Initial Safety Results from the PROPEL Trial Evaluating SBT101 as a Potential Gene Therapy for Spinal Cord Disease in Adult Males with X-linked Adrenoleukodystrophy

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Poster #857

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Introduction and Background

- X-linked adrenoleukodystrophy (ALD) is a progressive neurodegenerative disorder caused by pathogenic variants in the *ABCD1* gene, which is localized to the X chromosome and encodes the ALDP protein[1].
- Patients with ALD can develop a leukodystrophy, adrenal failure, progressive peripheral neuropathy and spinal cord disease with or without cerebral involvement[1].
- When cerebral involvement has not been documented, this phenotype has historically been referred to as adrenomyeloneuropathy (AMN).
- There are currently no treatments for AMN, leaving patients with a progressive disease that leads to lifelong physical disability.

Molecular mechanisms associated with AMN pathogenesis

ALDP transports very long chain fatty acids (VLCFA)-CoA esters into the peroxisome for degradation.

Absence of functional *ABCD1* leads to:

1. Increased VLCFA levels
2. Axonal degeneration in the long tracts of the spinal cord
3. Adrenal failure

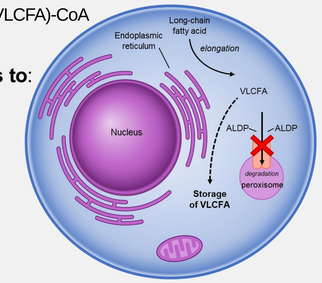


Figure1. adapted from: https://adrenoleukodystrophy.info/mutations-biochemistry/vlcfa
ALDP, adrenoleukodystrophy protein; AMN, adrenomyeloneuropathy; VLCFA, very long-chain fatty acid

SBT101

- SBT101 is a AAV9 vector delivering the functional **human *ABCD1*** gene, designed to restore ABCD1 protein expression in spinal cord cells, with the aim of halting disease progression or improve neurological pathology in adrenomyeloneuropathy (AMN).
- Preclinical studies in AMN mouse models have shown that SBT101 enables widespread spinal cord delivery, rapid transgene expression, and reduction of very long-chain fatty acids (VLCFAs).[2-4]

SBT101: a rAAV9 vector encoding the human *ABCD1* gene

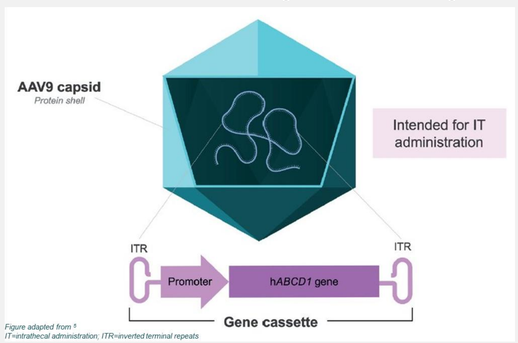


Figure adapted from [5]
IT=intrathecal administration; ITR=inverted terminal repeats

PROPEL: Phase 1/2 First in Human Clinical Study

Study Overview

Eligibility

***Key Inclusion*:**
- Men age 18-65 years
- Genetic diagnosis of AMN
- Myelopathy of mild to moderate severity
- EDSS score between 1 and 4.5

Key Exclusion:
- Individuals with evidence or a history of cerebral inflammatory disease
- Participation in other interventional studies
- Co-Morbidities (Cardio, Diabetes)

Methodology

Cohorts:
- **Low Dose (LD):** 1.0 × 10^{14} vg (total)
- **High Dose (HD):** 3.0 × 10^{14} vg (total)

Route of Administration: Intrathecal SBT101 infusion (Day 1)

Prophylactic Immune Management protocol:
- Day -1 to Day 90: IV methylprednisolone x 3 days, then oral prednisone/prednisolone (0.5 mg/kg/day) through at least Day 90, followed by a standard taper.

Endpoints:
- **Primary:** Safety and tolerability
- **Secondary:** Clinical assessments of mobility, bladder/bowel function, imaging, patient-reported outcomes, and biomarkers of response

Clinical Study Sites

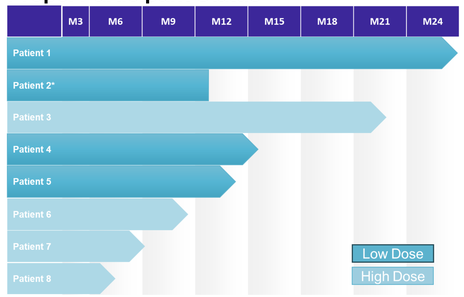
- University of Massachusetts Medical Center (UMass) • Amsterdam Medical Center (AMC)

Table 1: Patient demographics and baseline features — Low Dose | High Dose

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age at study entry	26	19	36	36	32	33	36	35
Age of diagnosis	22	18	31	34	28	32	11	32
Age at symptom onset	23	17	31	32	23	23	23	33
ABCD1 Mutation	C.1652G>A; P.GLY551ASP	C.1237G>C; P.ALA413PRO	C.146_159DEL; P.PRO49HISFS*141	C.1224+1G>T	C.892G>A; P.GLY298SER	P.LYS624FS	C.1390C>T P.ARG464*	C.1224+1G>T
Baseline EDSS	3.0	2.5	2.5	3.5	4.0	3.0	4.0	2.0
Baseline 6MWT (meters)	245	396	382.8	555	470	550	384	505
Baseline 5XSTS (seconds)	20	N/A	18.6	17	16.2	16.6	20.6	13.6
Baseline TUG (seconds)	18	N/A	10.3	11.6	11.6	7	9.4	8.6

6MWT: 6-minute Walk Test; 5xSTS: Five Times Sit to Stand Test; EDSS: Expanded Disability Status Scale; TUG: Timed Up and Go Test

Propel Participant Status



*As of 01 May 2025; *Patient died 05APR24*

Safety Overview

	Cohort 1 Low Dose N out of 4 (%) [Events]	Cohort 2 High Dose N out of 4 (%) [Events]
Participants With at Least One TEAE	4 (100) [93]	4 (100) [70]
Participants With Serious TEAEs	3 (75.0) [5]	1 (25.0) [1]
cALD conversion/progression	1[a] (25.0) [1]	1[b] (25.0) [1]
Deaths - All Causes	1[a] (25.0) [1]	0

Data cutoff: 2025-04-21

a) **Patient 2:** a 20-year-old male who received low-dose SBT101 and subsequently experienced gradual cerebral disease progression and systemic complications over 10 months. MRI showed progressive T2/FLAIR hyperintensities consistent with cALD without acute findings (no gadolinium enhancement on MRI). He was later found deceased at home; autopsy confirmed AMN/cALD, and the death was attributed to acute aspiration, deemed unrelated to study treatment.

b) **Patient 3:** a 36-year-old male who received high-dose SBT101. While initially stable, MRI at Month 18 showed progressive corticospinal tract T2/FLAIR hyperintensity and new midbrain gadolinium enhancement, suggestive of early cerebral involvement. The participant remains neurologically stable.

Safety Outcomes

Most Frequent TEAEs [N ≥ 3 events (in either cohort)]

Preferred Term	Cohort 1 (n=4): Low Dose N (%) [Events]	Cohort 2 (n=4): High Dose N (%) [Events]
Headache	3 (75.0) [4]	4 (100) [4]
Muscular weakness	2 (50.0) [2]	3 (75.0) [4]
Musculoskeletal stiffness	2 (50.0) [4]	2 (50.0) [2]
Micturition urgency	3 (75.0) [3]	1 (25.0) [1]
Interferon gamma assay positive	2 (50.0) [4]	1 (25.0) [1]
Back pain	2 (50.0) [3]	1 (25.0) [1]
Influenza	1 (25.0) [2]	2 (50.0) [2]
Acne	1 (25.0) [1]	2 (50.0) [2]
Asthenia	1 (25.0) [1]	2 (50.0) [2]
Fatigue	1 (25.0) [1]	2 (50.0) [2]
Insomnia	2 (50.0) [2]	1 (25.0) [1]
Paraesthesia	0	3 (75.0) [3]

Data cutoff: 2025-04-21

Serious Treatment Emergent Adverse Events* (TEAEs)

Serious TEAEs ≥1	Cohort 1 Low Dose N out of 4 (%) [Events]	Cohort 2 High Dose N out of 4 (%) [Events]
At Least One Serious TEAE	3 (75.0) [5]	1 (25.0) [1]
Individual Events:		
Gastroenteritis	1 (25.0) [1]	0
Pyelonephritis	1 (25.0) [1]	0
Muscular Weakness	1 (25.0) [1]	0
Myelitis Transverse	1 (25.0) [1]	0
Aspiration	1 (25.0) [1]	0
Deep Vein Thrombosis	0	1 (25.0) [1]

*All Serious TEAEs were deemed unrelated to study drug by the investigator

Data cutoff: 2025-04-21

Laboratory Values- Potentially Clinically Significant

Lab Parameter	Criteria Threshold	Cohort 1 : Low Dose N out of 4 (%)	Cohort 2: High Dose N out of 4 (%)
Hematology		0	0
Hemoglobin (g/L)	<80 or > 40 (& > ULN)	0	0
White Blood Cell Count (/uL)	< 2000 or > 35000	0	0
Platelet Count (/uL)	< 50000 or > 999000	0	0
Chemistry			
ALT (U/L)	> 2 x baseline	2 (50.0)	0
Alkaline Phosphatase (U/L)	> 2 x ULN	0	0
Total Bilirubin (mcmol/L)	> 2 x ULN	0	0
Creatinine (mcmol/L)	> 2 x ULN	0	1 (25.0) [1]

Data cutoff: 2025-04-21

Safety Summary (based on currently available data)

- **SBT101 infusion procedure was generally well tolerated. There were no events of infusion-related or hypersensitivity reactions.**
- **Prophylactic immune suppression with corticosteroids lasted approximately 5-6 months (mean) for participants that have completed this stage of treatment.**
- **All Serious TEAEs were considered "unlikely" or "unrelated" to SBT101.**
- **There were no clinically significant laboratory abnormalities observed.**

Safety Outcomes (Cont.)

Vector DNA Shedding

Participant ID (Low Dose / High Dose)	Blood: Vector DNA Max (copies/mL) [Visit]	Blood: First Negative Shedding <LLOQ [Visit]	Saliva: Vector DNA Max (copies/mL) [Visit]	Saliva: First Negative Shedding <LLOQ [Visit]
Patient 1	297,866 [Day 8]	Day 22	223,200 [Day 8]	Day 30
Patient 2	323,995 [Day 8]	Day 22	35,278 [Day 8]	Day 90
Patient 3	12,225,432 [Day 8]	Day 22	37,079 [Day 8]	Day 15
Patient 4	400,450 [Day 8]	Day 22	<LLOQ	Day 8
Patient 5	4,225 [Day 15]	Day 45	<LLOQ	Day 8
Patient 6	N/A	N/A	N/A	N/A
Patient 7	N/A	N/A	N/A	N/A
Patient 8	N/A	N/A	N/A	N/A

Urine (data not shown): All available samples were < LLOQ

NA: Not available (not yet collected/analyzed)
Data cutoff: 2025-04-21

Vector DNA shedding peaked early and cleared in blood and saliva within ~30–90 days. All urine samples were consistently below the lower limit of quantification (LLOQ), supporting a favorable safety profile by reducing the risk of secondary transmission or environmental exposure.

Conclusions

PROPEL is an ongoing Phase 1/2 trial evaluating the safety and efficacy of SBT101 gene therapy for adult males, administered as a one-time, intrathecal treatment.

Based on currently available data:

SBT101 was generally well tolerated at both low and high dose levels evaluated.
- All participants experienced at least one TEAE, **most of which were non-serious**.
- Common TEAEs were **mild to moderate** and were consistent with common or expected events related to disease and immunosuppression used in the study.
- **No clear dose-response relationship** with regards to safety. Serious adverse events were more frequent in the low-dose cohort (3 of 4 participants) compared to the high-dose cohort (1 of 4).
- No clinically significant **laboratory abnormalities** were observed.

Vector DNA shedding peaked early and cleared in blood and saliva within ~30–90 days. All urine samples were consistently below the lower limit of quantification (LLOQ).

Evidence of **cALD progression** was observed in two participants: one in the low-dose group (non-enhancing brain lesions, motor function loss, and death deemed unrelated to study treatment), and one in the high-dose group (enhancing brain lesion).

References

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