A Phase IIIb, Open Label Extension Study Evaluating The Safety And Tolerability of AMX0035 Up To 108 Weeks In Adult Participants with Amyotrophic Lateral Sclerosis (ALS) Previously Enrolled In Study A35-004 (PHOENIX)

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To assess safety and tolerability of AMX0035 for treatment of ALS.

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

Summary

ID

NL-OMON53858

Source
ToetsingOnline

Brief title
Phase IIIb study of AMX0035 for the treatment of ALS

Condition

- Neuromuscular disorders

Synonym
Disease of nerve cells that control muscles, Neurodegenerative syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Amylyx Pharmaceuticals Inc.
Source(s) of monetary or material Support: Amylyx;Inc.

Intervention

Keyword: AMX0035, Amyotrophic Lateral Sclerosis (ALS), Safety, Tolerability

Outcome measures

Primary outcome

To assess the long-term safety and tolerability of treatment with AMX0035, based on the incidence of all adverse events, adverse events leading to discontinuation of treatment or withdrawal from the study, and all serious adverse events in participants treated with AMX0035

Secondary outcome

To assess the impact of long-term treatment with AMX0035 on survival based on:

1. Overall survival of all-cause mortality 2. Ventilation free survival (defined as death, tracheostomy for respiratory distress or permanent non-invasive ventilation [>22 hours per day for 7 consecutive days]) To assess the impact of long-term treatment with AMX0035 on measures of ALS function and key events in disease progression based on: 1. Change from baseline in ALSFRS-R score at Week 108 2. To assess the incidence rate of the following significant ALS life-events over 108 weeks: a) Tracheostomy for assisted ventilation; b) Tracheostomy for management of secretions; c) Permanent Assisted Ventilation (PAV) [defined as >22 hours daily of mechanical ventilation for more than one week (7 days)]. The date of onset of PAV is the first day of the 7 days; d) Placement of feeding tube and clinically significant (i.e., requiring

hospitalization or emergency department [ED] visit) complication/intervention (e.g., displacement, replacement, complications requiring surgical intervention); e) Placement of infusion port (in the subset of participants receiving concurrent IV edaravone) and clinically significant (i.e., requiring hospitalization or ED visit) complication/intervention (e.g., thrombosis, bleeding, infection, replacement); f) Incidence and duration of hospitalizations lasting more than 24 hours.

Study description

Background summary

ALS is a very serious and fatal condition characterized by progressive degeneration of the upper and lower motor neurons. There are limited pharmacological options in the treatment of ALS and they focus on symptom treatment. The only existing authorized medicine for treating ALS in the European Union is Riluzole.
In a randomized, Phase II, placebo-controlled trial, AMX0035 administered orally for 24 weeks as add-on treatment to Investigator selected standard of care showed statistical significant and clinically meaningful benefit on a validated functional outcome (ALS Functional Rating Scale-Revised [ALSFRS-R]), allowing participants to maintain their independence longer. Secondary endpoints measuring breathing and muscle strength showed effects in the same direction and with similar magnitude as the primary endpoint although not statistically significant. AMX0035 did not demonstrate significant safety concerns and the most notable drug-related adverse events were diarrhea and nausea

Study objective

To assess safety and tolerability of AMX0035 for treatment of ALS.

Study design

This is a phase IIIb open label extension study. Adults with clinically definite or clinically probable ALS diagnosis, who meet all inclusion and exclusion criteria, will receive AMX0035. All participants will receive

open-label treatment with AMX0035, starting on day 1 with an oral dose twice daily (once in the morning and once in the evening) for the duration of the study. After the baseline visit (day 1), enrolled participants will visit every 12 weeks (± 2 weeks) until week 108 or the end-of-treatment (EOT) visit, followed by a safety follow-up approximately 28 days after the last dose. A follow-up assessment for survival is done every 12 weeks after the EOT visit until the time of death or end of study (EOS).

Intervention

All participants will receive oral (or by feeding tube) treatment with AMX0035 (a fixed dose combination of phenylbutyrate and taurursodiol). All participants will take 2 sachets per day (one dose in the morning and one dose in the evening) starting on day 1, throughout the study (in case twice a day is poorly tolerated, more information on dose interruptions and reductions is in section 6.3).
AMX0035 is supplied by Amylyx in the form of a cardboard box containing single-use sachets for approximately 1 month. Each bag of AMX0035 contains active ingredients in a powder formulation containing 3 g phenylbutyrate and 1 g taurursodiol. The powder AMX0035 is mixed with water and taken orally (or by feeding tube).

Study burden and risks

Side effects may occur following the use of AMX0035. It cannot be ruled out that side effects may occur that are serious, long-lasting or permanent. All possibilities will be used to minimize discomfort. The following side effects have been found in patients using AMX0035 in previous studies (occurrence in 1 out of 10, or more):
- Diarrhea
- Constipation
- Nausea
- Muscle weakness
- Falls
- Headaches
- Dizziness
- Viral infection of the upper respiratory system

The most common side effects of AMX0035 in ALS patients are diarrhea and nausea (about 1 in 5 people).
The study drug may also cause side effects that are currently unknown.

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. Previous participation in Study A35-004 (PHOENIX), including completion of the randomized-controlled phase through Week 48 (this timepoint may be upcoming at the time of screening). Participants who do not complete randomized-controlled phase through Week 48 for medical reasons may be included on a case-by-case basis, in consultation with the sponsor; 2. Capable of providing informed consent; 3. Capable and willing to follow trial procedures including visits to the trial clinic, remote visits, and survival status reporting requirements; 4. Women of childbearing potential (WOCBP; e.g., not post-menopausal for at least one year or surgically sterilea must agree to use adequate birth controlb for the duration of the trial and 3 months after the last dose of AMX0035; a. 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy. b. Acceptable contraception methods for use in this trial are: - Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants; Barier

methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm); - Intrauterine device (IUD); - Abstinence (no heterosexual sex); - Unique partner who is surgically sterile (men) or not of childbearing potential (female). 5. Women must not be pregnant or planning to become pregnant for the duration of the trial and 3 months after last dose of AMX0035; 6. Men must agree to practice contraception for the duration of the trial and for at least 3 months after last dose of AMX0035; 7. Men must not plan to father a child or to provide sperm for donation for the duration of the trial and 3 months after the last dose of AMX0035.

Exclusion criteria

1. History of known allergy to phenyl butyrate or bile salts; 2. Abnormal liver function defined as bilirubin levels and/or aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 5 times the upper limit of the normal (obtained within 12 weeks from first dose); 3. Renal insufficiency as defined by eGFR <60 mL/min/1.73m2 normal (obtained within 12 weeks from first dose); 4. Pregnant women or women currently breastfeeding; 5. Current severe biliary disease which may result in the Investigator medical judgement in biliary obstruction including for example active cholecystitis, primary biliary cirrhosis, sclerosing cholangitis, gallbladder cancer, gangrene of the gallbladder, abscess of the gallbladder; 6. History of Class III/IV heart failure (per New York Heart Association - NYHA); 7. Participant under severe salt restriction where the added salt intake due to treatment would put the participant at risk, in the Investigator clinical judgment; 8. Presence of unstable psychiatric disease, cognitive impairment, dementia or substance abuse that would impair ability of the participant to provide informed consent, according to Investigator judgment; 9. Clinically significant unstable medical condition (other than ALS) (e.g., cardiovascular instability, systemic infection, untreated thyroid dysfunction, severe laboratory test anomaly or clinically significant electrocardiogram [ECG] changes) that would pose a risk to the participant if he/she were to participate in the trial, according to Investigator judgment; 10. Currently enrolled in another trial (excluding Study A35-004 (PHOENIX)) involving use of an investigational therapy (or within 5 plasma half-lives) prior to first dose at Baseline Visit; 11. Implantation of Diaphragm Pacing System (DPS); 12. Currently or previously treated within the last 30 days (or 5 half-lives, whichever is longer) from first dose at the Baseline Visit or planned exposure during the treatment period to any prohibited medications listed in Section 6.7 of the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-01-2023
Enrollment:	25
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Phenylbutyrate and Taurusodiol
Generic name:	Phenylbutyrate and Taurusodiol

Ethics review

Approved WMO Date:	11-10-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-12-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-06-2023
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-02-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2022-002348-33-NL
ClinicalTrials.gov	NCT03488524
CCMO	NL82383.100.22