

CHAMPIONS: A phase 1/2 clinical trial with dose escalation of SB-913 ZFN-mediated in vivo human genome editing for treatment of MPS II (Hunter syndrome)

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February 7th, 2019

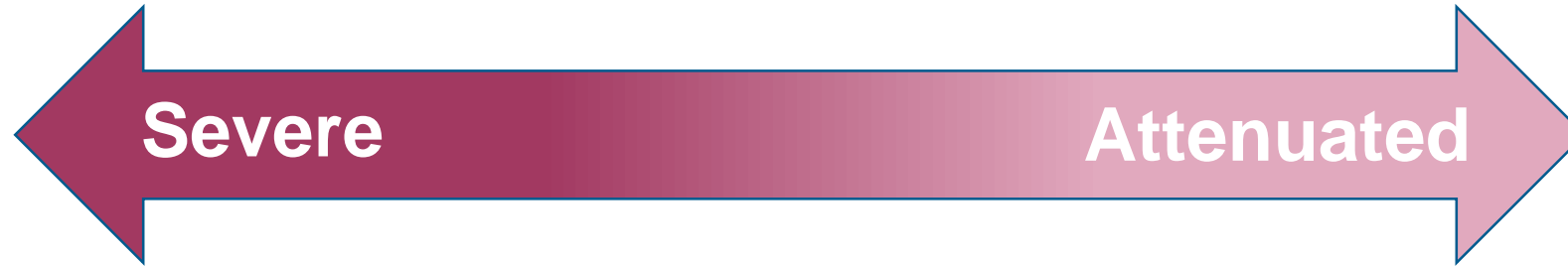
Orlando, FL

Mucopolysaccharidosis type II (MPS II or Hunter syndrome)



- Deficiency of lysosomal enzyme iduronate-2-sulfatase (IDS) caused by mutations in the IDS gene
- A rare, progressive X-linked recessive disorder (est. incidence 1:100,000)
- A spectrum of clinical disease occurs with onset of symptoms between 1 to 3 years in the severe form with early mortality, but about 1/3 of patients have an attenuated form
- Accumulation of the glycosaminoglycans (GAGs), dermatan sulfate and heparan sulfate, leads to tissue and organ damage
- Enzyme replacement therapy (ERT) does not address all symptoms of disease, e.g. neurocognitive decline

Spectrum of Disease in MPS II

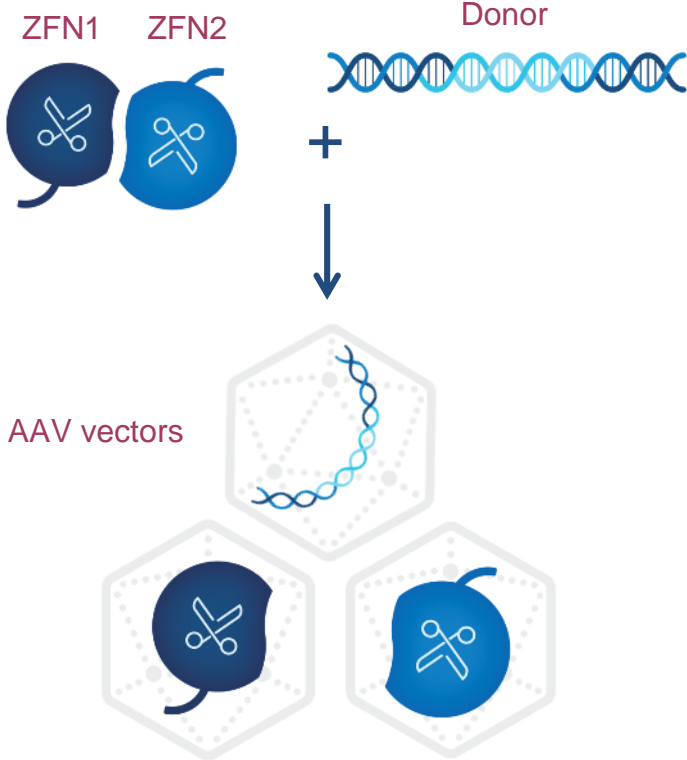


- Onset by 1 to 3 years of age
- Impaired intelligence
- Life expectancy 10 to 15 years

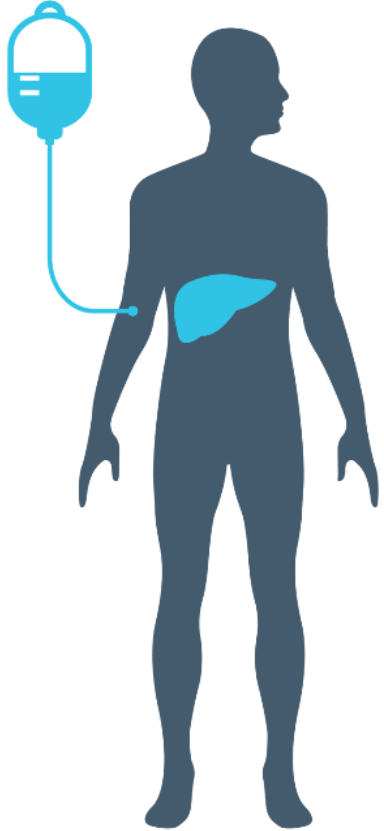
- Insidious onset
- Normal intelligence
- Variable life expectancy

ZFN-based Genome Editing Therapy: Potential Treatment for MPS II

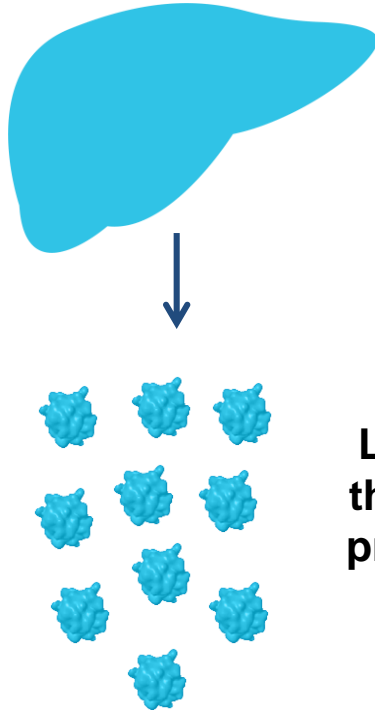
ZFN1, ZFN2 and corrective donor gene are packaged into adeno-associated viral (AAV) vectors



One-time peripheral IV administration over several hours



AAV targets liver and donor gene is precisely inserted into the first intron of the albumin gene



The First Clinical Trial for In Vivo Genome Editing

- CHAMPIONS is a Phase 1/2 open-label, dose-escalation study to assess the safety and tolerability of SB-913 in up to 9 adult subjects (>18y) with attenuated MPS II
- Study Drug: SB-913 consists of two ZFNs targeting the albumin locus and the human IDS gene packaged into AAV2/6 vectors
- Key exclusion criteria:
 - Pre-existing antibodies to AAV2/6 or polymorphisms of albumin gene
 - History of resistance or severe adverse reactions to ERT
 - History of liver or kidney dysfunction or contraindication to steroids

SB-913-1602: Study Objectives

Primary Objective:

- To evaluate the safety and tolerability of SB-913

Secondary Objectives:

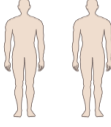
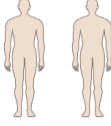
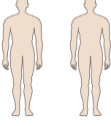
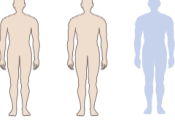
- To evaluate change from baseline in:
 - IDS activity in blood
 - GAG levels in urine
 - AAV2/6 clearance

Exploratory Objectives:

- Assessments to determine clinical, functional, and biochemical effects of SB-913

SB-913-1602: Study Design

- Three dose cohorts with 2 adult subjects each, followed by expansion of high-dose cohort (total of 9 adult subjects):

- 5e12 vg/kg* 
- 1e13 vg/kg* 
- 5e13 vg/kg*  + 

- Independent safety monitoring committee review prior to each dose escalation
- Subjects received oral prednisone prior to SB-913 and tapered over 20 weeks
- Subjects continued their weekly ERT infusions

* total AAV2/6 dose which includes 2 ZFNs and 1 donor vector in a fixed ratio of 1:1:8

SB-913-1602: Demographics and Follow Up

- Summary of safety data on 8 adult subjects analyzed as of **20 DEC 2018**
- Biochemical measurements on the first 6 subjects with up to 24 weeks follow-up

Demographics	
Subject Characteristics	Overall (N=8)
Age (Years)	
n	8
Mean (SD)	35.38 (15.59)
Median	34.00
Min-Max	19.00, 61.00
Sex, n (%)	
Male	8 (100)
Race, n (%)	
Asian	1 (12.5)
White	7 (87.5)

Approximate Exposure		
Subject	Dose Cohort	Follow-Up (Weeks)
1	1	57
2	1	49
3	2	39
4	2	34
5	3	25
6*	3	19
7	3	2
8	3	1

*Subject 6 was obese and received ~2x total dose of AAV based on body weight compared to subject 5

SB-913-1602: Serious Adverse Events (SAEs)

- Three serious adverse events (SAEs) were reported, one in each cohort
- All 3 SAEs were assessed as not related to the study drug by the site investigator, and considered secondary to the subject's MPS II disease
- All 3 subjects have recovered and remain on study

MedDRA Preferred Term	Cohort/ (Dose)	Study Day	Toxicity Grade	Outcome	Relationship to Study Drug	
Bronchitis	1 (5e12vg/kg)	20	3	Resolved	Not related	Secondary to subject's medical history of chronic pulmonary disease from MPS II
Atrial fibrillation	2 (1e13vg/kg)	52	2	Resolved	Not related	Secondary to subject's medical history of cardiac valve disease from MPS II
Umbilical hernia, obstructive	3 (5e13vg/kg)	121	3	Resolved*	Not related	Secondary to subject's underlying MPS II disease, medical history of hernias, and obesity

*per PI communication 30 JAN 2019

SB-913-1602: Study Drug-Related Adverse Events (AEs)

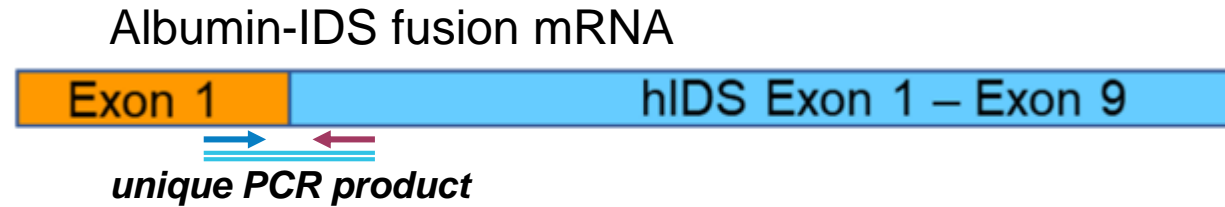
- Study drug-related AEs were mild or moderate and all resolved

MedDRA Preferred Term Severity	Cohort 1 (N=2) n [T]	Cohort 2 (N=2) n [T]	Cohort 3 (N=4) n [T]	Overall (N=8) n [T]
Any Event	2 [5]	1 [5]	2 [8]	5 [18]
Grade 1-Mild	2 [5]	1 [5]	2 [6]	5 [16]
Grade 2-Moderate	-	-	1 [2]	1 [2]
Pruritus	1 [2]	-	1 [1]	2 [3]
Flushing	-	1 [1]	1 [1]	2 [2]
Erythema	-	1 [2]	-	1 [2]
Transaminases increased	-	-	1 [3]	1 [3]
Alanine aminotransferase increased	-	1 [1]	-	1 [1]
Aspartate aminotransferase increased	-	1 [1]	-	1 [1]
Asthenia	1 [1]	-	-	1 [1]
Cold sweat	1 [1]	-	-	1 [1]
Dizziness	1 [1]	-	-	1 [1]
Dysgeusia	-	-	1 [1]	1 [1]
Headache	-	-	1 [1] [*]	1 [1]
Pyrexia	-	-	1 [1] [*]	1 [1]

N= Total number of subjects in each treatment group, n= number of subjects in each SOC, [T]= total number of adverse events.

^{*}Grade 2 event reported

SB-913-1602: Liver Biopsy to Assess Genome-Editing



- An RT-qPCR assay has been developed to identify the unique albumin-IDS mRNA transcript in liver biopsy tissue that is made after integration of the IDS gene into the targeted albumin locus
- Results were positive in both Cohort 2 subjects who received 1e13vg/kg dose, Cohort 3 results are pending

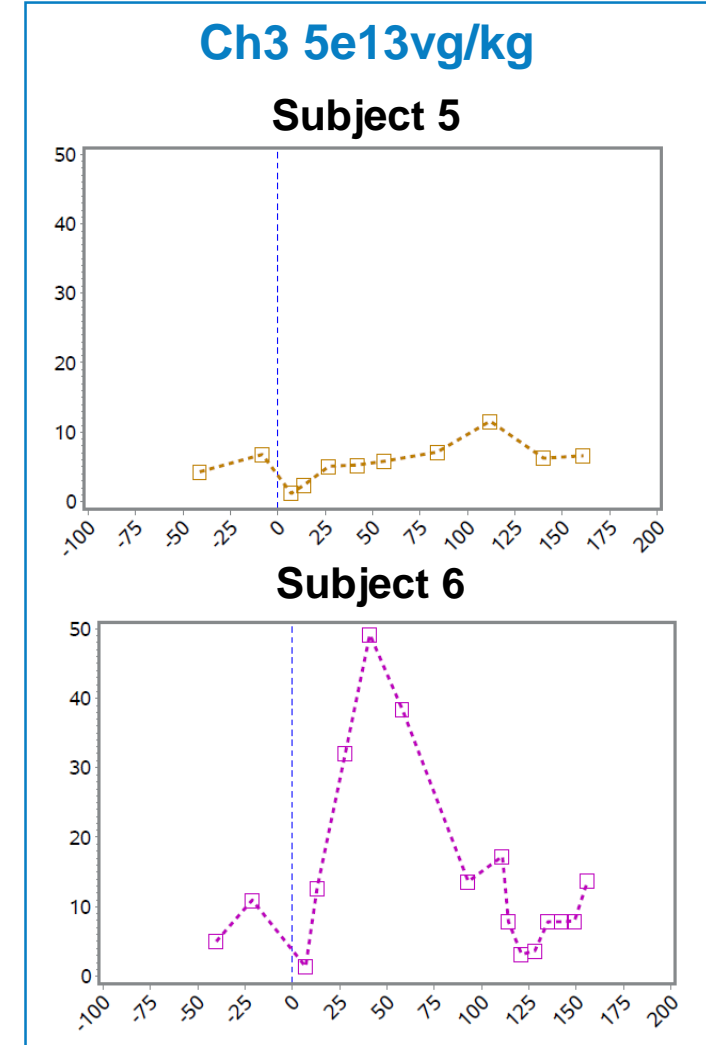
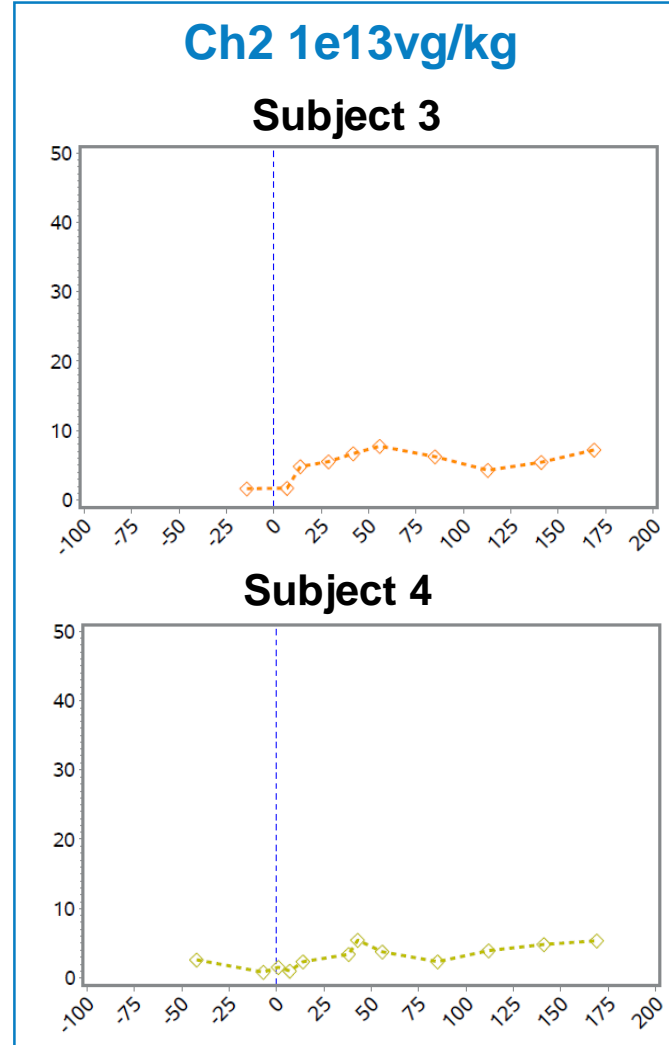
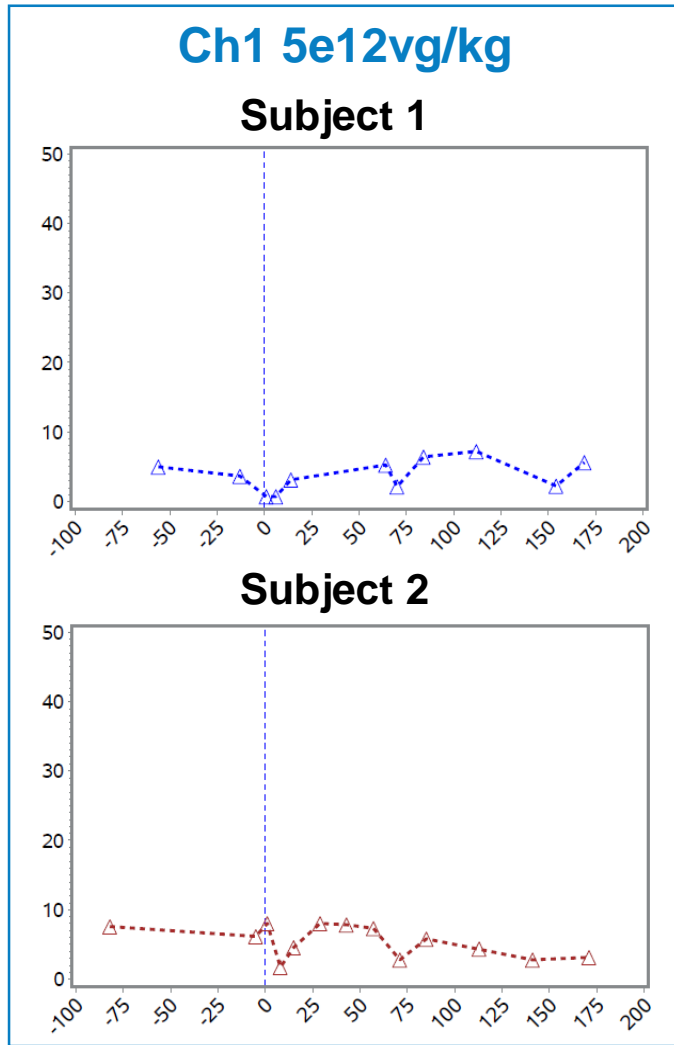
Week 24 Results	Cohort 1		Cohort 2		Cohort 3	
Subject	1	2*	3	4	5*	6
Integration Assay	-	n/a	+	+	n/a	pend

*no results available as liver biopsy procedure contraindicated due to anticoagulation therapy

- A less sensitive genomic DNA assay using MiSeq to detect insertions/deletions (“indels”) at target site in the albumin gene was negative in all samples tested (lower limit of quantitation ~ 1 in 1,000 genomes)

SB-913-1602: Plasma IDS Activity up to Week 24

Plasma IDS Activity*
(nmol/mL/hr)

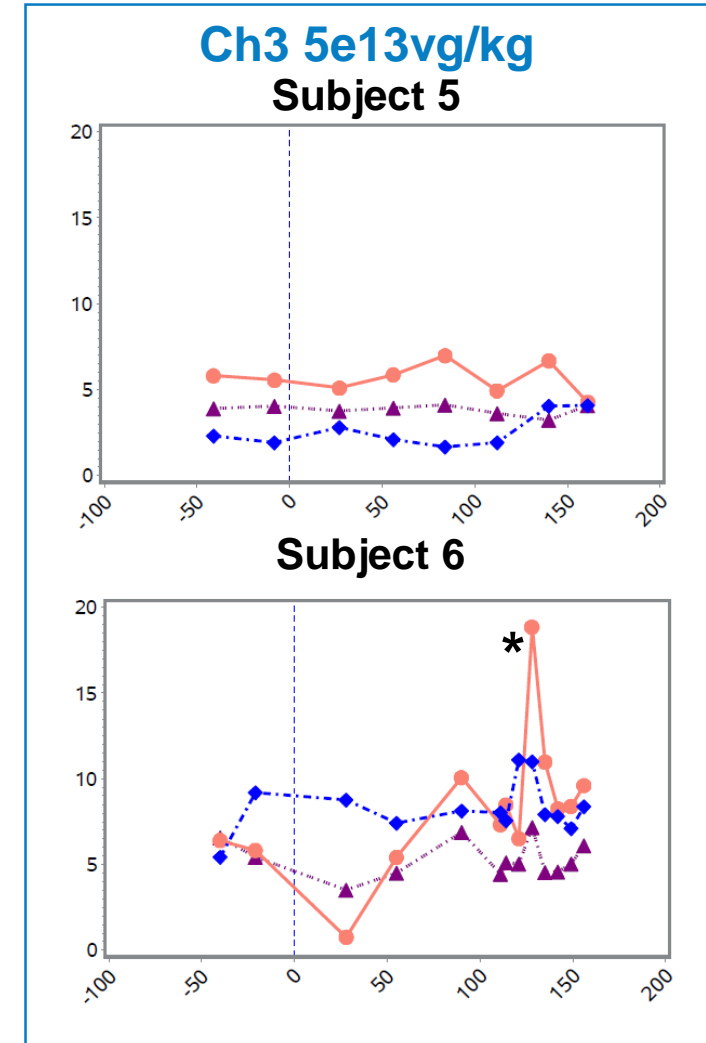
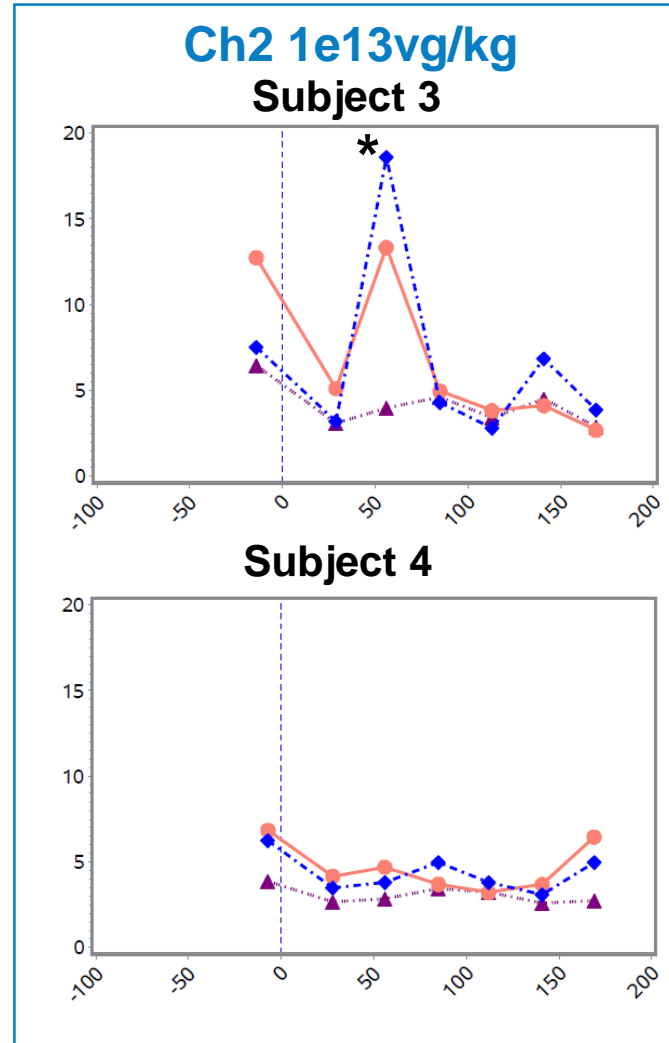
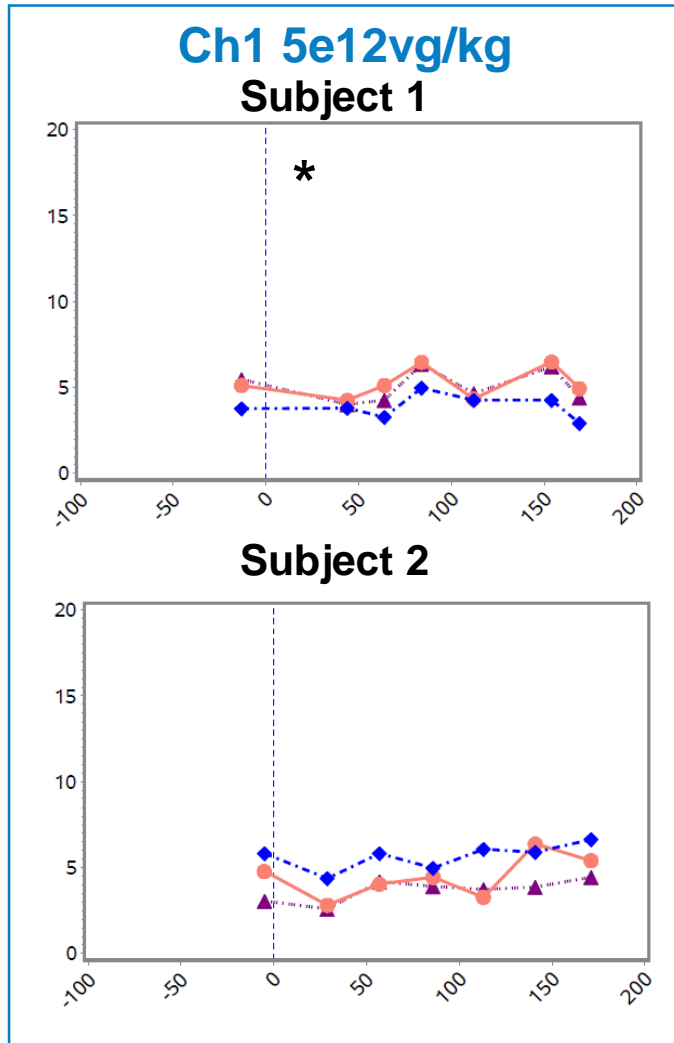


Study Day

*Highly-sensitive qualified fluorometric assay with lower limit of quantitation=0.78, samples obtained <96h post-ERT excluded
Reference ranges (nmol/mL/hr): Unaffected: 82-200 Baseline MPS II (>96h post-ERT): estimated 0-10

SB-913-1602: Urine GAG Results up to Week 24

GAG Level
(g/mol creatinine)



- ▲▲▲ Dermatan sulfate, urine
- Heparan sulfate, urine
- ◆◆◆ Total Glycosaminoglycans (GAGs)

Study Day

* SAE reported, subject hospitalized

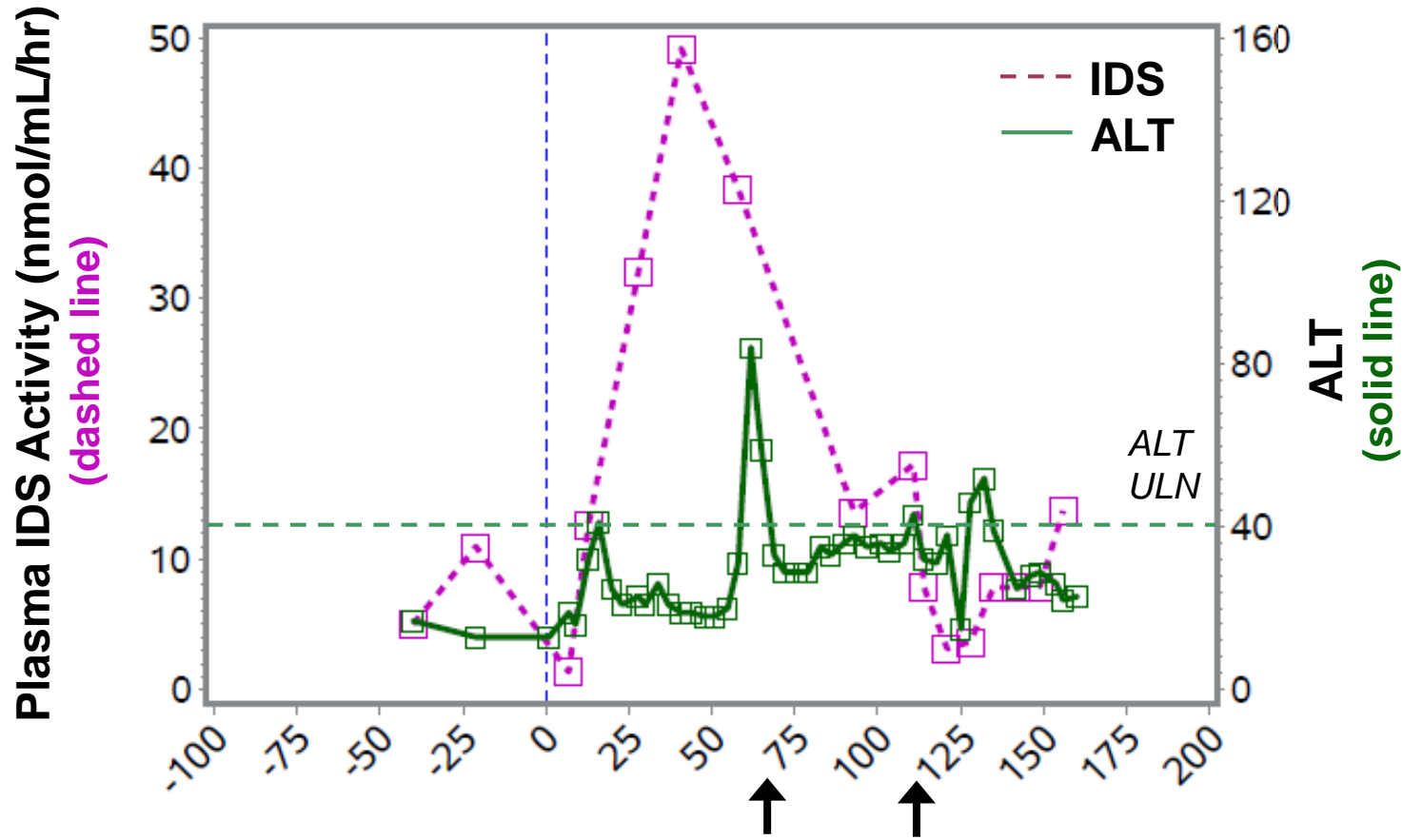
Normal reference ranges (g/mol creatinine):

Dermatan sulfate: 0 - 4.59 Heparan sulfate: 0 - 1.07 Total GAG: 0 - 6.5

Data cut-off date: 10 JAN 2019

SB-913-1602: Subject 6 Development of Transaminitis

Subject 6: Ch3 5e13vg/kg



↑ Indicates timing of prednisone dose increase to 60mg

- Mild (Grade 1) increases in liver function tests reported on study Day 62, 111, and 128
- Prednisone dose increased to 60mg PO daily and then tapered
- Subject also had SAE of incarcerated umbilical hernia on Day 121 unrelated to study drug

SB-913-1602: ERT Withdrawal

- ERT withdrawal has been initiated under protocol-specified schedule with monitoring of safety, IDS/GAG biochemical markers, and functional measures
- Three subjects (2 in Ch2 and 1 in Ch3) have started ERT withdrawal, 1 subject in Ch2 is planning to restart ERT after approximately 3 months due to fatigue and concurrent increase in GAGs (*per PI communication on 02 FEB 2019*)
- ERT withdrawal will begin in other subjects and analysis of data is ongoing

SB-913-1602: Summary of Results

- SB-913 was administered to 8 subjects with attenuated MPS II at a dose of up to 5×10^{13} vg/kg and was generally well-tolerated
- Adverse events related to study drug were mild or moderate and resolved. No serious adverse events related to the study drug were reported
- Analysis of liver tissue showed evidence of albumin-IDS mRNA transcript in both subjects at the 1×10^{13} vg/kg dose after 24 weeks, suggesting that genome editing had occurred (analysis of the 5×10^{13} vg/kg dosed subject is pending)
- A substantial increase in plasma IDS activity was observed in 1 subject at the 5×10^{13} vg/kg dose, however this decreased after development of mild transaminitis
- Expansion with 3 additional subjects at the 5×10^{13} vg/kg dose is complete and a trial of ERT withdrawal for all subjects is planned

Acknowledgements

- The MPS II patients and their families
- The study principal investigators:
 - Dr. Paul Harmatz, UCSF Benioff Children's Hospital Oakland
 - Dr. Joseph Muenzer, University of North Carolina at Chapel Hill
 - Dr. Carlos Prada, Cincinnati Children's Hospital Medical Center
 - Dr. Heather Lau, NYU School of Medicine
 - Dr. Chester Whitley, University of Minnesota
 - Dr. Barbara Burton, Ann & Robert H. Lurie Children's Hospital of Chicago
 - Dr. Can Ficicioglu, Children's Hospital of Philadelphia
 - Dr. Simon Jones, Manchester Hospital UK
- The study coordinators and research assistants at the clinical sites
- This study was sponsored by Sangamo Therapeutics