. History of hepatitis C infection or positive test result at Screening for HCV antibody. 12. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [anti-HBc]). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HBsAg, negative

anti-HBc, and positive anti-HBs) are eligible to participate in the study. 13. Chronic, recurrent, or serious infection (e.g., pneumonia, septicemia), as determined by the Investigator, within 90 days prior to Screening or between Screening and Day -1 14. For the following parameters, if a participant has an out-of-range result that is not clinically significant (as determined by the Investigator), the test may be repeated once during the Screening period. The participant may be enrolled if the repeated result is within the reference range. • Any value for ALT, AST, bilirubin, or serum creatinine that is above the ULN at Screening or Baseline. • Any value of hemoglobin that is < 7.45 mmol/L (approx. < 12 g/dL) at Screening or Baseline. • Any value for platelets that is below the lower limit of normal at Screening or Baseline. • Any value out of normal range for absolute or differential WBC counts at screening or Baseline. Participants with absolute WBC counts within the normal range but with variations from normal ranges for differential WBC counts that are not clinically significant (as determined by the Investigator) can be included in the study. 15. Current enrollment or a plan to enroll in any interventional clinical study of a drug, biologic, or device, in which an investigational treatment or approved therapy for investigational use is administered within 3 months (or 5 half-lives of the agent, whichever is longer) prior to randomization. 16. Use of any prescription medication, over-the-counter oral medication that is known to alter hepatic or renal clearance (excluding acetaminophen/paracetamol), or nutraceutical (e.g., St. John*s wort, ginseng, ginkgo biloba) within 28 days prior to Day -1; use of other over-the-counter oral medication, vitamins, dietary supplements, or antacids within 14 days prior to Day -1; and an unwillingness or inability to refrain from this use during study participation, unless specifically permitted elsewhere within this protocol. 17. History of alcohol or substance abuse (as determined by the Investigator), a positive drug/alcohol test at Screening or Day 1, or alcohol use within 48 hours prior to randomization, or an unwillingness to refrain from alcohol 3 months after dosing, and then for the rest of the study with a limit of 6 units per week with no more than 2 units a day. An unwillingness to refrain from illicit or recreational drugs during the study. Participants who test positive for cannabinoids due to occasional marijuana use, as determined by the Investigator, and who agree to refrain from using marijuana for the duration of the study may be enrolled at the Investigator*s discretion, after consultation with Biogen. 18. History or evidence of habitual use of tobacco- or nicotine-containing products within 90 days of Screening and unwillingness to abstain for 3 months after dosing. 19. Out of the ordinary, excessive exercise (as determined by the Investigator) within 48 hours of Day -1, per Investigator discretion. 20. Three or more copies of either SMN1 or SMN2. Participants with zero SMN2 copies may be enrolled at the Sponsor*s discretion. 21. Blood donation (1 unit or more) within 90 days prior to Screening, plasma donation from 1 week prior to Screening, and platelet donation from 6 weeks prior to Screening. Part B: - Severe or serious AEs related to onasemnogene abeparvovec therapy that are ongoing during Screening - Interval of <180 days between onasemnogene abeparvovec therapy and first BIIB115 dose - Ongoing steroid treatment

following onasemnogene abeparvovec at time of screening - History of drug induced liver injury or liver failure per Hy's law definition - History of thrombotic micrangiopathy - Treatment with any SMN2-splicing modifier (nusinersen or risdiplam) after receiving onasemnogene abeparvovec. Treatment with nusinersen <12 months from the first dose of BIIB115. - Any reason, anatomical or otherwise (including abnormal hematology/coagulation),that presents increase of risk of complication from the LP procedures, CSF circulation, or safety assessments, including a history of hydrocephalus or implanted shunt for CSF drainage - Permanent ventilation, defined as tracheostomy or =16 hours ventilation/day continuously for =21 days in the absence of an acute reversible event NOTE: Other protocol defined Inclusion/Exclusion criteria may apply.

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:	Pending
Start date (anticipated):	30-08-2022
Enrollment:	42
Type:	Anticipated

Ethics review

Approved WMO

Date:	14-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	02-08-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-12-2023
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
EU-CTR	CTIS2023-505643-39-00
EudraCT	EUCTR2022-000956-12-NL
CCMO	NL81625.000.22