# An AAV9 encoding human ABCD1 (SBT101) shows functional improvement following spinal cord delivery in a rodent model of adrenomyeloneuropathy

Poster Tu-34

A Pujol,[1] A Bosch,[2] IME Dijkstra,[3] S Kemp,[3] YRJ Jaspers,[3] S Verdés,[2] S Fourcade,[1] C Guilera,[1] M Leal-Julià,[2] A Onieva,[2] V Vasireddy,[4] SW Clark,[4] DW Anderson,[4] K Kozarsky[4]

[1]Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, Barcelona, Spain; [2]Department of Biochemistry and Molecular Biology and Institute of Neurosciences, Universitat Autònoma de Barcelona, Bellaterra, Spain; [3]Laboratory Genetic Metabolic Diseases, Department Clinical Chemistry, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [4]SwanBio Therapeutics, Inc., Philadelphia, PA, USA

## INTRODUCTION

- Adrenomyeloneuropathy (AMN) is an inherited neurodegenerative disease caused by mutations in the gene that encodes the ABCD1 protein, and is characterized by a slowly progressive spastic paraparesis in adults that ultimately leads to a loss of mobility, incontinence and debilitating pain.[1–3]
  - Symptoms of AMN typically occur first in adulthood and affect virtually all males with the mutation and > 80% of females with the mutation.
  - The *ABCD1* gene encodes a peroxisomal membrane protein that transports very long-chain fatty acids (VLCFAs) into the peroxisome.
  - Loss of ABCD1 function owing to mutations can lead to VLCFA accumulation within affected organs, oxidative stress at the cellular level and inflammatory demyelination in the spinal cord.
- There is currently no treatment for AMN, leaving patients with progressive neurodegeneration and lifelong disability.
- We are developing SBT101, an adeno-associated virus serotype 9 (AAV9)-based gene therapy encoding a functional copy of the h*ABCD1* gene, as a candidate treatment for patients with AMN (Figure 1).
- Here, we assessed the effect of SBT101 in a double-knockout (DKO) mouse model of AMN that exhibits key behavioral features of the human disease and increased VLCFA levels.

**Figure 1:** Structure of SBT101

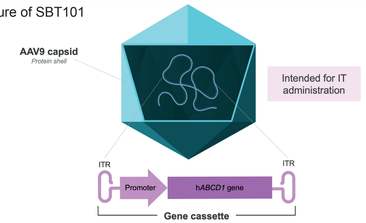



Figure adapted from Li C and Samulski RJ. *Nat Rev Genet* 2020;21:255–72. The promoter was CAG
AAV9, adeno-associated virus serotype 9; ATP, adenosine triphosphate; CAG, cytomegalovirus immediate–early enhancer/chicken β-actin promoter/chimeric intron; h*ABCD1*, human ATP-Binding Cassette sub-family D Member 1; IT, intrathecal; ITR, inverted terminal repeat

## Objective

- To evaluate the dose-dependent effect of intrathecally administered AAV9-hABCD1 (SBT101) on the behavior and function of *Abcd1*/*Abcd2* DKO mice (*Abcd1*$^{-/y}$/*Abcd2*$^{-/-}$) compared with AAV9-Null vector administered to both wild type (WT) and DKO control mice.

## Methods

- DKO male mice aged 7–8 months received a single lumbar intrathecal (IT) bolus administration of SBT101 (3.3E10 vector genomes [vg]/animal [an] or 3.3E11 vg/an).
- Control WT and DKO male mice received empty vector (AAV9-Null; 1.5E11 vg/an).
- Animal grip strength was evaluated at 15 months and 18 months of age, followed by *post mortem* analysis of h*ABCD1* messenger RNA expression and VLCFAs in lumbar spinal cord.

## Results

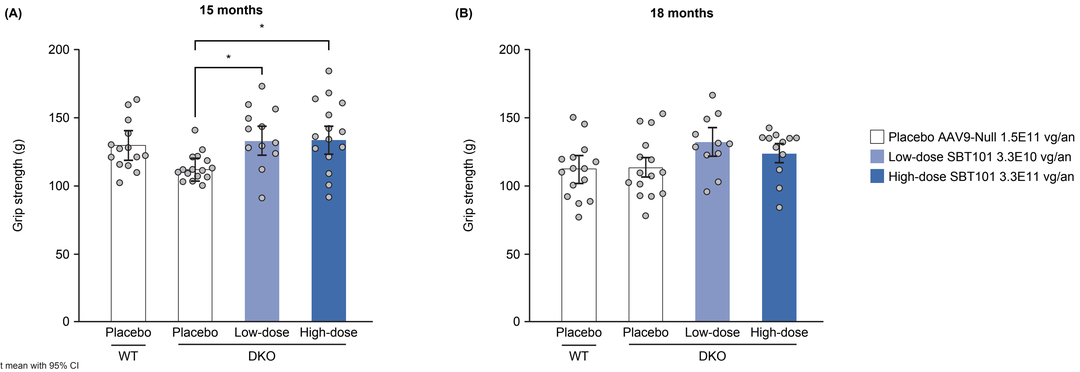
### Treatment tolerance

- IT administration of SBT101 at doses up to 3.3E11 vg/an and of AAV9-Null at 1.5E11 vg/an were well tolerated by DKO and WT mice, respectively.

### Improved grip strength

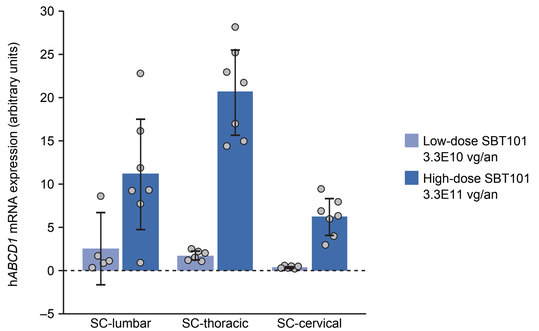
- In DKO mice, SBT101 at 3.3E10 vg/an and 3.3E11 vg/an significantly ($p < 0.01$) increased four-paw grip strength at 15 months of age compared with AAV9-Null controls, in a non-dose-dependent manner (Figure 2A).
  - Grip strength was maintained at 18 months of age (Figure 2B).
  - Improvements in grip strength after SBT101 administration within DKO mice approached the level of grip strength observed in WT mice.

**Figure 2:** Effect of SBT101 on grip strength in DKO mice at (A) 15 months and (B) 18 months of age



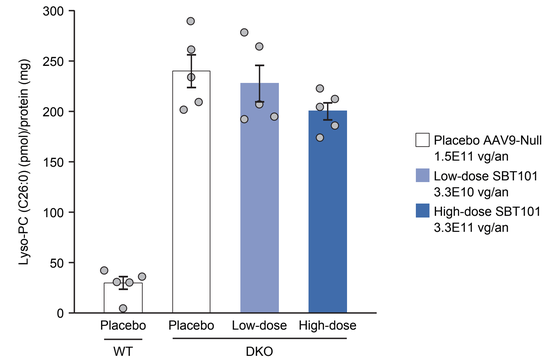

Data represent mean with 95% CI
*$p < 0.01$
AAV9, adeno-associated virus serotype 9; an, animal; CI, confidence interval; DKO, double knockout; g, grams; vg, vector genomes; WT, wild type

**Figure 3:** Effect of SBT101 on h*ABCD1* mRNA expression in DKO mice at 18 months of age




Data represent mean with 95% CI
an, animal; CI, confidence interval; DKO, double knockout; ATP, adenosine triphosphate; h*ABCD1*, human ATP-Binding Cassette sub-family D Member 1; mRNA, messenger RNA; SC, spinal cord; vg, vector genomes

**Figure 4:** Effect of SBT101 on VLCFA levels in DKO mice at 18 months of age




Data represent mean with 95% CI
AAV9, adeno-associated virus serotype 9; an, animal; CI, confidence interval; DKO, double knockout; lyso-PC, lysophosphatidylcholine; vg, vector genomes; VLCFA, very long-chain fatty acid; WT, wild type

### Increase in h*ABCD1* mRNA expression

- Administration of SBT101 was associated with a dose-dependent increase in h*ABCD1* messenger RNA (mRNA) expression in the lumbar, thoracic and cervical spinal cord of DKO mice at approximately 10–11 months after administration (Figure 3).

### Reduction in VLCFA levels

- Compared with AAV9-Null vector, administration of SBT101 was associated with trends towards dose-dependent reductions in VLCFA levels in the lumbar spinal cord of DKO mice at approximately 10–11 months after administration (Figure 4).
  - VLCFA levels were reduced by 5% and 16%, respectively, with SBT101 doses of 3.3E10 vg/an and 3.3E11 vg/an.

## CONCLUSIONS

- IT delivery of SBT101 to DKO mice (*Abcd1*$^{-/y}$/*Abcd2*$^{-/-}$) demonstrated a dose-dependent improvement in four-paw grip strength, and an increase in h*ABCD1* mRNA expression and a reduction in VLCFA levels in the spinal cord.
  - These findings are consistent with previous studies reporting functional improvement and reduction in VLCFA levels.[4,5]
- These data support further preclinical development of SBT101 as a candidate treatment for patients with AMN.

**Author contributions:** All authors have made substantial contributions to study conception/design, drafting the poster or revising it critically for scientific accuracy and important intellectual content, and have provided their final approval

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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; 4. Gong Y *et al. Mol Ther* 2015;23(Suppl 1):824–34; 5. Gong Y *et al. Mol Ther* 2016;24:S118–9.

**Abbreviations:** AAV9, adeno-associated virus serotype 9; AMN, adrenomyeloneuropathy; an, animal; ATP, adenosine triphosphate; DKO, double knockout; h*ABCD1*, human ATP-Binding Cassette sub-family D Member 1; IT, intrathecal; ITR, inverted terminal repeat; lyso-PC, lysophosphatidylcholine; mRNA, messenger RNA; SC, spinal cord; SD, standard deviation; SEM, standard error of the mean; vg, vector genome; VLCFA, very long-chain fatty acid; WT, wild type

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