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: 17-05-2018
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Primary objective: To study the safety and tolerability of BIIB078 in adults with C9ORF72-ALS.Secondary objective: To study the pharmacokinetics (PK) profile of BIIB078.

Ethical review	Not approved
Status	Will not start
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON46750

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

Incidence of adverse and serious adverse events.

Secondary outcome

- Serum BIIB078 concentration

- Serum PK parameters:

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

- AUC from time 0 to time of the last measurable concentration (AUClast)

- Maximum observed concentration (Cmax)

- Time to reach Cmax (Tmax)

- Terminal elimination half-life (t*)

Study description

Background summary

Amyotrophic lateral sclerosis 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 study the safety and tolerability of BIIB078 in adults with C9ORF72-ALS.
Secondary objective: To study the pharmacokinetics (PK) profile of BIIB078.

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 subjects with C9ORF72-ALS. Up to 4 dose levels of BIIB078 will be administered up to 5 times, over approximately 3 months.

Intervention

Subjects within each of the 4 cohorts will be randomized in a 3:1 (active: placebo) ratio overall to receive BIIB078 or placebo.
The first 2 dose levels will be administered to approximately 8 subjects (6 active and 2 placebo) at each level.
The third dose level will be administered to approximately 12 subjects (9 active and 3 placebo).
The fourth dose level will be administered to approximately 16 subjects (12 active and 4 placebo).

The following doses of BIIB078 are planned:
Cohort 1: 5 mg
Cohort 2: 20 mg
Cohort 3: 60 mg
Cohort 4: 120 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 subjects 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

1. Ability of the subject or his/her legally authorized representative (e.g., spouse) 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 national and local subject privacy regulations.
2. Age >= 18 years old at the time of informed consent.
3. All subjects 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. In addition, subjects should not donate sperm or eggs for the duration of the study and for at least 5 months after their last dose of study treatment.
4. 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.
5. Slow vital capacity (SVC) >= 50% of predicted value as adjusted for sex, age, and height (from the sitting position).
6. Subjects 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). Subjects taking concomitant riluzole must be willing to continue with the same dose regimen throughout the study, unless the

Investigator determines that riluzole should be discontinued for medical reasons, in which case it may not be restarted during the study.
7. Subjects 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). Subjects taking concomitant edaravone must be willing to continue with the same dose regimen throughout the study, unless the Investigator determines that edaravone should be discontinued for medical reasons, in which case it may not be restarted during the study. Edaravone may not be administered on dosing days of this study.
8. ALS Cognitive Behavioral Screen (ALS-CBS) score >= 11 for the cognitive portion; >= 33 for the behavioral portion.
9. 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.
10. 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. Coagulation tests may be repeated once at the local laboratory if, in the opinion of the Investigator, values of the initial tests are out of range but not clinically significant. Subjects with nonclinically significant and stable out-of-range values may be eligible to enroll in the study at the discretion of the Investigator, and after a consultation with the Sponsor.
11. Has an informant/caregiver who, in the Investigator*s judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject*s cognitive and functional abilities at Screening. An informant/caregiver should be available at Screening, and the participation of the informant/caregiver for the duration of the study is encouraged.

Exclusion criteria

Medical History
1. History of drug abuse or alcoholism <= 6 months of Screening that would limit participation in the study, as determined by the Investigator.
2. Tracheostomy.
3. History of a deep venous thrombosis or pulmonary embolism since the date of ALS diagnosis or <= 2 years of Screening, whichever duration is greater.
4. Ongoing medical condition (e.g., wasting or cachexia, severe anemia) that would, in the opinion of the Investigator, interfere with the conduct or assessments of the study.
5. Significant cognitive impairment or unstable psychiatric illness, including psychosis, suicidal ideation, suicide attempt, or untreated major depression <= 90 days of Screening, which in the opinion of the Investigator would interfere with the study procedures.
6. History of allergies to substances that will be used for the LP (e.g., anesthetics, if used per institutional practice).
7. Presence of risk of bleeding that could place a subject at an increased risk for intraoperative or postoperative bleeding. These could include, but are not limited to, anatomical factors at or near the LP site (e.g., vascular abnormalities, neoplasms, or other abnormalities) and underlying disorders of the coagulation cascade, platelet function, or platelet count (e.g., hemophilia, Von Willebrand*s disease, liver disease).

8. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter.
9. Presence of an implanted intravenous port/catheter.
10. Clinically significant abnormalities in hematology or blood chemistry parameters, as determined by the Investigator, which would render the subject unsuitable for enrollment.
11. Clinically significant, as determined by the Investigator, 12-lead electrocardiogram (ECG) abnormalities, including corrected QT interval using Fridericia*s correction method of >450 ms for males and >470 ms for females.
12. Alanine aminotransferase , aspartate aminotransferase , or total bilirubin levels >= 2 times the upper limit of normal. Patients with previously established Gilbert*s syndrome and elevated levels of bilirubin consistent with such syndrome are allowed in the study.
Infections
13. History of or positive test result at Screening for human immunodeficiency virus. The requirement for testing at Screening may be omitted if it is not permitted by local regulations.
14. History of, or positive test result at Screening for, hepatitis C virus antibody.
15. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody immunoglobulin G, and positive HBcAb) or vaccination (defined as positive hepatitis B surface antibody [HBsAb]) are eligible to participate in the study.
16. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period.
Medications
17. Treatment with another investigational drug (including investigational drugs for ALS through compassionate use programs) or biological agent within 1 month of Screening or 5 half-lives of study agent, whichever is longer.
18. Treatment with antiplatelet or anticoagulant therapy <= 14 days before Screening (with the exception of aspirin <= 325 mg/day) or anticipated use during the study, including but not limited to clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban.
Other
19. Current or anticipated need, in the opinion of the Investigator, of a diaphragm pacing system during the study period.
20. Female subjects who are pregnant or currently breastfeeding.
21. Concurrent enrollment in any other interventional study. Participation in a noninterventional study focused on ALS natural history may be allowed at the discretion of the Investigator and after consultation with the Sponsor.
22. Inability to comply with study requirements.
23. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

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:	Will not start
Enrollment:	3
Type:	Anticipated

Ethics review

Approved WMO

Date:	17-05-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Not approved

Date:	18-10-2018
Application type:	First submission
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	NL64964.000.18