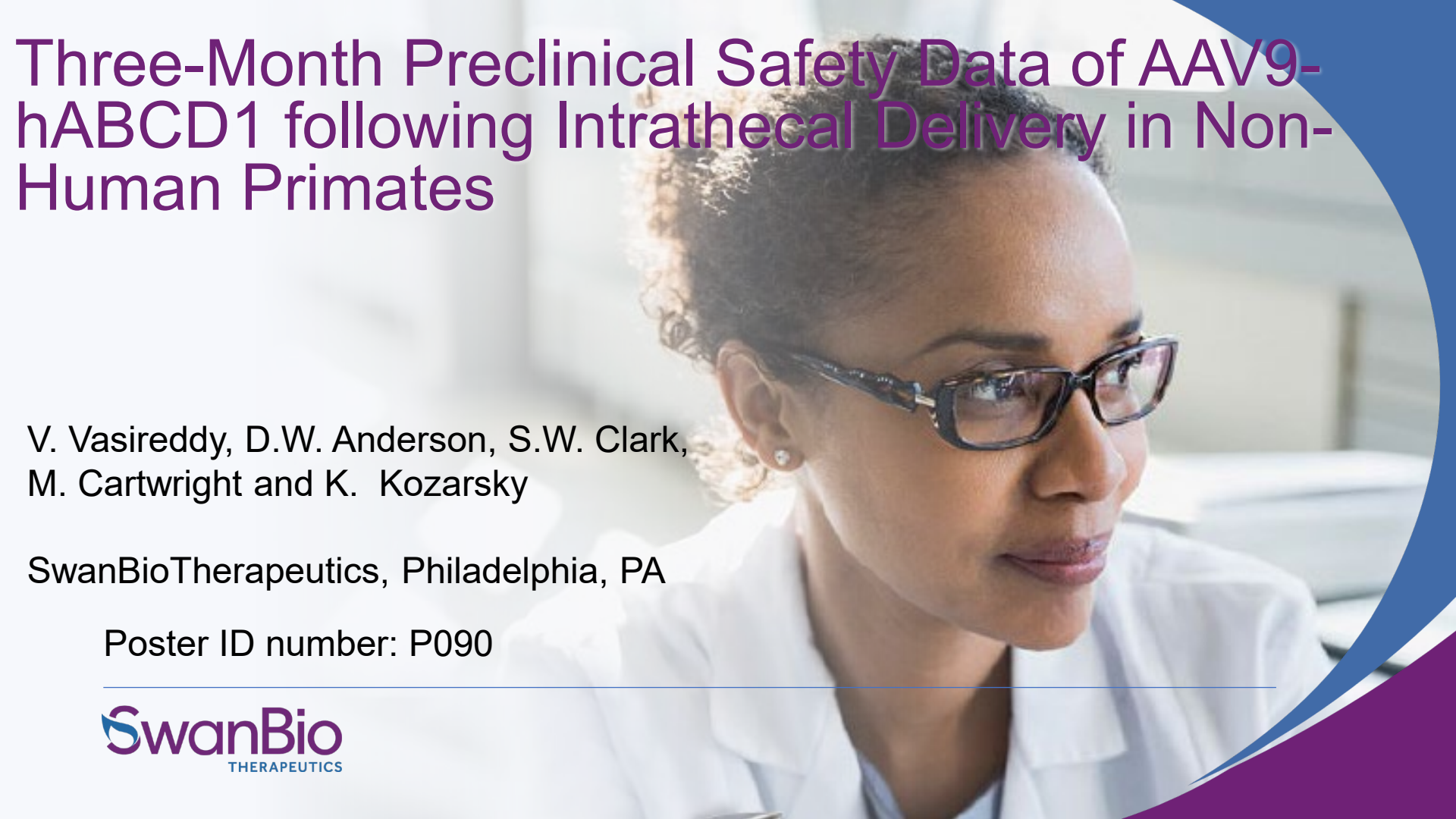
Three-Month Preclinical Safety Data of AAV9-hABCD1 following Intrathecal Delivery in Non-Human Primates



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Introduction

The inherited neurodegenerative disorder adrenomyeloneuropathy (AMN) is a form of X-linked Adrenoleukodystrophy (ALD), characterized by a slowly progressive muscle weakness leading to loss of mobility, incontinence, and debilitating pain. Mutations in the *ABCD1* gene encoding an ATP Binding Cassette subfamily D member-1 protein were identified to be responsible for AMN. ABCD1 is responsible for transporting very long chain fatty acids (VLCFAs) from cytosol into the peroxisome for degradation. Deficiency of ABCD1 results in the accumulation of saturated VLCFAs in tissues and body fluids, in turn leading to progressive axonopathy affecting sensory ascending and motor descending spinal cord tracts that manifests in aging patients. Thus far there are no therapies available for AMN, leaving the patients with progressive neurodegeneration with lifelong disability.

Objectives

- To evaluate the toxicity of SBT101, an AAV9-based gene therapeutic encoding a functional human native *ABCD1*, when administered as a single dose via intrathecal (IT) infusion to male cynomolgus monkeys
- To assess the reversibility or persistence of any SBT101 mediated effects after 13- or 26-weeks post dosing

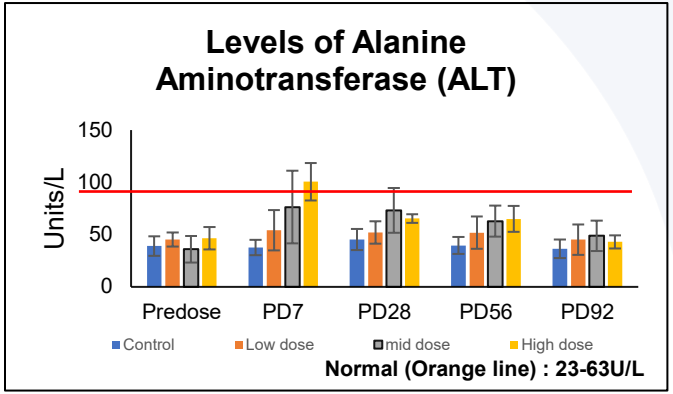
Preclinical Safety of SBT101 in NHP

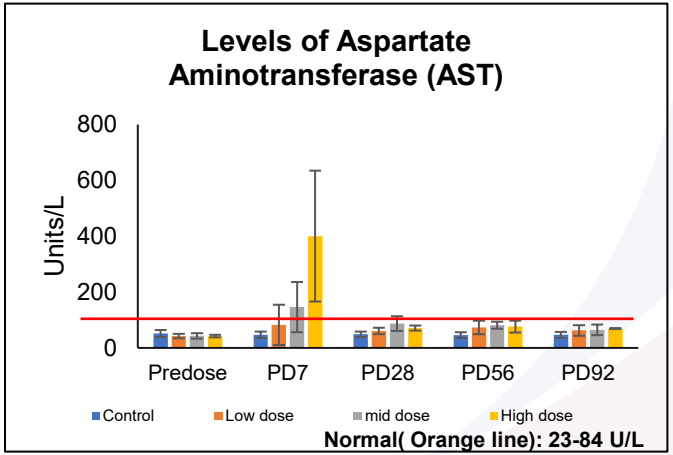
Study Design

- Male Cynomolgus
- N= 3-4 animals/ group
- Age: ~2 yr old
- Capsid: AAV9
- Transgene: hABCD1
- Promoter: CBA
- ROA: IT-Lumbar Infusion
- Doses/animal:
  - Control: Placebo
  - Low: 1.5E13 vg
  - Mid: 3.5E13 vg
  - High: 7.5E13 vg
- In-life: 3 months

Observations

- No test article related AE
- No test article related mortality, macroscopic observations, or organ weight effects
- No effects on hematology, coagulation, urinalysis, or CSF clinical pathology
- No changes in FOB, ECG, ophthalmology
- Transient dose dependent increases in ALT and AST within the first 28 days that resolved by day 56





Summary: No observable AEs and transient Clinical Chem changes were identified in animals receiving all doses of SBT101 over a 92 day period

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Preclinical histopathology of SBT101 in NHP at 13 weeks

- Test article-related neuronal necrosis (minimal – moderate), characterized by:
  - Nerve cell bodies with a loss of nissl substance and darkly eosinophilic staining cytoplasm, often irregularly bordered and shrunken in size (Fig.1 - white arrows)
  - Several layer thick ring of mononuclear cells at their outer margins (Fig.2 - black circle).
- Spinal cord + DRG - Increased incidence of pathological changes in dosed animals when compared to controls for:
  - Axonal degeneration (minimal-moderate), where minimum is the lowest, and severe is the highest pathological scoring, with slight in the middle on a 1-5 scale. Mononuclear infiltrates (minimal-slight)
- Heart - Increased incidence of pathological changes in dosed animals when compared to controls for:
  - Mononuclear cell infiltrates (minimal to slight)

Fig.1: Number of degenerate/necrotic nerve cells in thoracic DRG of NHP with low dose SBT101

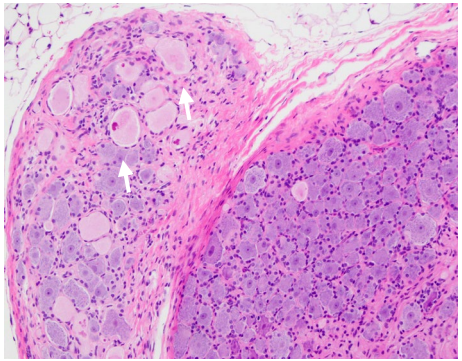

Fig.2:Cluster of mononuclear cells in cervical DRG of NHP with high dose of SBT101

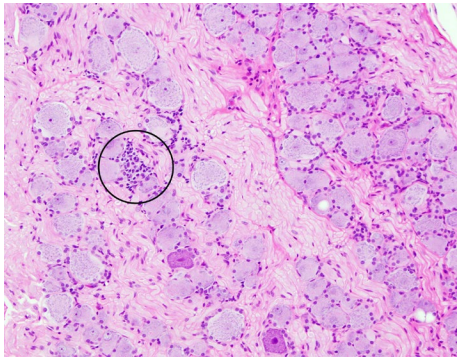

Table 1: Incidence of pathological changes following SBT101 at 13 weeks

Dose Level (vg/animal)			0	1.50E+13	3.40E+13	7.60E+13
Number examined			3	3	3	3
Dorsal Root Ganglia						
Cervical	Degeneration, axon	Minimal				
	Infiltrate, mononuclear cell	Minimal				
	Necrosis, neuron	Minimal				
Thoracic	Degeneration, axon	Minimal				
	Infiltrate, mononuclear cell	Minimal				
	Necrosis, neuron	Minimal				
		Moderate				
Lumbar	Degeneration, axon	Minimal				
		Slight				
		Moderate				
	Infiltrate, mononuclear cell	Minimal				
		Slight				
	Necrosis, neuron	Minimal				
		Slight				
Sacral	Degeneration, axon	Slight				
		Moderate				
	Infiltrate, mononuclear cell	Minimal				
		Slight				
	Necrosis, neuron	Minimal				
Spinal Cord						
Cervical	Degeneration, axon	Minimal				
		Slight				
		Moderate				
Thoracic	Degeneration, axon	Minimal				
		Slight				
Lumbar	Degeneration, axon	Minimal				
		Slight				
		Moderate				
Peripheral tissues						
Heart	Infiltrate, mononuclear cell	Minimal				
		Slight				

Scale	# of incidents
	0
	1
	2
	3

Summary: Minimal to slight histological changes in the spinal cord, dorsal root ganglion (DRG) and peripheral tissue, in all animals irrespective of treatment group at 13 weeks.

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Biodistribution of SBT101 in NHP at 13 weeks

	Control			1.5E13 vg			3.46e13 vg			7.62e13 vg		
	P0001	*P0002*	*P0003*	*P0101*	*P0102*	*P0103*	*P0201*	*P0202*	*P0203*	*P0301*	*P0302*	*P303*
Dorsal Root Ganglia												
Cervical	0	0	0	1	1	1	1	1	1	1	1	7
Thoracic	0	0	0	6	2	4	2	1	2	2	3	7
Lumbar	0	0	0	1	1	2	4	1	1	4	5	6
Sacral	0	0	0	1	1	7	6	1	3	6	7	7
Spinal Cord Region												
Cervical	0	0	0	0	1	1	1	1	4	2	1	4
Thoracic	0	0	0	1	1	1	3	1	3	2	1	7
Thorocolumbar	0	0	0	1	1	1	5	1	7	6	1	4
Lumbar	0	0	0	1	1	1	4	1	1	7	6	7

Scale	vg/copies DNA
-	<LOD (50)
1	50 - 625,000
2	625,001 - 1,250,000
3	1,250,001 - 1,875,000
4	1,875,001 - 2,500,000
5	2,500,001 - 3,125,000
6	3,125,001 -,3,750,000
7	3,750,001 +

- SBT101 transduces SC and DRG efficiently
- Biodistribution of AAV9 vector genomes is dose dependent
- Tissue distribution of hABCD1 transgene is ongoing

Summary: SBT101 efficiently delivers AAV9 vector genomes to the spinal cord and DRG in a dose dependent manner

Antibody titers against AAV9 in SBT101 administered NHP at 13 weeks

SERUM

Groups	Animal ID	Predose	D14	D92
control	P0001	-	-	-
	P0002	-	-	-
	P0003	-	-	-
Low dose (1.5E13)	P0101	-	-	4
	P0102	0	4	3
	P0103	-	3	3
Mid dose (3.4E13)	P0201	-	1	0
	P0202	0	4	-
	P0203	-	0	4
High dose (7.6E13)	P0301		5	-
	P0302	0	3	5
	P0303	0	4	4

CSF

Groups	Animal ID	Predose	D14	D92
control	P0001	-	-	-
	P0002	-	-	-
	P0003	-	-	-
Low dose (1.5E13)	P0101	-	-	-
	P0102	0	0	0
	P0103	-	-	0
Mid dose (3.4E13)	P0201	-	-	0
	P0202	-	-	1
	P0203	-	0	1
High dose (7.6E13)	P0301	-	0	2
	P0302	-	-	0
	P0303	-	0	0

- Serum AAV9-Anti Drug Antibody (ADA) titers are higher than CSF
- AAV9-ADA titers in serum and CSF are dose dependent
- CSF AAV9-ADA titers are absent or lower than serum titers

<1/20	-
1/20 to 1/1000	0
1/1001 to1/6000	1
1/60001 to 1/15000	2
1/15001 to 1/25000	3
1/25001to 1/625000	4
>1/625000	5

Summary: At 13 weeks AAV9-ADA in serum are persistent with minimal to moderate titers

Conclusions- 3 months Analysis

- Following intrathecal delivery of SBT101 at 3 doses in NHPs there were no Adverse Events reported at any time during the in-life portion of the study
- No SBT101 related neurobehavioral, functional and clinical changes were noted during the interim dosing phase
- The interim histopathological analysis of dorsal root ganglia and regions of the spinal cord were generally minimal to slight
- Following intrathecal delivery of SBT101 to the lumbar region of the spinal cord, AAV9 vector genomes are distributed throughout the spinal cord in a dose dependent manner (1.5E13 to 7.6E13 vg/animal), with the highest levels of vg recorded at 7.6E13 vg/animal
- In conclusion, intrathecal administration of SBT101 at doses up to 7.6E13 vg/animal to male monkeys was well tolerated up to 13 weeks. Due to the minimal impact of the finding on the health of the animals, the no observed adverse effect level (NOAEL) is at least 7.6E13 vg/animal

Conclusions- 6 months Analysis

- All animals survived to their scheduled terminal sacrifice
- No SBT101 related behavioral changes were noted during the terminal dosing phase

Ongoing

- The reversibility or persistence of any SBT101 mediated effects after 6 months of post dosing

THANK YOU