A Phase 1 Multiple-Ascending-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB078 Administered Intrathecally to Adults with C9ORF72-Associated Amyotrophic Lateral Sclerosis

Published: 05-03-2019
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Primary objective: To stu dy the safety and tolerability of BIIB078 in adults with C9ORF72-ALS.Secondary objective: To evaluate the pharmacokinetics (PK) profile of BIIB078 and to evaluate the effects of BIIB078 on clinical function.

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

Summary

ID

NL-OMON55647

Source
ToetsingOnline

Brief title
245AS101 - ALS

Condition

- Neuromuscular disorders

Synonym
Amyotrophic lateral sclerosis, neurodegenerative disease

Research involving

Human

Sponsors and support

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

Intervention

Keyword: ALS, MAD, Phase 1

Outcome measures

Primary outcome

Number of Participants with adverse and serious adverse events.

Secondary outcome

* Serum BIIB078 concentrations

* Serum PK parameters:

* Area under the concentration-time curve (AUC) from time 0 to infinity

* AUC from time 0 to time of the last measurable concentration

* Maximum observed concentration (Cmax)

* Time to reach Cmax

* Terminal elimination half-life (t*)

An additional secondary objective is to evaluate the effects of BIIB078 on

clinical function.

The additional secondary endpoints that relate to this objective are as follows:

* Change from baseline in ALSFRS-R scores

* Change from baseline in percent of predicted slow vital capacity

* Change from baseline in muscle strength, as measured by hand-held dynamometry

* Change from baseline in bulbar strength, as measured by the Iowa Oral

Pressure Instrument

Study description

Background summary

Amyotrophic lateral sclerosi s is a disease that causes motor nerve cells to gradually break down and die. In most patients, the cause of ALS is not known, and doctors describe patients in this group as *sporadic ALS* patients. In a separate small group of ALS patients (C9ORF72 ALS patients), the disease is caused by a genetic mutation in the C9ORF72 gene. The mutation of the C9ORF72 gene leads to the production of abnormal C9ORF72 gene products that are likely to be toxic to cells and could possibly lead to nerve cell death.

Study objective

Primary objective: To stu dy the safety and tolerability of BIIB078 in adults with C9ORF72-ALS.
Secondary objective: To evaluate the pharmacokinetics (PK) profile of BIIB078 and to evaluate the effects of BIIB078 on clinical function.

Study design

This is a Phase 1, randomized, double-blind, placebo-controlled, MAD evaluation of the safety, tolerability, and PK of BIIB078, administered via an lumbar puncture to approximately 72 subjects with C9ORF72-ALS. Up to 6 dose levels of BIIB078 will be administered 5 times, over approximately 3 months for cohorts 1 through 3, and up to 8 times over approximately 6 months for Cohorts 4, 5 and 6.

Intervention

Subjects within each of the 5 cohorts will be randomized in a 3:1 (active:placebo) ratio overall to receive BIIB078 or placebo. The first dose level was administered to 8 subjects (6 active and 2 placebo). Dose levels 2 and 3 were each administered to 12 subjects (9 active and 3 placebo). The fourth and fifth dose levels will each be administered to approximately 20 subjects (15 active and 5 placebo). Subjects who withdraw may be replaced in a cohort at the discretion of the Sponsor.
The following doses of BIIB078 are planned:
Cohort 1: 5 mg
Cohort 2: 10 mg
Cohort 3: 20 mg
Cohort 4: 35 mg

Cohort 5: 60 mg
Cohort 6: 90 mg

Study burden and risks

Given the severity of the disease and the high unmet medical need in ALS, this study will be an evaluation of BIIB078 in subjec ts
with C9ORF72-ALS. The proposed MAD study design will minimize the number of patients who are exposed to sub-therapeutic
doses and/or dosing durations. For each subject, a review of all available safety and tolerability data will be performed after the first
dose is administered, and subjects will only continue with the multiple dosing regimen if no safety concerns are noted.

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

- Ability of the participant to understand the purpose and risks of the study, to provide signed and dated informed consent, and to authorize the use of confidential health information in accordance with national and local participant privacy regulations; or, in the event of the participant's physical incapacity to sign, to confirm that understanding and consent orally to a legally authorized representative (LAR) for the express purpose of having said informed consent and authorization signed on his/her behalf.
- All participants of childbearing potential must agree to practice highly effective contraception during the study and be willing and able to continue contraception for 5 months after their last dose of study treatment.
- Must meet the possible, laboratory-supported probable, probable, or definite criteria for diagnosing ALS according to the World Federation of Neurology El Escorial criteria and have documentation of a clinical genetic test demonstrating the presence of a pathogenic mutation in C9ORF72.
-Slow vital capacity (SVC) * 50% of predicted value as adjusted for sex, age, and height (from the sitting position).
- Participants taking concomitant riluzole at study entry must be on a stable dose for * 30 days prior to the first dose of study treatment (Day 1).
- Participants taking concomitant edaravone at study entry must be on a stable dose for * 60 days prior to the first dose of study treatment (Day 1).
- ALS Cognitive Behavioral Screen (ALS-CBS) score * 11 for the cognitive portion; * 33 for the behavioral portion.
- Medically able to undergo the study procedures, and to adhere to the visit schedule at the time of study entry, as determined by the Investigator.
- Screening values of coagulation parameters including platelet count, international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (APTT) should be within normal ranges.
- Has an informant/caregiver who, in the Investigator's judgment, has frequent and sufficient contact with the participant as to be able to provide accurate information about the participant's cognitive and functional abilities at Screening.

Exclusion criteria

- History of drug abuse or alcoholism * 6 months of Screening that would limit

participation in the study, as determined by the Investigator.
- Tracheostomy.
- Prescreening ALSFRS-R slope less than 0.4 point/month, where prescreening ALSFRS-R slope is defined as follows: (48-ALSFRS-R score at Screening) / (months from date of symptom onset to date of Screening).
- History of or positive test result at Screening for human immunodeficiency virus.
- History of, or positive test result at Screening for, hepatitis C virus antibody.
- Treatment with another investigational drug or biological agent within 1 month of Screening or 5 half-lives of study agent, whichever is longer.
- Treatment with an antiplatelet or anticoagulant therapy that cannot safely be interrupted for lumbar puncture (LP) according to local standard of care and/or institutional guidelines, in the opinion of the Investigator or Prescriber.
- Current or anticipated need, in the opinion of the Investigator, of a diaphragm pacing system during the study period.
- Female participants who are pregnant or currently breastfeeding.

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):	12-07-2019
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO Date:	05-03-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-07-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	04-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-08-2021
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	EUCTR2017-000294-36-NL
CCMO	NL69083.000.19