Methodology Study of Novel Electrophysiological, Physical, and Imaging Outcome Measures to Assess the Progression of Amyotrophic Lateral Sclerosis

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

Summary

ID

NL-OMON43721

Source
ToetsingOnline

Brief title
Methodology

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: Biogen

Intervention

Keyword: additional outcome measures, ALS

Outcome measures

Primary outcome

The primary endpoints for each outcome measure are the longitudinal

standardized mean change from Baseline to the Month 6 Visit and the

longitudinal standardized mean change from Baseline to the Month 12 Visit. The

following outcome measures may be explored:

electrophysiological measures

* Compound muscle action potential (CMAP)

Motor unit number estimation (MUNE); optional, to be administered at each

site*s Investigator*s discretion

* Motor unit number index (MUNIX)

Respiratory measures

* Slow vital capacity (SVC)

Spinal cord MRI measures, for sites and subjects participating in the imaging

substudy only

* Volumetric measures based on structural MRI

* Region-of-interest measures based on diffusion MRI

Functional measures

* ALSFRS-R

Secondary outcome

Within-subject test-retest reliability between the 2 repeated measurements

occurring on Day 1 and Day 7 (±5 days) for each measure

* Correlations between 6- and 12-month changes in all exploratory measures with

18- and 24-month changes in ALSFRS-R and survival

* Correlation between 6-month changes for all muscle electrophysiological

measures

* Correlation between 6-month changes for all spinal cord MRI measures

Correlation between 6-month changes for all functional measures

* The standardized mean change over time of composite measures derived from

multiple domains

* Feasibility of using measures in future POC studies

Study description

Background summary

The negative result of dexpramipexole in the 2013 Phase 3 study (EMPOWER) highlighted a pattern that has been longstanding in the ALS drug development space: positive Phase 2 study results often fail to translate to Phase 3. One key determinant of this failure is the lack of reliable and predictive outcome measures appropriate for Phase 2 proof-of-concept (POC) studies in ALS. For example, the ALS Functional Rating Scale-Revised (ALSFRS-R) is a widely used

and well-regarded Phase 3 outcome measure; however, given the variability in this measure over short time intervals, and the lack of sensitivity during early and late stages of disease, the need for additional ALS outcome measures has become pressing.
This study will assess a set of potential outcome measures to determine their relative utility for incorporation into future ALS POC studies. The measures to be tested in this study have been selected based on the need to assess additional domains not presently captured by ALSFRS-R and, where available, data obtained using these measures in smaller exploratory studies.
By determining and comparing the standardized mean change over time for these measures, we hope to identify the most appropriate measures for incorporation into future Phase 2 ALS clinical studies. We also plan to examine the correlation between these novel measures and the ALSFRS-R score slope throughout the study.

Study objective

Primary:
The primary objectives of the study are to estimate and rank-order the longitudinal standardized mean changes over 6 months and over 12 months, for a set of novel outcome measures administered to subjects with ALS, in order to identify measures that are more sensitive to disease progression than ALSFRS-R. The top-ranked outcome measures will be considered for use in future ALS POC clinical studies.
The proposed outcomes include electrophysiological, muscle strength, respiratory, spinal cord magnetic resonance imaging (MRI), and functional measures.
Secondary:
The secondary objectives of this study are as follows:
* To evaluate the test-retest reproducibility of each outcome measure.
* To determine correlations between 6- and 12-month changes in all exploratory measures with 18- and 24-month changes in ALSFRS-R and survival.
* To assess correlations between/among the various measures.
* To obtain biological samples in order to identify molecular correlates to the clinical measures and to further characterize previously identified and novel molecular biomarkers of disease progression for incorporation into future clinical studies.

Study design

Study Overview
This is a longitudinal, noninterventional, nonrandomized, multicenter, prospective study conducted in subjects with ALS. Duration of study participation for each subject will be up to approximately 2 years. Subjects will be enrolled to receive a battery of electrophysiological, clinical, and functional tests, and to provide biological samples in order to assess disease

progression. Approximately 200 subjects are planned to complete the study. Approximately 250 subjects may be enrolled in order to minimize effects of attrition. A subset of up to approximately 60 subjects will be enrolled into an imaging substudy, to undergo spinal cord imaging at Baseline, Month 6, and Month 12 Visits. Subjects who drop out in the first 3 months of their participation in the study will be replaced. Additional subjects may be enrolled if any study participants choose to enroll in an interventional trial in the first 6 months of their participation in this study. Subjects who choose to participate in an interventional trial at any time after their Screening Visit will be able to continue in this study. It is anticipated that up to approximately 25 sites will be activated in the United States, Canada, and Europe.
Overall Study Duration and Follow-Up
The study period will consist of a Screening Visit; a Baseline/First Test Visit; a Retest Visit; Follow-Up Visits at Months 3, 6, 9, and 12; and Telephone Assessments at Months 1, 2, 4, 5, 18, 21, and 24.
In order to minimize the burden on subjects, some Follow-Up Visit assessments may be collected over the phone within 7 days prior to the clinic visit. These assessments may include the ALSFRS-R and concomitant medications.
Duration of participation for each subject will be approximately 2 years. The planned duration of the study overall will be approximately 38 months, which includes up to 14 months for subject enrollment and 24 months of study participation per subject.
Study Stopping Rules
Biogen may terminate this study in accordance with the CTA

Study burden and risks

For the nature and extent of the burden, please see the schedule of events section of the protocol and section E4 of this form. For the risks, please see section E9. With regards to the benefit: participation in this study, it will not mean that the subject's disease will be cured or that he /she will suffer less from his/her disease. But the subject will contribute to increased knowledge about the treatment of ALS.

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 to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Aged 18 to 80 years, inclusive, at the time of informed consent.
3. A diagnosis of sporadic or familial ALS, defined as meeting the possible, 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]). Subjects meeting the definition of possible ALS must have both upper motor neuron (UMN) and lower motor neuron (LMN) signs/symptoms in at least 1 region.
4. ALS onset within *2 years.
5. Subjects not participating in the MRI substudy must have an upright SVC *50% of predicted value for age, height, and sex.
6. Subjects participating in the MRI substudy must have an upright SVC *65% of predicted value for age, height, and sex.
7. Women of childbearing potential must practice effective contraception for at least the first 12 months of the study. Further details of contraceptive requirements for this study are provided in Section 13.5.

Exclusion criteria

1. History of or positive test result at Screening for human immunodeficiency virus (HIV).

2. History of or positive test result at Screening for hepatitis C virus (HCV) antibody or hepatitis B virus ([HBV] defined as positive for hepatitis B surface antigen [HBsAg] and hepatitis B core antibody [HBcAb]).
3. Possibility of neuromuscular weakness other than ALS.
4. Presence of significant cognitive impairment, clinical dementia, or psychiatric illness, precluding informed consent.
5. Diagnosis of other neurodegenerative disease (e.g., Parkinson*s disease, Alzheimer*s disease, etc.)
6. History of unstable or severe cardiac, pulmonary, oncologic, hepatic, or renal disease, or other medically significant illness that would affect the specified assessments.
7. Active bacterial or viral infection at Screening or a serious infection (e.g., pneumonia, septicemia) within 30 days before Screening.
8. Enrollment in an interventional study at Screening. Subjects who enroll in a Biogen interventional study subsequent to the Screening Visit may remain in this methodology study; they do not need to be withdrawn.
9. History of substance or alcohol abuse (as determined by the site Investigator) within the last year that makes the subject unsuitable for enrollment.
10. Habitual use of any tobacco product, defined as >1 cigarette per day (or equivalent) within the last year, that makes the subject unsuitable for enrollment.
11. Pregnancy.
12. Inability to comply with study requirements.
13. Unspecified reasons that, in the opinion of the site Investigator, make the subject unsuitable for enrollment or unlikely to be able to complete, at a minimum, the Month 6 Visit.
In addition to criteria 1 through 13, a subset of subjects who consent to the lumbar puncture (LP) will not be allowed to undergo the LP procedure (but may still participate in the study, if all other eligibility criteria are met) if any of the following exclusion criteria exist at Screening:
14. Use of anticoagulants, with the exception of aspirin, or presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that is not managed optimally, and could place a subject at an increased risk for intraoperative or postoperative bleeding. These can include, but are not limited to, anatomical factors at or near the LP site (e.g., vascular abnormalities, neoplasms, or other abnormalities) or abnormal platelet or coagulation test values at Screening (see study reference manual for a listing of normal ranges).
In addition to criteria 1 through 13, a subset of subjects who will participate in the spinal cord imaging substudy will be excluded from substudy entry (but may still participate in the study, if all other eligibility criteria are met) if any of the following exclusion criteria exist at Screening:
15. Presence of any condition that can interfere with subject safety, or with generating reliable MRI scans including, but not limited to, the inability to lie still for up to 90 minutes, claustrophobia, body weight exceeding 320.0 lbs. or girth exceeding the magnet bore, presence of a metal device affected by MRI (e.g., any type of electronic, mechanical or magnetic implant, cardiac pacemaker, aneurysm clips, implanted cardiac defibrillator) or potential ferromagnetic foreign body (metal slivers, metal shavings, or other metal objects).
16. Inability to complete all MRI scans (up to 12 months) due to disease burden and rate of progression, in the opinion of the site Investigator.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-10-2016
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	04-10-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
CCMO	NL54743.041.15