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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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

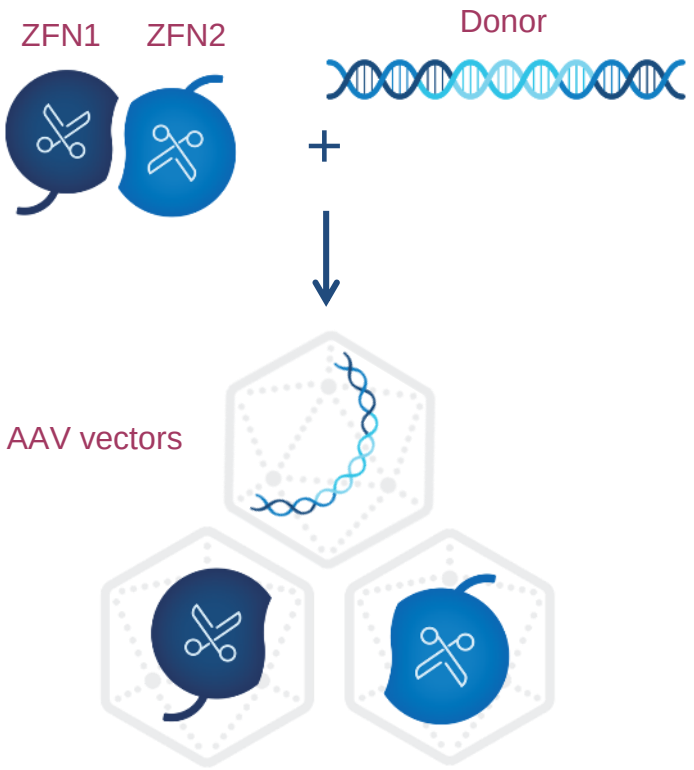
Severe ⟷ **Attenuated**

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

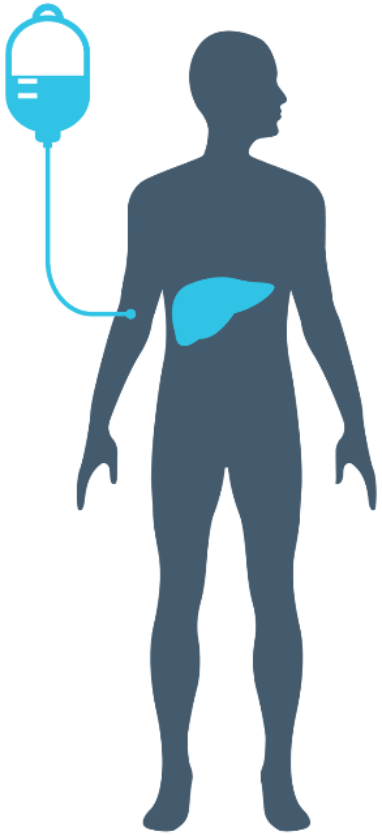
- Insidious onset
- Normal intelligence
- Variable life expectancy

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

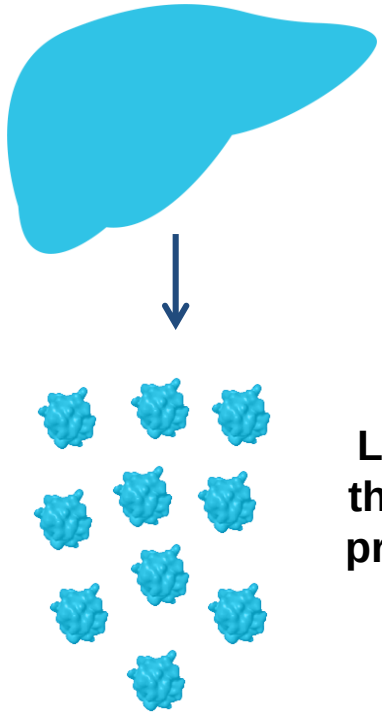
ZFN1, ZFN2 and corrective donor gene are packaged into adeno-associated viral (AAV) vectors



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



Liver secretes the therapeutic protein into the blood

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*

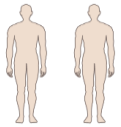
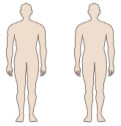
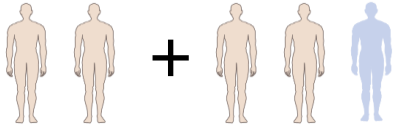
Secondary Objectives:

- 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*

Data cut-off date: 20 DEC 2018

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*

Data cut-off date: 20 DEC 2018

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

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

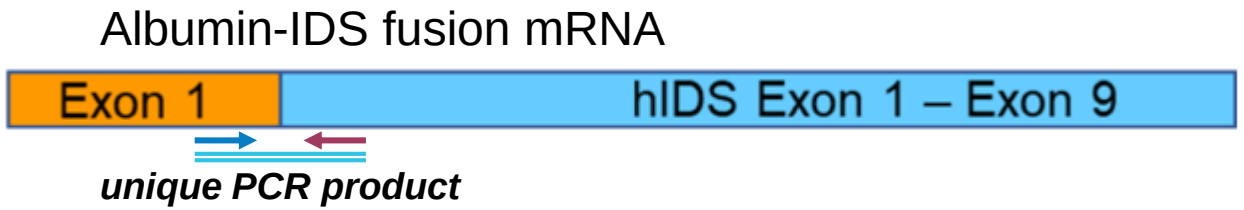
MedDRA Preferred Term Severity	Cohort 1 (N=2) n [T]	Cohort 2 (N=2) n [T]	Cohort 3 (N=4) n [T]	Overall (N=8) n [T]
Any Event	2 [5]	1 [5]	2 [8]	5 [18]
Grade 1-Mild	2 [5]	1 [5]	2 [6]	5 [16]
Grade 2-Moderate	-	-	1 [2]	1 [2]
Pruritus	1 [2]	-	1 [1]	2 [3]
Flushing	-	1 [1]	1 [1]	2 [2]
Erythema	-	1 [2]	-	1 [2]
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

Data cut-off date: 20 DEC 2018

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

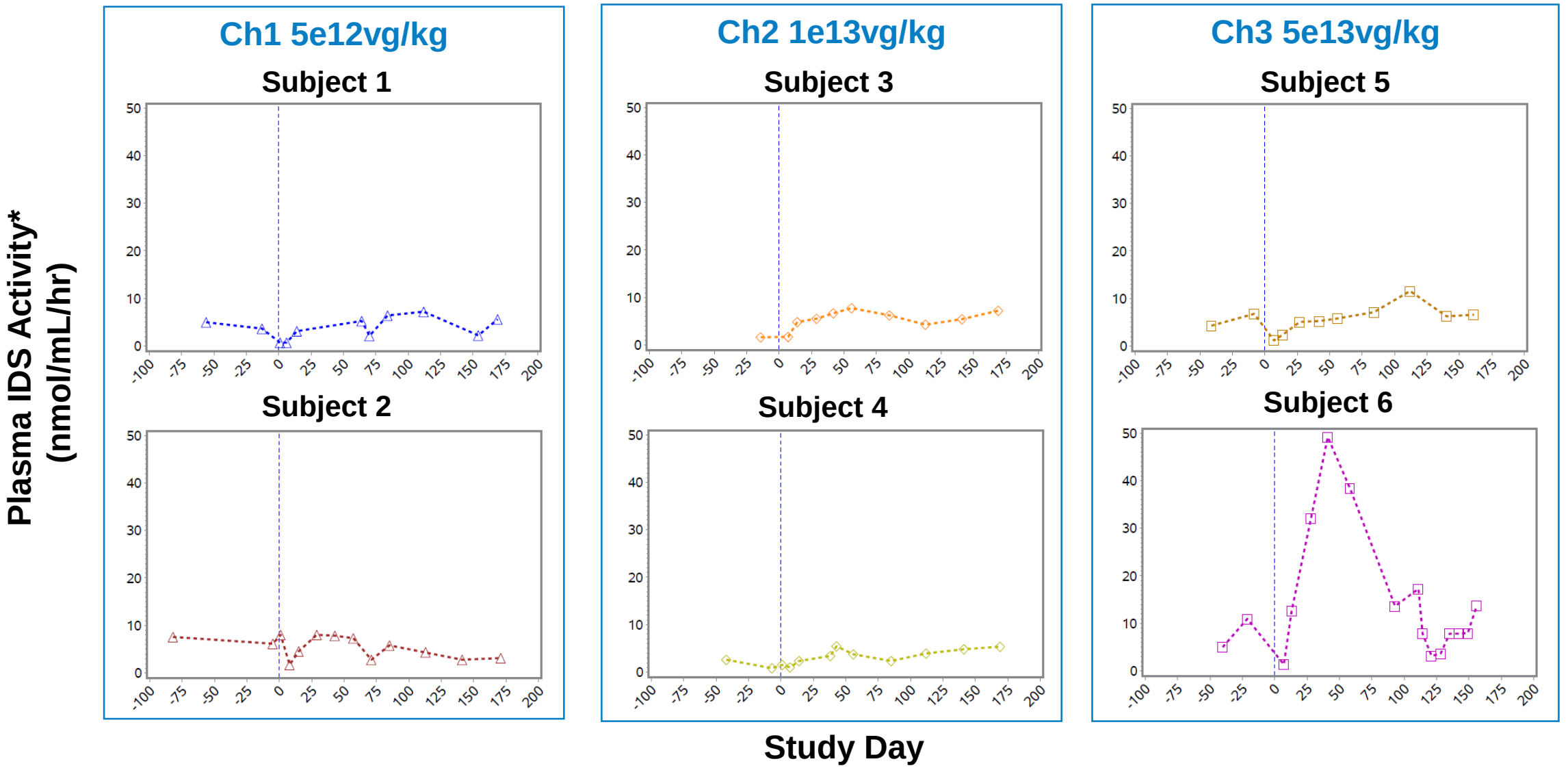
Week 24 Results	Cohort 1		Cohort 2		Cohort 3	
Subject	**1**	**2***	**3**	**4**	**5***	**6**
Integration Assay	-	*n/a*	+	+	*n/a*	pend

*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)

Data cut-off date: 10 JAN 2019

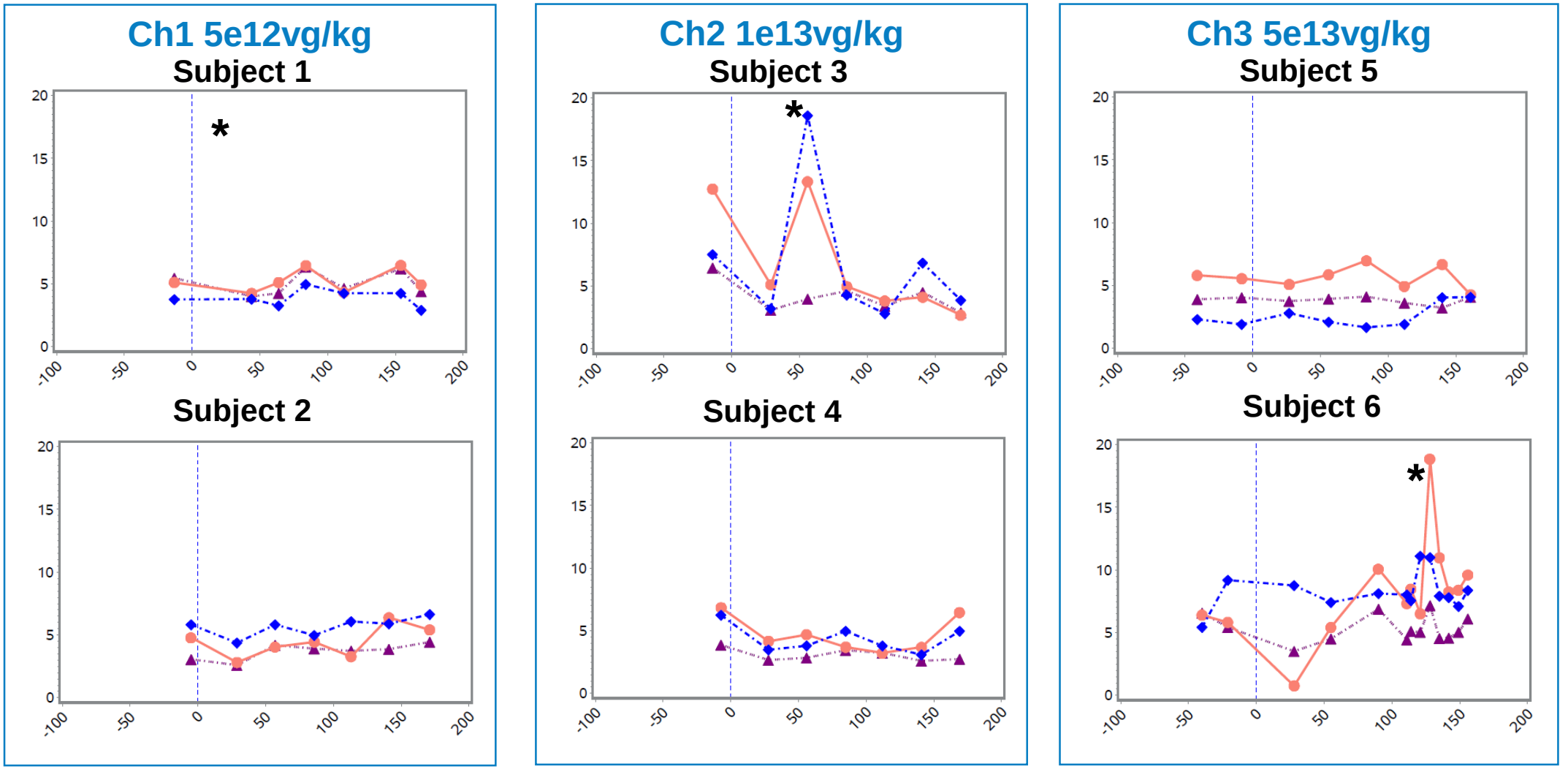
SB-913-1602: Plasma IDS Activity up to Week 24



**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

Data cut-off date: 10 JAN 2019

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



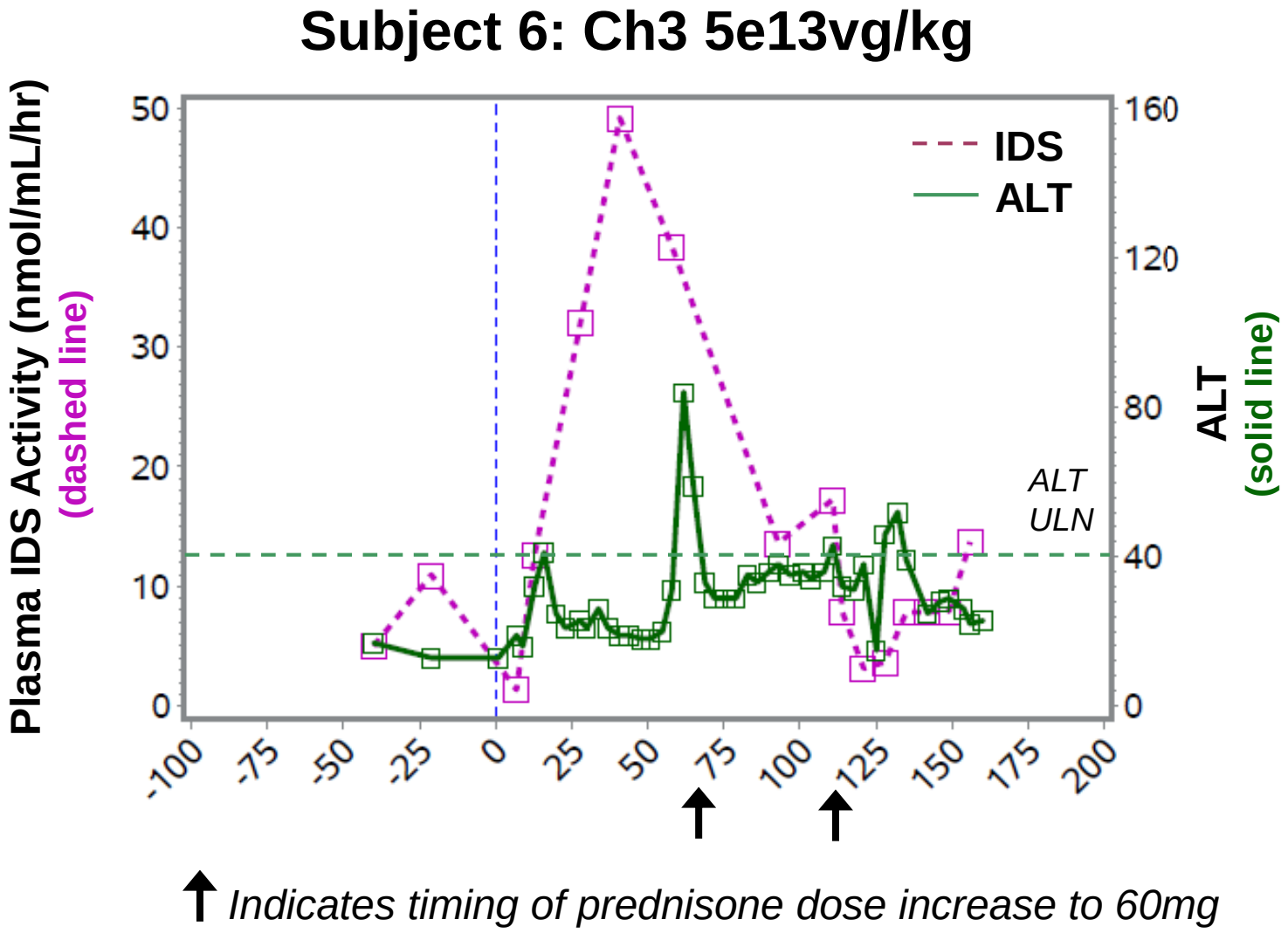
* *SAE reported, subject hospitalized*

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



↑ *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

Data cut-off date: 10 JAN 2019

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 5e13 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 1e13vg/kg dose after 24 weeks, suggesting that genome editing had occurred (analysis of the 5e13vg/kg dosed subject is pending)
- A substantial increase in plasma IDS activity was observed in 1 subject at the 5e13vg/kg dose, however this decreased after development of mild transaminitis
- Expansion with 3 additional subjects at the 5e13 vg/kg dose is complete and a trial of ERT withdrawal for all subjects is planned

Acknowledgements

- The MPS II patients and their families
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