CYGNET: a prospective multicentre observational study of disease progression in patients with adrenomyeloneuropathy

EPO-599

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INTRODUCTION

- Adrenomyeloneuropathy (AMN) is a rare genetic disease caused by pathogenic variants in the *ABCD1* gene, which encodes a peroxisomal membrane transporter known as ABCD1 protein that transports molecules, including very long-chain fatty acids, into the peroxisomes for degradation (Figure 1).
- AMN is characterized by a predominantly progressive dying-back axonopathy that leads to lifelong disability.[1–3]
  - Symptoms include progressive stiffness and leg weakness, impaired vibration sensation and proprioception, pain, and bowel and bladder disturbances, resulting in loss of mobility and quality of life.
  - Symptoms typically occur first in adulthood and affect virtually all males and approximately 80% of females who carry the *ABCD1* gene variant.
- The natural history of AMN is poorly understood and there are currently no approved treatment options available.

STUDY HYPOTHESIS

- Quantification of AMN disease progression and investigation of efficacy of a drug during a clinical trial is challenging because of the substantial phenotypical and inter-individual variability.
- One solution to address this variability is to instrument traditional functional motor tasks (TFTs) using technology, such as wireless motion sensors, to characterize disease progression in the AMN population and define clinically relevant changes in the outcome measures.
- To further reduce the variability, the frequency of TFTs can be increased by using wireless motion sensors in the home setting.

OBJECTIVE

- To assess the natural history and disease progression of AMN, to inform future clinical trial design, including gene therapy.

Figure 1: Molecular mechanisms associated with adrenoleukodystrophy/AMN pathogenesis

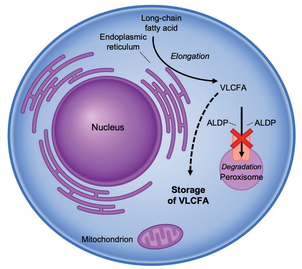


Figure adapted from: https://adrenoleukodystrophy.info/mutations-biochemistry/vlcfa
ALDP, adrenoleukodystrophy protein; AMN, adrenomyeloneuropathy; VLCFA, very long-chain fatty acid

METHODS

Study design

- CYGNET (ClinicalTrial.gov identifier: NCT05008874) is a prospective, multicentre, observational study of disease progression in patients with AMN.
- Anticipated recruitment is approximately 80 patients.
- Patient eligibility criteria are shown in Table 1.

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
Male adults aged ≥ 18 years	Diagnosed, or a history of diagnosis of, cerebral inflammatory disease
Diagnosed adrenoleukodystrophy/AMN based on elevated VLCFA assay and pedigree analysis	
Clinical evidence of spinal cord involvement with EDSS score 1–6.5	

AMN, adrenomyeloneuropathy; EDSS, Expanded Disability Status Scale; VLCFA, very long-chain fatty acid

Study endpoints

- Prospectively collected study endpoints are shown in Table 2.
- Balance and gait assessments will be completed while the patient is wearing the portable inertial sensor system Opal (Portland, OR, USA) on the lumbar spine and both feet.
  - Balance and gait variables will be calculated using Mobility Lab software.

Table 2: Study endpoints

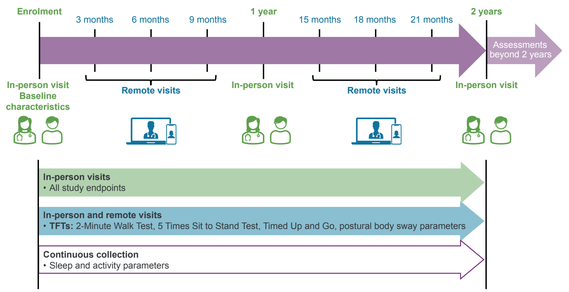
Endpoints
Change in the following variables from baseline to month 12 and month 24
• *TFTs* – 6-Minute Walk Test – 2-Minute Walk Test – Timed Up and Go – Dual Tasked Timed Up and Go – 5 Times Sit to Stand Test Assessed using the Opal (Mobility Lab), a multi-sensor system applied to the patient's lower back and feet • *Disease severity and functional impairment* – EDSS, MSWS-12, SSPROM  • *Sleep and activity parameters*  Assessed using the CentrePoint Insight Watch, a wireless Bluetooth device that will monitor activity 24 hours per day throughout the study • *Gait and balance* – Lower extremity miniBESTest, postural body sway parameters[a] • *QoL* – PGI, PGI-C, PGI-S, MSQoL-54
Change in nerve conduction parameters over 12 and 24 months[b]
Health services utilization: includes 'length of hospital stay', 'number of emergency room visits' and 'number of physiotherapy sessions'
Number of falls resulting in emergency department visit or hospitalization

[a]Assessed using the Opal (Mobility Lab) and force plate, if available
[b]Optional sub-study that trial sites and patients will need to opt in to
EDSS, Expanded Disability Status Scale; miniBESTest, Mini Balance Evaluation System Test; MSQoL-54, Multiple Sclerosis Quality of Life-54; MSWS-12, Multiple Sclerosis Walking Scale-12; PGI, Patient Global Impression; PGI-C, Patient Global Impression–Change; PGI-S, Patient Global Impression–Severity; QoL, quality of life; SSPROM, Severity Score System for Progressive Myelopathy; TFT, traditional functional motor test

Patient assessments

- Prospective endpoint assessments will be carried out during both routine, annual, in-person study visits and quarterly remote visits (Figure 2).
- Other assessments conducted throughout the study include concomitant medications/therapies, and urinary and bowel symptoms in adrenoleukodystrophy/AMN.
- Relevant retrospective information regarding clinical manifestations, gait, balance and strength assessments, laboratory results and imaging will be extracted from historical medical records using an electronic case report form.

Figure 2: Schedule of assessments



TFT, traditional functional motor test

Statistical methods

- All endpoints will be analysed using descriptive statistics.
- Rate of change over time, and estimates of between and within participant variability will be analysed.
- Univariate and multivariate analyses will be performed to:
  - identify baseline characteristics that predict accelerated progression of the disease in patients
  - explore singular or multiple parameters that demonstrate rate of change consistent with progression of disease.

RESULTS

Baseline characteristics

- Baseline characteristics for the first 21 patients enrolled in CYGNET are shown in Table 3.

Recruitment update

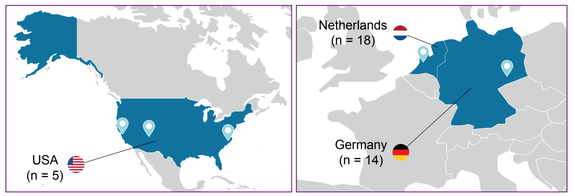
- Recruitment is ongoing, with an estimated study completion date of May 2025.
  - As of 2 June 2022, 37 patients have been recruited in Germany, the Netherlands and the USA, across five active sites (Figure 3).

Table 3: Baseline demographics and disease characteristics for initial 21 patients enrolled in CYGNET

Characteristic	Initial patients enrolled (n = 21)
Age, years, median (range)	41.0 (21–74)
Race, n (%)	
Asian	1 (4.8)
White	19 (90.5)
Unknown	1 (4.8)
Adrenal insufficiency	
Participants diagnosed, n (%)	9 (42.9)
Time since diagnosis, years, mean (SD)	14.9 (13.8)
Number of reported falls in the last year, median (range)	0 (0–104)
Participants reporting any falls in the past year, n (%)	5 (23.8)
Number of hospitalizations in the last year, median (range)	0 (0–1)
Participants hospitalized in the last year, n (%)	1 (4.8)
EDSS score	
Mean (SD)	4.26 (1.81)
1–3, n (%)	7 (33.3)
3.5–5, n (%)	5 (23.8)
> 5, n (%)	9 (42.9)

EDSS, Expanded Disability Status Scale; SD, standard deviation

Figure 3: Enrolment by country



Markers indicate active site locations, and n values denote patients enrolled

CONCLUSIONS

- CYGNET is an ongoing prospective, multicentre, observational study of patients with AMN designed to assess disease progression and inform future therapeutic clinical trial design, including gene therapy.

For more information,
look up NCT05008874 on ClinicalTrials.gov
or
contact us at clinicaltrials@swanbiotx.com

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References: 1. van Geel BM *et al. Ann Neurol* 2001;49:186–94; 2. Berger J *et al. Biochimie* 2014;98:135–42; 3. Corre CS *et al. Orphanet J Rare Dis* 2021;16:14

Abbreviations: ALDP, adrenoleukodystrophy protein; AMN, adrenomyeloneuropathy; EDSS, Expanded Disability Status Scale; miniBESTest, Mini Balance Evaluation System Test; MSQoL-54, Multiple Sclerosis Quality of Life-54; MSWS-12, Multiple Sclerosis Walking Scale-12; PGI, Patient Global Impression; PGI-C, Patient Global Impression–Change; PGI-S, Patient Global Impression–Severity; QoL, quality of life; SD, standard deviation; SSPROM, Severity Score System for Progressive Myelopathy; TFT, traditional functional motor task; VLCFA, very long-chain fatty acid

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