Prospective, Retrospective, Multicenter, Observational Study of Disease Progression in Adults with Inherited Forms of Spastic Paraplegia

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Study Objectives:• To characterize disease progression (clinical and rehabilitation) in adults diagnosed with AMN• To characterize the change in Quality of Life (QoL) parameters• To characterize the change in electrophysiological (EP) parameters• To…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON54146

Source
ToetsingOnline

Brief title
Not applicable

Condition

- Neurological disorders congenital

Synonym
Spastic paraplegia / adrenomyeloneuropathy

Research involving
Human

Sponsors and support

Primary sponsor: SwanBio Therapeutics, Ltd

Source(s) of monetary or material Support: Industry

Intervention

Keyword: Adrenoleukodystrophy, Observational, Parapegia

Outcome measures

Primary outcome

Retrospective disease-related medical history will be collected.

To assess disease progression, disease-related outcomes will be collected and assessments will include the following: physical examination (including height and weight), neurological examination, EDSS, Severity Score System for Progressive Myelopathy (SSPROM), postural body sway, miniBESTest, Timed Up and Go (TUG), 2 Minute Walk Test (2MWT), 6 Minute Walk Test (6MWT), 5Timest Sit to Stand Test (5XSST), Instrumented Gait Analysis, and overall activity and sleep data from use of a CentrePoint Insight watch. If a clinical MRI was performed during the study, the report will be collected.
Patient-reported Outcomes (PRO) assessments will include Urinary and Bowel Symptoms in ALD/AMN, Multiple Sclerosis Quality of Life-54 (MSQoL-54), Multiple Sclerosis Walking Scale-12 (MSWS-12), and Activities-specific Balance Confidence Scale (ABC).
For the Electrophysiology Sub-study, assessments will include a nerve conduction study (NCS).

Safety assessments will include the collection of concomitant medications, concomitant therapies, and study procedure-related serious adverse events

(SAEs) and adverse events (AEs).

Secondary outcome

Not applicable

Study description

Background summary

Progressive weakness and spasticity of the legs are characteristics of numerous disorders and conditions, including those that are inherited neurological disorders. Adrenomyeloneuropathy (AMN) is an example of an inherited form of spastic paraplegia.
Adrenoleukodystrophy (ALD) is a progressive neurodegenerative disorder caused by a mutation in the ABCD1 gene localized to the X-chromosome (Xq28). The ABCD1 gene encodes a peroxisomal adenosine triphosphate (ATP) binding cassette transporter responsible for transport of very long chain fatty acids (VLCFA) from the cytosol into the peroxisome for degradation. A mutation in ABCD1 results in reduction in the degradation of the VLCFA by peroxisomal β-oxidation, and saturated VLCFA, in particular C26:0, accumulate in tissues and body fluids (i.e., brain, nervous system, adrenal glands). One of the key clinical symptoms during aging of ALD patients is a slowly progressive axonopathy affecting sensory ascending and motor descending spinal cord tracts with 100% penetrance in men, an ALD phenotype knows as AMN. There are no treatment options available, which leaves AMN patients with a progressive disorder that leads to lifelong physical disability. The progressive dying-back axonopathy represents the core clinical feature of AMN, with onset usually between 20 and 30 years of age in male participants. The initial symptoms include progressive stiffness and weakness of the legs, impaired vibration and position senses in the lower limbs, falls, sphincter disturbances and impotence, as well as scarce scalp hair (alopecia). About 66% of male AMN patients have adrenocortical insufficiency (Addison disease). Abnormal magnetic resonance imaging (MRI) signals of white matter in the centrum ovale, pyramidal tracts in the brainstem and internal capsules have frequently been observed in AMN, but no gadolinium enhancement is present, indicating an intact blood-brain barrier and the absence of an acute inflammatory process.

SwanBio Therapeutics is developing SBT101, a recombinant adeno-associated virus 9 (AAV9) encoding the functional ABCD1 gene, for treatment of AMN to correct underlying gene defects in the central nervous system (CNS). Development of SBT101 has the potential to address a significant clinical need for AMN patients for whom there are no curative treatment options available.

The course of AMN-related disabilities over time is poorly or incompletely understood due to a limited number of patients and lack of treatments. This study will help obtain a better understanding of the progression of disease with AMN and facilitate efficient clinical development

Study objective

Study Objectives:
• To characterize disease progression (clinical and rehabilitation) in adults diagnosed with AMN
• To characterize the change in Quality of Life (QoL) parameters
• To characterize the change in electrophysiological (EP) parameters
• To estimate variability of outcome measures
• To support the definition of a minimal clinically important difference (MCID) for the AMN population
• To evaluate the medical-economic impact of AMN

Study design

This is an observational study to determine the natural history of AMN in adult male participants (aged >=18 years) with a confirmed diagnosis of ALD. All participants will have clinical evidence of spinal cord involvement with minimum Expanded Disability Status Scale (EDSS) score of one, and will be able to walk with <=2 walking aids for about 20 meters (EDSS = 6.5) at the Baseline Visit. Participants with evidence of active or history of cerebral inflammatory disease (with Gadolinium-enhancing lesion) will be excluded. Participants with pathologic brain lesion(s) (e.g., ischemic, neoplastic, demyelinating, etc.) other than the typical lesion of AMN will also be excluded. Typical AMN brain lesion is defined as Gadolinium non-enhancing lesion affecting corticospinal tracts.
A minimum of 80 participants will be enrolled in the study. In addition to the prospective data collection over 24 months, relevant retrospective information about clinical manifestations, gait, balance and strength assessments, laboratory values, and imaging will be extracted from the historical medical records of the participants and documented in the electronic Case Report Form (eCRF).
Participants will be asked to wear the CentrePoint Insight Watch that will collect overall activity and sleep data. Participants will undergo assessments at the clinic at the Baseline, Month 12, Month 24, Months 36, Month 48, and Month 60 visits and complete a Telemedicine Visit every 3 months (Month 3, 6, 9, 15, 18, and 21) and then every 6 months until Month 60 (Months 30, 42, and 54). The assessments performed at each visit will be as predefined by the Schedule of Assessments and include clinical, physical, and neurological examinations, assessments of gait, balance, and strength, as well as patient-reported QoL questionnaires.
The total study duration for a participant from enrollment to the last visit in

this study is expected to be approximately 60 months (±8 weeks). Patients will be asked to opt-in to long-term follow-up to Month 60 at the Month 24 visit.

Sub-study
There will be an optional Electrophysiology Sub-study in addition to the main study. The trial site and participant will need to opt in before any data is collected. Participation in the Electrophysiology Sub-study will not impact enrollment in the main study.
For this, an EP assessment will be conducted to assess the function of peripheral nerve, dorsal root ganglia, and spinal roots. The EP assessment should be performed at the Baseline, Month 12, Month 24, Month 36, Month 48 and Month 60 visit.

Study burden and risks

Participating patients will undergo additional assessments during their standard of care annual visit to the clinic. At the first (baseline) visit questionnaires will be completed as well. These questionnaires can be completed prior to the clinic visit in year 1, 2, 3, 4, and year 5.

In between the annual clinic visit there will be a video-call visit (telemedicine visit) once per quarter and once per 6 months after 2 years, during which the patient need to undergo a number of movement assessments.

During the clinic visit the following activities will take pace: Physical examination, collection of demographic data, discussion of medical history, checking eligibility criteria, discussion adverse events, discussion of concomitant medication. Thensubject will complete several questionnaires (only during baseline) and several tests related to movement capabilities will be performed.
An activity tracker, a movement sensor kit to be used for the assessments during the video call visit (Opal mobility lab), and a mobile device for completion of the questionnaires will be provided to the patient. Extensive instructions will be provided for all.

A visit to the clinic will take approximately 2 days. If needed accommodation for the subject will be provided.

The video-call visit (telemedicine visits) will take approximately 1 hour

Completion of the questionnaires will take about 1 hour.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male adults aged >=18 years
2. Diagnosed with ALD based on elevated VLCFA assay and pedigree analysis
3. Clinical evidence of spinal cord involvement with EDSS score between 1 and 6.5. The number of patients with normal pyramidal function on the Functional System Score (FSS) of the EDSS scale, or EDSS >=5.5 will be limited to 10 (ten) for each criterion.
4. The participant provided written informed consent prior to any study procedures being performed

Exclusion criteria

1. Diagnosed with cerebral inflammatory disease. Cerebral inflammatory disease is diagnosed with the presence of inflammatory (Gadolinium-enhancing) lesion(s) on a brain MRI.
Note: Absence of cerebral inflammatory disease will be confirmed at Visit 1

with review of a MRI scan or report performed within 12 months prior to the Baseline Visit.
2. In AMN participants, pathological changes identified on a brain MRI except for the abnormalities that can be observed in AMN participants.
3. Any conditions that make it impossible to perform MRI studies (including allergy to Gadolinium or contrast agents).
4. Unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, or endocrine disease (other than adrenal insufficiency) or other abnormality, which may impact the ability to participate in the study or that may potentially confound the study results. It is the responsibility of the Investigator to assess the clinical significance; however, consultation with the Medical Monitor may be warranted.
5. Participant who, in the opinion of the Investigator, has any other medical or psychological condition or social circumstances which would impair their ability to participate reliably in the assessments, or who may increase the risk to themselves or others by participating.
6. The participant is employed by SwanBio Therapeutics, Contract Research Organization (CRO), or trial site (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is an immediate family (e.g. spouse, parent, child, sibling) member of a SwanBio Therapeutics, CRO, or trial site employee.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-06-2021
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	26-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	NL76596.018.21