Selection of clinical doses for SBT101, an AAV9-hABCD1 vector for the treatment of adrenomyeloneuropathy

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Disclosures

- **DW Anderson** – employee and stock/shareholder of SwanBio
- **CA Maguire** – received financial interests/consultancy fees from Chameleon Biosciences, Skylark Bio and Sphere Gene Therapeutics; received research support/grants from BridgeBio, Capital, SwanBio and Waypoint; is an advisory board member/received consultancy fees from CLS Therapeutics; and received royalties for licensing agreements from BridgeBio, Partners Healthcare, Skylark Bio, Sphere Bio and SwanBio
- **C Ng** – has nothing to disclose
- **Y Gong** – has nothing to disclose
- **F Eichler** – received research support/grants from ASPA Therapeutics, Bluebird Bio, Ionis Pharmaceuticals, Minoryx, Sio Pharmaceuticals; received consultancy fees from Autobahn, Poxel, SwanBio, Takeda, Taysha, UpToDate; is a founder of and stock/shareholder in SwanBio
- **S Fourcade** – has nothing to disclose
- **C Guilera** – has nothing to disclose
- **A Pujol** – received research support/grants and consultancy fees from SwanBio
- **A Onieva** – has nothing to disclose
- **M Leal-Julià** – has nothing to disclose
- **S Verdés** – has nothing to disclose
- **A Bosch** – received research support/grants and consultancy fees from SwanBio
- **IME Dijkstra** – has nothing to disclose
- **S Kemp** – received research support/grants and consultancy fees from SwanBio
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Introduction

- Adrenomyeloneuropathy (AMN) is a slowly progressing spinal cord disease
  - Characterized by a dying-back axonopathy leading to sensory ataxia and progressive spastic paraplegia, loss of mobility, incontinence, pain and sexual dysfunction
  - Symptoms typically occur in adulthood
- AMN is caused by mutations in the *ABCD1* gene, which encodes a peroxisomal membrane transport protein called adrenoleukodystrophy protein
  - ABCD1 transports very-long-chain fatty acids (VLCFAs) from the cytosol into the peroxisome for degradation
- Currently, there are no approved therapies available for AMN

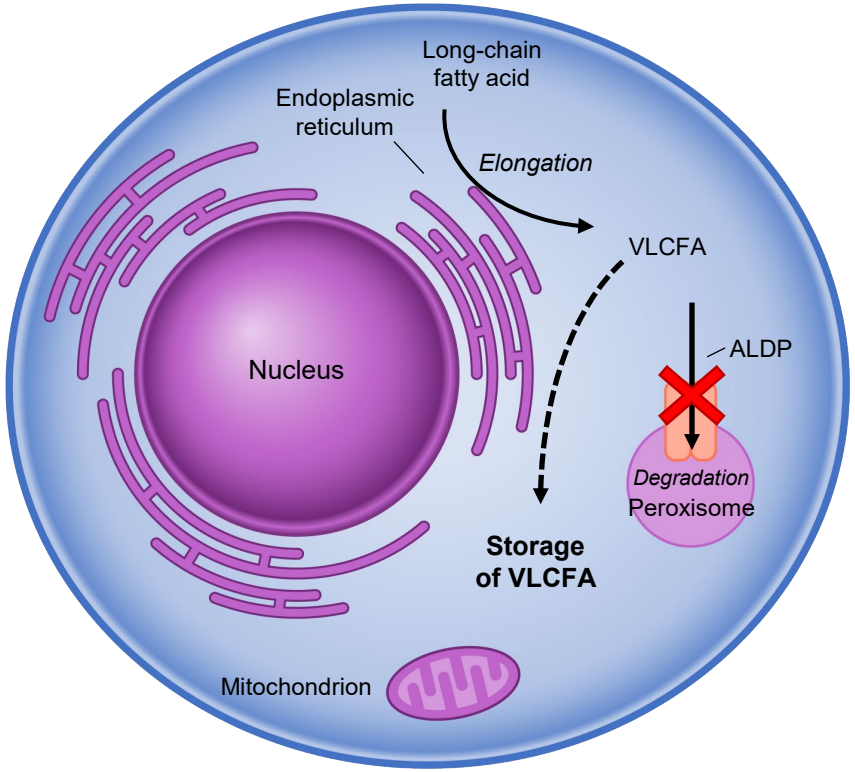
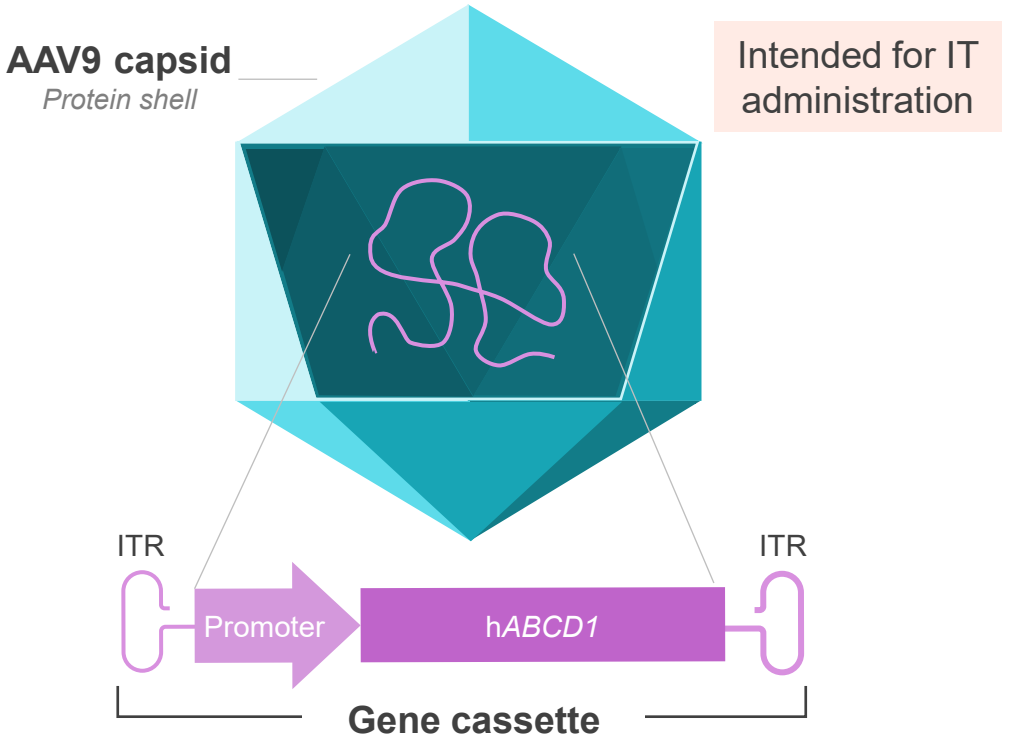


Figure adapted from: https://adrenoleukodystrophy.info/mutations-biochemistry/vlcfa
ABCD1, ATP-Binding Cassette sub-family D Member 1; ALDP, adrenoleukodystrophy protein; AMN, adrenomyeloneuropathy; ATP, adenosine triphosphate; VLCFA, very long-chain fatty acid

Adeno-associated Virus (AAV) Gene Therapy

- We are developing SBT101, an AAV9-based gene therapy encoding a functional copy of the hABCD1 gene, as a candidate treatment for patients with AMN
- Proof of concept on the potential benefit of AAV9-ABCD1 gene addition was previously shown in vitro and in vivo using the known AMN mouse model[1,2]

Objective: To determine clinical doses for SBT101 in a planned phase 1/2 study in patients with AMN, based upon efficacy, biodistribution and safety data from multiple preclinical studies in mice and nonhuman primates (NHPs)

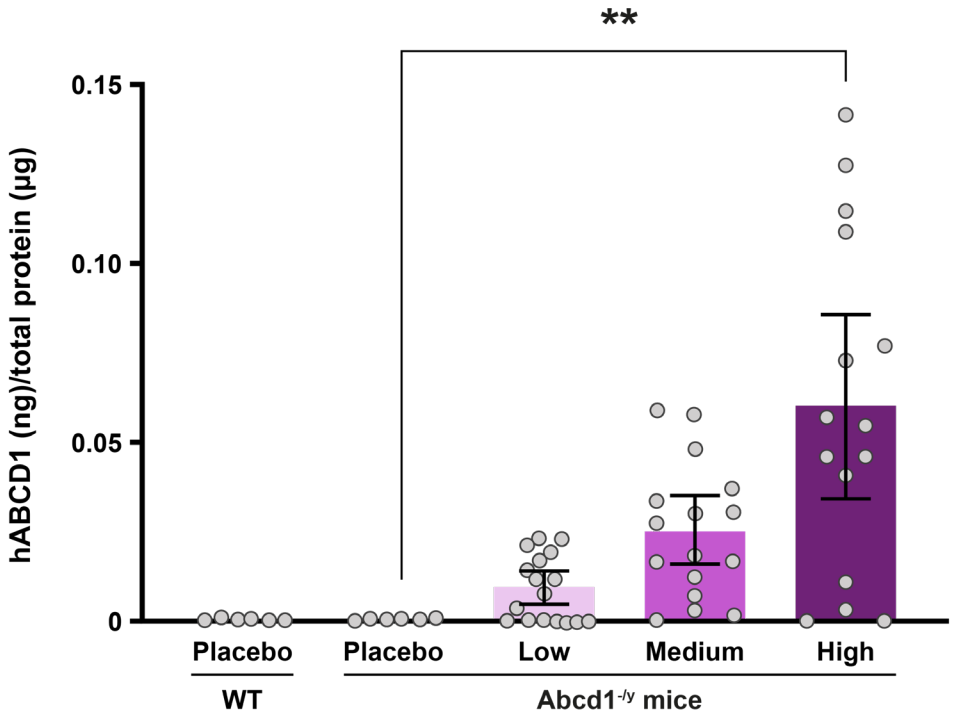


[1]Gong *et al. Mol Ther* 2015;23(5):824–34; [2]Gong *et al. Hum Gen Ther* 2019;30(5):544–55.
Figure adapted from: Li and Samulski. *Nat Rev Genet* 2020;21:255–72
AAV9, adeno-associated virus serotype 9; AMN, adrenomyeloneuropathy; ATP, adenosine triphosphate; h*ABCD1*, human ATP-Binding Cassette sub-family D Member 1; IT, intrathecal; ITR, inverted terminal repeat; NHP, nonhuman primate

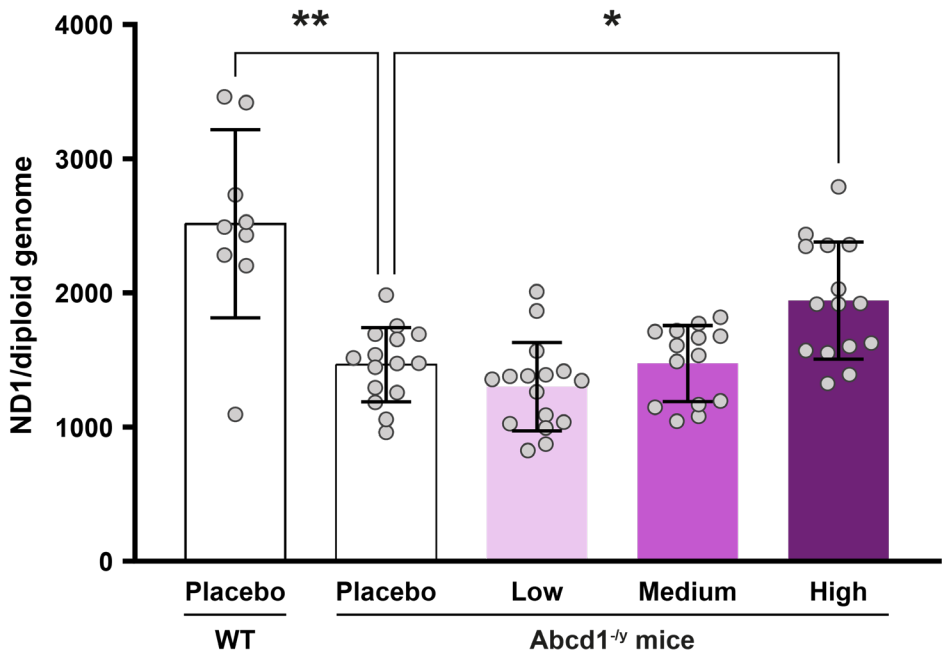
Effect of SBT101 in *Abcd1*-knockout Mice

Single IT injection of SBT101 at 2.0E9, 6.0E9 or 2.0E10 vg/an in *Abcd1*-knockout mice aged 20–23 months, 8 weeks in life

Dose-dependent increase in hABCD1 protein at 8 weeks post dosing



Improvement in mitochondrial DNA levels at 8 weeks post dosing



One-time SBT101 dose

Low	2.0E9 vg/an
Medium	6.0E9 vg/an
High	2.0E10 vg/an

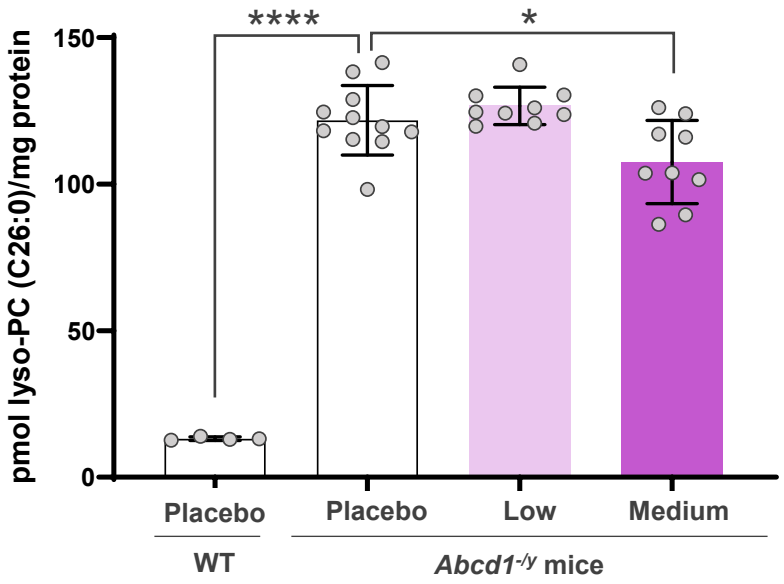
Data represent mean ± 95% CI
*$p < 0.01$; **$p < 0.0001$: one-way analysis of variance followed by Dunnett's *post hoc* test versus placebo
an, animal; ATP, adenosine triphosphate; CI, confidence interval; hABCD1, human ATP-Binding Cassette sub-family D Member 1; NADH, nicotinamide adenine dinucleotide; ND1, NADH dehydrogenase 1; vg, vector genomes; WT, wild type

VLCFA Levels in *Abcd1*-knockout Mice

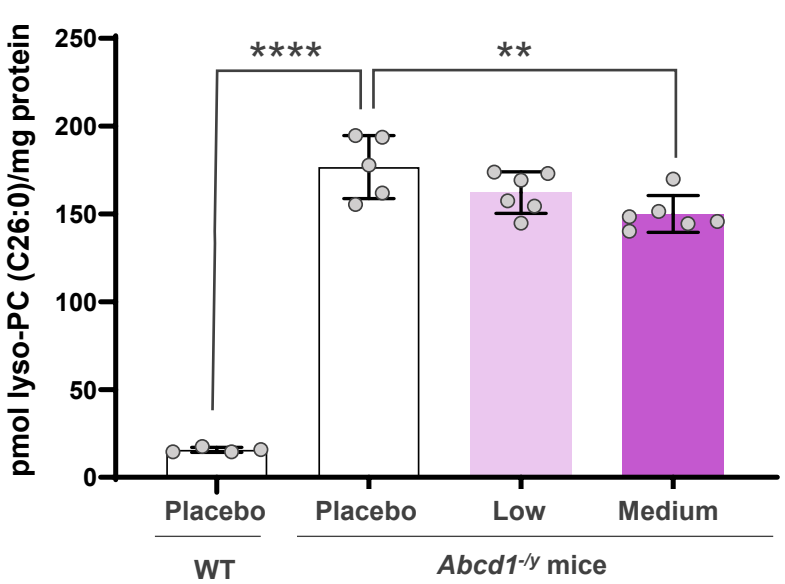
Single IT injection of SBT101 at 5.5E10 or 1.6E11 vg/an in *Abcd1*-knockout mice aged 9–11 weeks, 13 and 24 weeks in life

- Compared with placebo, administration of low- and medium-dose SBT101 led to significant reductions in VLCFA levels of 12% and 15%, respectively, in *Abcd1*-KO mice

13 weeks post administration



24 weeks post administration



One-time SBT101 dose

Low	5.5E10 vg/an
Medium	1.6E11 vg/an

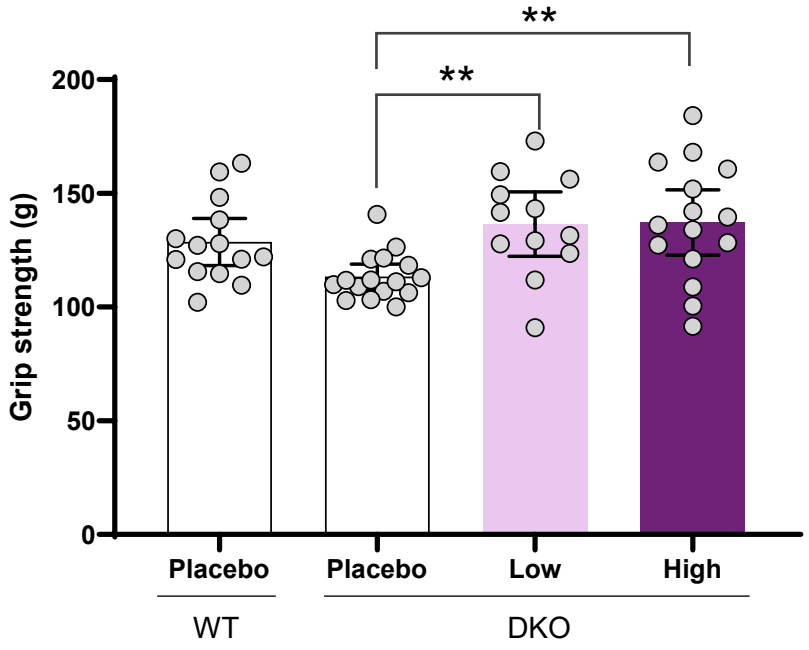
* $p < 0.05$; ** $p < 0.01$; **** $p < 0.0001$. Data represent mean ± standard deviation

Abcd1, ATP Binding Cassette subfamily D member-1; an, animal; ATP, adenosine triphosphate; lysoPC, lysophosphatidylcholine; vg, vector genomes; VLCFA, very long-cain fatty acids; WT, wild-type

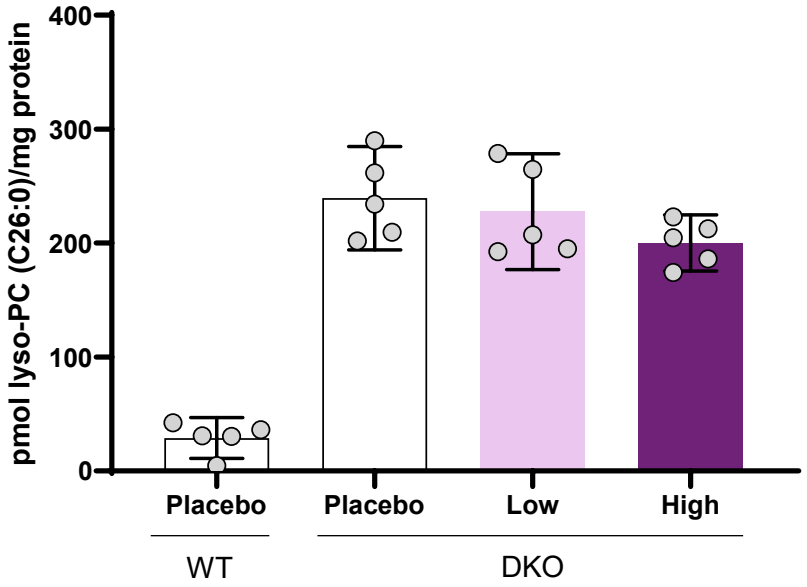
Effect of SBT101 in *Abcd1*/*Abcd2* DKO Mice

Single IT injection of SBT101 at 3.3E10 or 3.3E11 vg/an in *Abcd1/Abcd2*-DKO mice aged 9 months

Effect of SBT101 on grip strength at 15 months of age



Dose-dependent decrease in VLCFA levels at 18 months of age



One-time SBT101 dose

Low	3.3E10 vg/an
High	3.3E11 vg/an

For more details see A Pujol *et al.* Poster Tu-34

Data represent mean ± 95% CI
**$p < 0.0001$: one-way analysis of variance followed by Dunnett's *post hoc* test versus placebo
an, animal; ATP, adenosine triphosphate; CI, confidence interval; DKO, double knockout; hABCD1, human ATP-Binding Cassette sub-family D Member 1; NADH, nicotinamide adenine dinucleotide; ND1, NADH dehydrogenase 1; vg, vector genomes; WT, wild type

Safety Study on SBT101 in NHPs

Single IT lumbar infusion of AAV9-hACBD1 over 6 hours in male cynomologus monkeys

Experimental cohorts

	Group	Dose, vg/an	Time of sacrifice, weeks
Cohort 1	Control	-	13
	Low Dose	1.50E13	13
	Medium Dose	3.46E13	13
	High Dose	7.62E13	13
Cohort 2	Control	-	26
	Low Dose	1.50E13	26
	Medium Dose	3.46E13	26

- IT administration of SBT101 resulted in detectable tissue-specific transduction of vector genomes and expression of hABCD1 mRNA throughout the spinal cord

For more details on this NHP safety study, see V Vasireddy *et al.* Poster M-43

an, animal; NHP, nonhuman primate; vg, vector genomes

Safety Study on SBT101 in NHPs: Preclinical Histopathology

- No observable AEs and only transient clinical chemistry changes observed over a 92-day period: no SBT101-related effects on clinical, ophthalmological, neurobehavioral or cardiac observations, and transient dose-dependent increases in ALT/AST levels resolved over time
- Minimal to moderate histopathological findings were observed in the DRG and spinal cord in all dosed animals at 13 weeks, irrespective of treatment group
- Histological changes were limited to minimal to moderate axonal degeneration in the cervical, thoracic, and lumbar spinal cord at 26 weeks

		13 weeks				26 weeks		
		SBT101, vg/an				SBT101, vg/an		
		Placebo	1.50E13	3.46E13	7.62E13	Placebo	1.50E13	3.46E13
DRG, Cervical	Degeneration, axon	0	0	1	0	0	0	0
		0	0	0	0	0	0	0
		0	0	0	0	0	0	0
	Infiltrate, mononuclear cell	0	1	1	1	0	1	1
		0	1	1	1	0	0	1
		0	0	1	0	0	0	0
	Necrosis, neuron	0	1	1	1	1	0	3
		0	1	1	0	0	0	0
		0	0	0	0	0	0	0
DRG, Thoracic	Degeneration, axon	0	1	1	0	0	0	0
		0	0	1	0	0	0	0
		0	0	0	0	0	0	0
	Infiltrate, mononuclear cell	0	1	1	1	0	0	1
		0	1	0	1	0	0	0
		0	1	0	0	0	0	0
	Necrosis, neuron	0	3	1	1	1	1	3
		0	0	0	0	1	0	0
		0	0	0	0	0	0	0
DRG, Lumbar	Degeneration, axon	3	3	1	1	0	0	0
		0	2	1	1	0	0	0
		0	0	2	0	0	0	0
	Infiltrate, mononuclear cell	1	1	1	2	1	1	1
		1	1	1	1	0	1	0
		0	1	1	0	0	0	0
	Necrosis, neuron	0	2	1	1	1	0	3
		0	1	1	0	1	0	0
		0	1	0	0	0	0	0

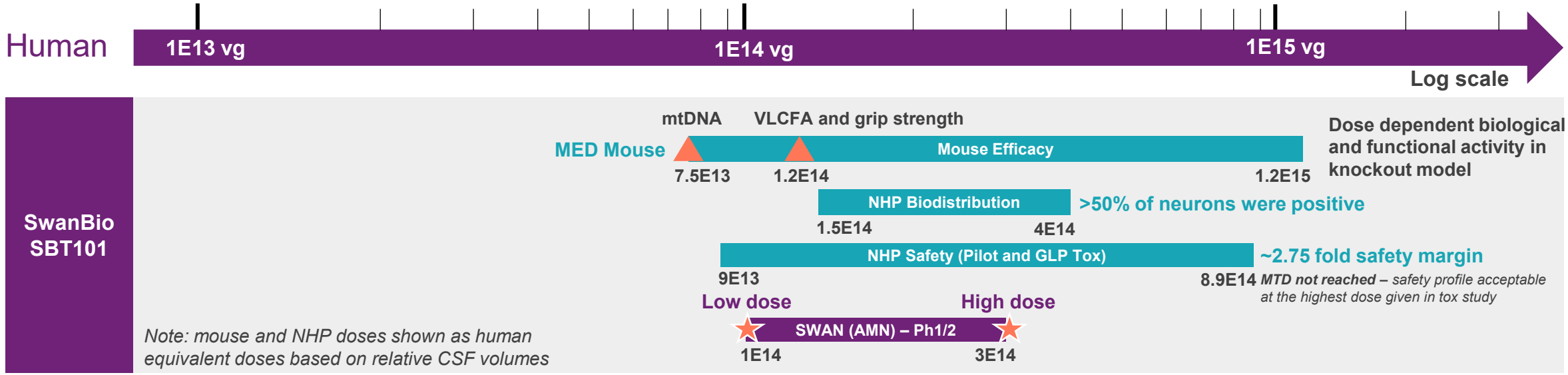
		13 weeks				26 weeks		
		SBT101, vg/an				SBT101, vg/an		
		Placebo	1.50E13	3.46E13	7.62E13	Placebo	1.50E13	3.46E13
DRG, Sacral	Degeneration, axon	0	3	2	2	0	0	1
		0	2	2	0	0	0	0
		0	0	2	0	0	0	0
	Infiltrate, mononuclear cell	0	2	1	2	0	1	1
		0	1	1	1	0	1	1
		0	1	0	0	0	0	1
	Necrosis, neuron	0	1	1	1	0	0	0
		0	0	0	0	0	0	0
		0	0	0	0	0	0	0
Spinal cord, Cervical	Degeneration, axon	2	3	2	0	0	0	2
		0	2	1	0	0	0	1
		0	1	1	0	0	0	0
Spinal cord, Thoracic	Degeneration, axon	1	2	2	0	0	1	1
		0	1	1	0	0	0	0
		0	1	0	0	0	0	0
Spinal cord, Lumbar	Degeneration, axon	0	2	3	2	0	1	3
		0	2	1	1	0	0	0
		0	1	0	0	0	0	0

5 Severe 4 Marked 3 Moderate 2 Slight 1 Minimal 0 Unremarkable

For more details on this NHP safety study, see V Vasireddy *et al.* Poster M-43

AEs, adverse events; ALT, alanine transaminase; an, animal; AST, aspartate transaminase; DRG, dorsal root ganglia, NHP, nonhuman primate; vg, vector genomes

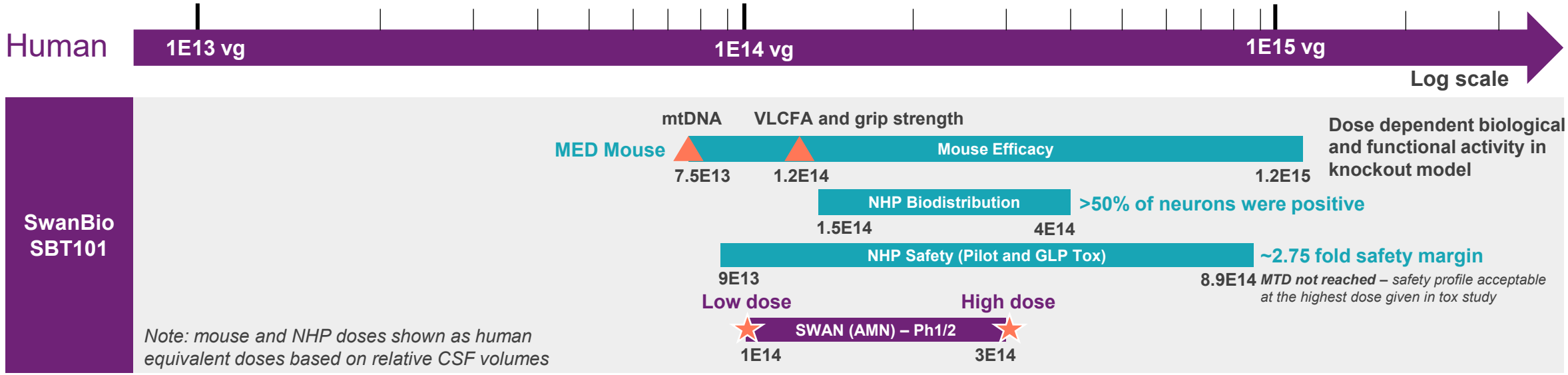
Preclinical Support for SBT101 Phase 1/2 Doses



For more details on supporting data in mice and NHPs see Pujol *et al.* Poster Tu-34 and Vasireddy *et al.* Posters M-43 and W-48

AMN, adrenomyeloneuropathy; CSF, cerebrospinal fluid; GLP. Good laboratory practice; MED, minimum effective dose; MTD, maximum tolerated dose; mtDNA, mitochondrial DNA; NHP, nonhuman primate; tox, toxicity; vg, vector genomes; VLFCA, very long-chain fatty acid

Preclinical Support for SBT101 Phase 1/2 Doses



For more details on supporting data in mice and NHPs see Pujol *et al.* Poster Tu-34 and Vasireddy *et al.* Posters M-43 and W-48

Conclusions

- By using efficacy, biodistribution and safety data as a basis and taking the differences in CSF volumes across species into consideration, a first-in-human dose range of SBT101 was calculated for patients with AMN to be 1.0E14 to 3.0E14 vg/person
- In conclusion, these results provide a range of doses for selected SBT101 delivery in humans that is predicted to be clinically relevant in patients with AMN

AMN, adrenomyeloneuropathy; CSF, cerebrospinal fluid; GLP. Good laboratory practice; MED, minimum effective dose; MTD, maximum tolerated dose; mtDNA, mitochondrial DNA; NHP, nonhuman primate; tox, toxicity; vg, vector genomes; VLFCA, very long-chain fatty acid

Acknowledgments

- The authors thank Dr David Gothard of Oxford PharmaGenesis, Oxford, UK for providing medical writing support, which was sponsored by SwanBio, in accordance with Good Publication Practice guidelines

Funding

- This study was funded by SwanBio Therapeutics Ltd

Thank you for listening