

# A Phase 1/2 Multiple-Ascending-Dose Study With a Long-Term Open-Label Extension to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Effect on Disease Progression of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without PolyCAG Expansion in the ATXN2 Gene

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Part 1: The primary objective is to evaluate the safety and tolerability of BIIB105 in participants with amyotrophic lateral sclerosis (ALS) or poly-CAG expansion (polyQ)-ALS. Part 2: The primary objective is to evaluate the long-term safety and...

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	Neuromuscular disorders
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON52649

### Source

ToetsingOnline

### Brief title

ALSpire

## Condition

- Neuromuscular disorders

### Synonym

Amyotrophic lateral sclerosis (ALS), neurodegenerative disease

### Research involving

Human

## Sponsors and support

**Primary sponsor:** Biogen

**Source(s) of monetary or material Support:** the pharmaceutical industry

## Intervention

**Keyword:** Amyotrophic Lateral Sclerosis, Ataxin-2 Gene, BIIB105, Poly-CAG expansion

## Outcome measures

### Primary outcome

Part 1: Number of Participants with Adverse Events (AEs) and Serious

Adverse Events (SAEs)

Part 2: Number of Participants with AEs and SAEs

### Secondary outcome

Part 1: The secondary objectives are to assess the pharmacokinetic (PK) profile

in serum and cerebrospinal fluid (CSF), and to evaluate the

biomarker effect of BIIB105 in participants with ALS or polyQ-ALS.

Parts 1 and 2: The secondary objectives are to assess the long-term PK profile

of BIIB105 in serum and CSF of participants with ALS or polyQALS;

to evaluate the long-term biomarker effect of BIIB105 in participants with ALS

or polyQ-ALS, and, where relevant, to assess the impact of earlier initiation

of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of

BIIB105 (i.e., at start of Part 2) on biomarkers; to evaluate the long-term effect of BIIB105 on measures of clinical function and, where relevant to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on measures of clinical function.

#### Part 1:

1. Serum Concentration of BIIB105
2. CSF Concentrations of BIIB105
3. Area Under the Serum Concentration-Time Curve from Time Zero to Infinity (AUC<sub>inf</sub>)
4. Area Under the Serum Concentration-Time Curve From Time Zero to Time of the Last Measurable Concentration (AUC<sub>last</sub>)
5. Maximum Observed Serum Concentration (C<sub>max</sub>)
6. Time to Reach Maximum Observed Serum Concentration (T<sub>max</sub>)
7. Elimination Half-Life (t<sub>1/2</sub>) in Serum
8. Change From Baseline in Plasma Levels of Neurofilament Light Chain (NfL)

#### Integrated Parts 1 and 2:

1. CSF Through PK Concentration of BIIB105
2. Serum PK Concentration of BIIB105
3. Change From Part 1 Baseline (Cohorts D1, D2) or part 2 baseline (Cohorts A, B, C1, C2) in Plasma Levels of NfL

4. Change From Part 1 Baseline (Cohorts D1, D2) or part 2 baseline (Cohorts A, B, C1, C2) in Slow Vital Capacity (SVC)
5. Change From Part 1 Baseline (Cohorts D1, D2) or part 2 baseline (Cohorts A, B, C1, C2) in Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) Score
6. Change From Part 1 Baseline (Cohorts D1, D2) or part 2 baseline (Cohorts A, B, C1, C2) in Muscle Strength, as Measured by Handheld Dynamometry (HHD)
7. Time to Death or Permanent Ventilation
8. Time to Death
9. Time to Death, Incorporating Post-Study Withdrawal or Study Completion Vital Status Data

## Study description

### Background summary

Amyotrophic lateral sclerosis (ALS) is a disease that causes the nerve cells that control muscles (also known as motor neurons) to gradually break down and die. Motor neurons are responsible for muscle movements. In patients with ALS, as the motor neurons die, control over muscle movement is lost. 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, the disease may be at least partially caused by a mutation in a gene called Ataxin-2 (ATXN2), also known as polyQ-ALS. It has been shown that people with a mutation in the ATXN2 gene (called polyQ mutations) are at a higher risk of developing more aggressive ALS. Animal studies have shown that decreasing levels of ATXN2 were related to increased survival and improved motor function in mice.

BIIB105 is a novel ASO being developed for the treatment of ALS. The ASO targets the ATXN2-mRNA for degradation, as a means to decrease ATXN2 protein.

## Study objective

Part 1: The primary objective is to evaluate the safety and tolerability of BIIB105 in participants with amyotrophic lateral sclerosis (ALS) or poly-CAG expansion (polyQ)-ALS.

Part 2: The primary objective is to evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.

Parts 1 and 2: The primary objective is to evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.

## Study design

This is a Phase 1, randomized, double-blind, placebo-controlled, MAD evaluation of the safety, tolerability, and PK of BIIB105, administered IT to approximately 70 participants

(48 participants with ALS and 22 participants with polyQ-ALS) at approximately 13 sites globally. Up to 4 dose levels of BIIB105 will be administered up to 5 times over approximately 3 months.

Additionally, participants with polyQ-ALS (Cohort D2) must complete a 4-month or longer Natural History Run-in Period (inclusive of the Screening Period) prior to dosing.

## Intervention

Participants with ALS:

- Cohort A: BIIB105 5 mg (6 participants) or placebo (2 participants)
- Cohort B: BIIB105 20 mg (6 participants) or placebo (2 participants)
- Cohort C1: BIIB105 60 mg (9 participants) or placebo (3 participants)
- Cohort D1: BIIB105 120 mg (15 participants) or placebo (5 participants)

Participants with polyQ-ALS:

- Cohort C2: BIIB105 60 mg (3 participants) or placebo (1 participant)
- Cohort D2: BIIB105 120 mg (12 participants) or placebo (6 participants)

Participants in each cohort will receive 3 loading doses administered every 2 weeks (on Days 1, 15, and 29), followed by 2 maintenance doses administered once every 4 weeks (on Days 57 and 85), for a total of 5 doses over approximately 12 weeks.

## Study burden and risks

Participants are not expected to receive therapeutic benefit from participation in the study. The study has been designed with appropriate dose escalation, safety monitoring, and stopping rules to minimize risks to participants.

The results of this study may offer key insights into the development of a disease-modifying therapy for ALS. This is a first in human study, thus the

risk in humans is unknown.

Nonclinical work with Atxn2 homozygous knockout mice suggests that ATXN2 reduction could be associated with risks of metabolic complications (adult-onset obesity and insulin resistance) and subtle neurological deficits such as motor hyperactivity and abnormal fear conditioning [Huynh 2009; Kiehl 2006; Lastres-Becker 2008]. Human data from the Genome-Wide Association Studies database suggest that variation in ATXN2 could be associated with changes in blood pressure and cardiometabolic phenotypes [Auburger 2014]. From the nonclinical safety studies in NHPs, the adverse effect level was considered to be 60 mg based on severe but reversible and monitorable clinical signs: 1 of 3 animals exhibited increased muscle tone, whole body spasms, and tremors that required administration of diazepam. The animal fully recovered by 24 hours. No adverse metabolic effects were seen in toxicology studies. Participants will be monitored in the clinical setting with neurological and physical examinations and careful monitoring of blood chemistries, among other safety assessments. Although LP is generally considered a safe procedure, certain complications can occur in a subset of patients. These may include, but are not limited to, back pain, headache, nausea, infection, bleeding, radicular pain and numbness, and bruising or injury at the injection site. These potential risks can be mitigated by using atraumatic needles, avoiding contraindicated medications, and testing coagulation and platelet counts prior to the procedure. Importantly, life-threatening cerebral herniation is a possible complication of a lumbar puncture procedure.

## 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

Key Inclusion Criteria:

Part 1:

- Ability of the participant to understand the purpose and risks of the study and indicate informed consent, and the ability of the participant or the participant's legally authorized representative to provide signed and dated informed consent and authorization to use protected health information in accordance with national and local privacy regulations.
- All women of childbearing potential and all men must ensure that highly effective contraception is used during the study and for at least 6 months for female participants and 8 months for male participants after their last dose of study treatment.
- No known presence or family history of mutations in the the dismutase 1 (SOD1) or fused in sarcoma (FUS) genes.
- Participants in Cohorts A, B, C1 and D1, must meet the laboratory supported probable, probable, or definite criteria for diagnosing ALS according to the World Federation of Neurology El Escorial criteria (revised according to the Airlie House Conference 1998 [Brooks 2000]). Participants in Cohort C2 and D2, must meet any of the prior conditions, but may also only meet clinically possible criteria for diagnosing ALS, or exhibit weakness attributable to ALS in the presence of ataxin-2 protein (ATXN2) intermediate repeats.
- In participants in Cohorts C2 and D2, confirmed intermediate cytosineadenine-uanine/cytosine-adenine-adenine (CAG/CAA) repeat expansion in the ataxin-2 gene or RNA (ATXN2) gene as defined by at least 1 allele carrying 30 to 33 CAG/CAA repeats.
- Slow vital capacity (SVC) criteria:
  - In participants in Cohorts A, B, C1, and D1, SVC  $\geq$ 60% of predicted value as adjusted for sex, age, and height (from the sitting position).
  - In participants in Cohorts C2 and D2, SVC  $\geq$ 50% of predicted value as adjusted for sex, age, and height (from the sitting position).
- If taking riluzole, participant must be on a stable dose for  $\geq$ 30 days prior to Day 1 and expected to remain at that dose until the final study visit, unless the Investigator determines that it should be discontinued for medical

reasons, in which case it may not be restarted during the study.

- Participants taking concomitant edaravone at study entry must be on a stable dose for  $\geq 60$  days prior to the first dose of study treatment (Day1).

Participants 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.

- 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.

Part 2:

- Ability of the participant to understand the purpose and risks of the study and indicate informed consent, and the ability of the participant or the participant's legally authorized representative to provide signed and dated informed consent and authorization to use protected health information in accordance with national and local privacy regulations

- Participants must have completed Study 275AS101 Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, C2; Day 176 Visit for Cohorts D1, D2).

- Participants from Cohorts A, B, C1, and C2 must have a washout of  $\geq 16$  weeks between the last dose of study treatment received in Study 275AS101 Part 1 and the first dose of BIIB105 received in Study 275AS101 Part 2. Participants from Cohorts D1 and D2 do not require a washout period.

- If taking riluzole, participant must be on a stable dose for  $\geq 30$  days prior to Day 1 and expected to remain at that dose until the final study visit, unless the Investigator determines that it should be discontinued for medical reasons, in which case it may not be restarted during the study.

- Participants taking concomitant edaravone at study entry must be on a stable dose for  $\geq 60$  days prior to the first dose of study treatment (Day 1).

Participants 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.

- Screening values of coagulation parameters including platelet count, INR, PT, and aPTT should be within normal ranges.

NOTE: Other protocol defined Inclusion criteria may apply.



## Exclusion criteria

### Key Exclusion Criteria:

#### Part 1 :

- History or positive test result at Screening for human immunodeficiency virus (HIV).
- Current hepatitis C infection.
- Current hepatitis B infection.
- History of alcohol or substance abuse  $\leq 6$  months of Screening that would limit participation in the study, as determined by the Investigator.
- Current or anticipated need, in the opinion of the Investigator, of a diaphragm pacing system during the study period.
- Presence of tracheostomy.
- In participants from Cohorts A, B, C1, and D1, history of myocardial infarction, as determined by the Investigator.
- In participants from Cohorts A, B, C1, and D1, poorly controlled type 1 or 2 diabetes mellitus defined as HbA1c  $\geq 8\%$  during Screening.
- In participants in Cohorts A, B, and C1, prescreening ALSFRS-R slope  $> -0.4$  points/month, where prescreening ALSFRS-R slope is defined as: (ALSFRS-R score at Screening - 48) / (months from date of symptom onset to date of Screening). This criterion is not applicable for Cohorts C2, D1, and D2.
- Treatment with another investigational drug (including investigational drugs for ALS through compassionate use programs) or biological agent within 1 month or 5 half-lives of study agent, whichever is longer, before Screening.
- Treatment with an approved disease-modifying therapy for ALS other than riluzole or edaravone within 1 month or 5 half-lives of therapy, whichever is longer, before completion of screening.
- 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.
- Female participants who are pregnant or currently breastfeeding and those intending to become pregnant during the study.

#### Part 2:

- History or positive test result at Screening for HIV. If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for HIV during screening for Part 2 but are clinically symptomatic, they may enroll in Part 2 at the discretion of the Investigator.
- Current hepatitis C infection. If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for hepatitis C during screening for Part 2 but are clinically asymptomatic, they may enroll in Part 2 at the discretion of the Investigator.
- Current hepatitis B infection. If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for hepatitis B during screening for Part 2 but are clinically asymptomatic, they may enroll in Part 2 at the discretion of the Investigator.
- History of alcohol or substance abuse  $\leq 6$  months of Screening that would

limit participation in the study, as determined by the Investigator.

- Current or anticipated need, in the opinion of the Investigator, of a diaphragm pacing system during the study period.
- In participants from Cohorts A, B, C1, and D1, history of myocardial infarction, as determined by the Investigator.
- In participants from Cohorts A, B, C1, and D1, poorly controlled type 1 or 2 diabetes mellitus defined as HbA1c  $\geq$  8% during Screening.
- Treatment with another investigational drug (including investigational drugs for ALS through compassionate use programs; excluding BIIB105) or biological agent within 1 month or 5 half-lives of study agent, whichever is longer, before Screening.
- Treatment with an antiplatelet or anticoagulant therapy that cannot safely be interrupted for LP according to local standard of care and/or institutional guidelines, in the opinion of the Investigator or Prescriber.
- Female participants who are pregnant or currently breastfeeding and those intending to become pregnant during the study.

NOTE: Other protocol defined Exclusion criteria may apply.

## Study design

### Design

Study phase:	2
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):	25-09-2020
Enrollment:	10
Type:	Actual

## Ethics review

Approved WMO

Date: 03-06-2020

Application type: First submission

Review commission: CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date: 18-11-2020

Application type: First submission

Review commission: CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date: 18-03-2021

Application type: Amendment

Review commission: CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date: 14-04-2021

Application type: Amendment

Review commission: CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date: 08-09-2021

Application type: Amendment

Review commission: CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date: 09-09-2021

Application type: Amendment

Review commission: CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date: 06-05-2022

Application type: Amendment

Review commission: CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	16-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	21-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	14-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	21-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	22-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	05-08-2024
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**

<b>Register</b>	<b>ID</b>
EudraCT	EUCTR2020-000207-36-NL
CCMO	NL73598.000.20