EMPOWERS: A phase 1/2 clinical trial of SB-318 ZFN-mediated in vivo human genome editing for treatment of MPS I (Hurler syndrome)

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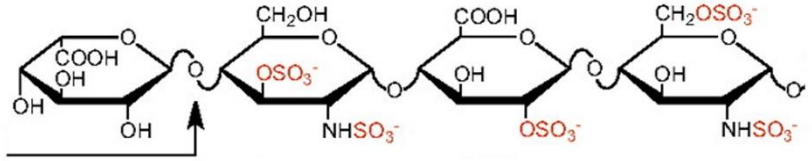
Mucopolysaccharidosis type I (MPS I or Hurler Syndrome)

- Autosomal recessive genetic disorder due to deficiency of the lysosomal enzyme α-L-Iduronidase (IDUA)
- Leads to the accumulation of the glycosaminoglycans (GAGs), dermatan and heparan sulfate throughout the body



IDUA

Spectrum of Disease in MPS I

Hurler
MPS I H

- Progressive developmental delay
- Progressive skeletal dysplasia
- Severe respiratory disease
- Obstructive airway disease
- Death before age 10 years

Hurler-Scheie
MPS I H/S

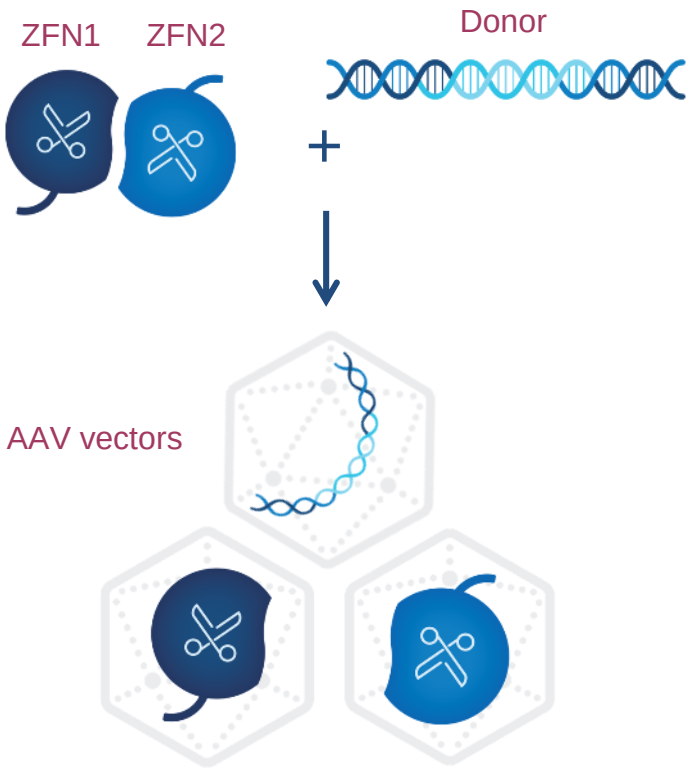
- Little or no intellectual deficit
- Respiratory disease
- Obstructive airway disease
- Cardiovascular disease
- Joint stiffness/contractures
- Skeletal abnormalities
- Decreased visual acuity
- Death in teens and 20’s

Scheie
MPS I S

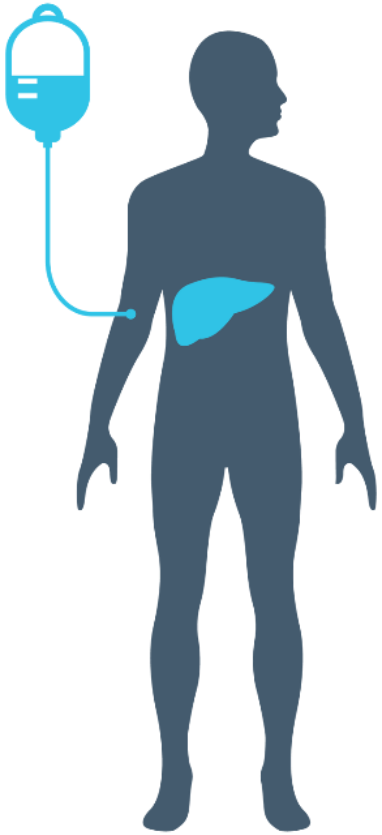
- Normal intelligence
- Less progressive physical problems
- Joint stiffness
- Valvular heart disease
- Death in later decades

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

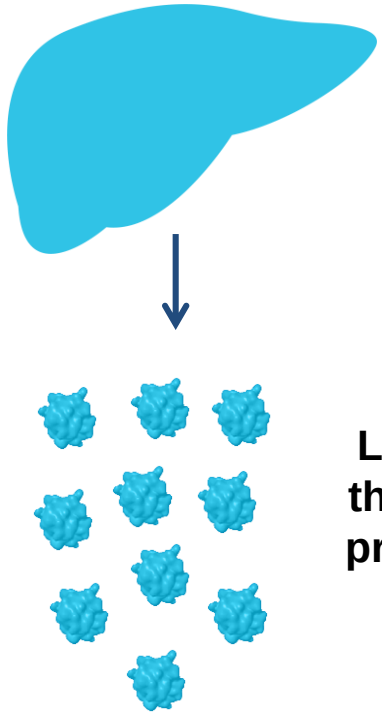
ZFN1, ZFN2 and corrective donor gene are packaged into adeno-associated viral (AAV) vectors



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 in MPS I

- EMPOWERS is a Phase 1/2 open-label, dose-escalation study to assess the safety and tolerability of SB-318 in up to 9 adult subjects (>18y) with attenuated MPS I

- Study Drug: SB-318 consists of two ZFNs targeting the albumin locus and the human IDUA 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-318-1502: Study Objectives

Primary Objective:

- *To evaluate the safety and tolerability of SB-318*

Secondary Objectives:

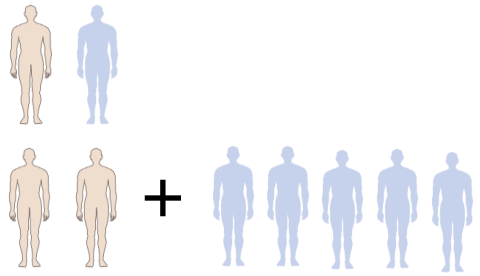
- To evaluate change from baseline in:
  - IDUA activity in plasma and blood leukocytes
  - GAG levels in urine
  - AAV2/6 clearance

Exploratory Objectives:

- Assessments to determine clinical, functional, and biochemical effects of SB-318

SB-318-1502: Study Design

- Two dose cohorts with 2 subjects each, potential expansion of 5 additional subjects (total of 9 subjects):
  - 1e13 vg/kg*
  - 5e13 vg/kg*



- Independent safety monitoring committee review prior to each dose escalation recommended reducing first cohort to 1 subject based on safety data from ongoing ZFN trials and to optimize benefit/risk given one-time administration
- Subjects continued their weekly ERT infusions
- Subjects received oral prednisone prior to SB-318 dosing which is tapered over 20 weeks

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

SB-318-1502: Demographics and Follow Up

- Summary of safety data on 3 adult subjects analyzed as of **20 DEC 2018**
- Biochemical measurements on these 3 subjects analyzed up to **10 JAN 2019**

Demographics

Subject Characteristics	Overall (N=3)
Age (Years)	
n	3
Mean (SD)	**29.00** (7.21)
Median	27.00
Min-Max	23.00, 37.00
Sex, n (%)	
Female	1 (33.3)
Male	2 (66.7)
Race, n (%)	
Asian	2 (66.7)
White	1 (33.3)

N= Total number of subjects, n= number of subjects in each group

Approximate Exposure

Subject	Dose Cohort	Follow-Up (Weeks)
1	1	**22**
2	2	**9**
3	2	**5**

Data cut-off date: 20 DEC 2018

SB-318-1502: Adverse Event (AE) Summary

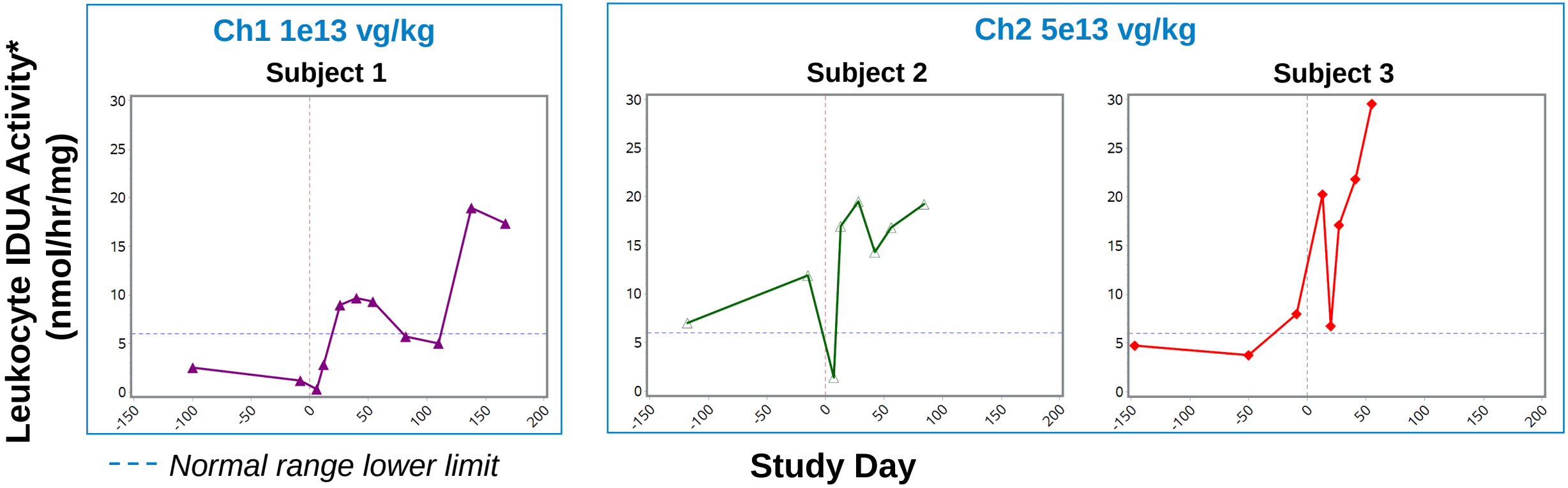
- All subjects reported mild or moderate AEs, consistent with ongoing MPS I disease
- No AEs related to the study drug were reported and no serious AEs were reported
- No AEs of elevated liver function tests were reported

MedDRA Preferred Term (PT)	Cohort 1 (N=1) n [T]	Cohort 2 (N=2) n [T]	Overall (N=3) n [T]
Any TEAE Grade 1-Mild Grade 2-Moderate	1 [2] 1 [1] 1 [1]	2 [4] 2 [3] 1 [1]	3 [6] 3 [4] 2 [2]
Acne	-	2 [2]*	2 [2]
Headache	1 [1]	-	1 [1]
Musculoskeletal stiffness	-	1 [1]	1 [1]
Oropharyngeal pain	-	1 [1]	1 [1]
Upper respiratory tract infection	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-318-1502: Leukocyte IDUA Activity Results

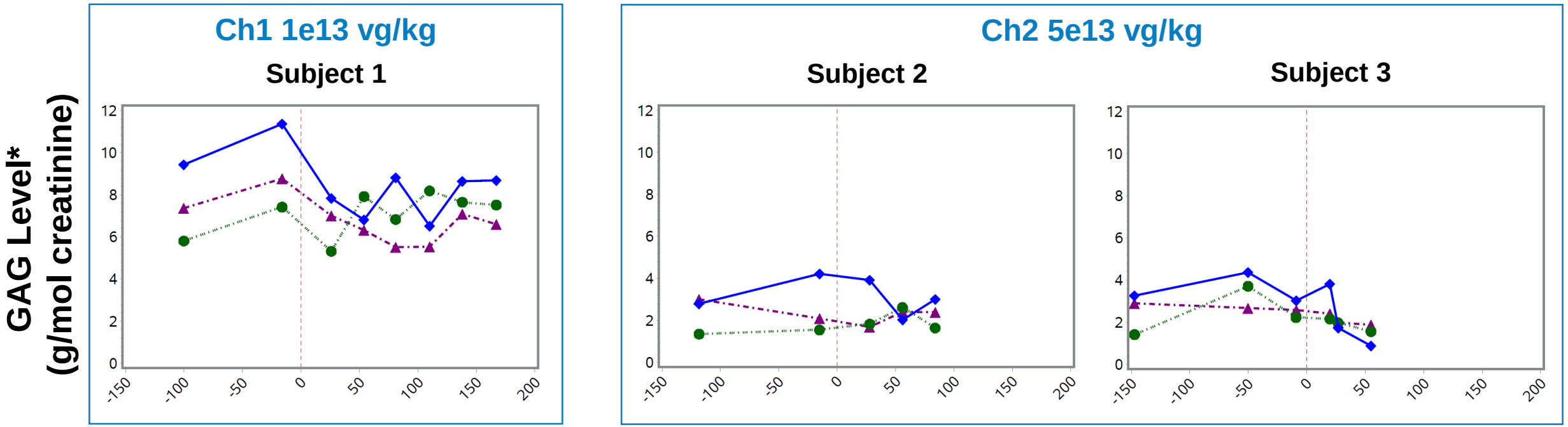


Greenwood Genetics validated diagnostic assay, samples obtained <96h post-ERT excluded
Reference ranges: Normal: 6.0-71.4 nmol/hr/mg MPS I (ERT-naïve): 0-1.0 nmol/hr/mg

- Plasma IDUA activity was also measured and was not significantly changed from pre-treatment values

Data cut-off date: 10 JAN 2019

SB-318-1502: Urine GAG Results



Normal reference ranges:
Dermatan sulfate: 0 - 4.59 g/mol creatinine
Heparan sulfate: 0 - 1.07 g/mol creatinine
Total GAG: 0 - 6.5 g/mol creatinine

**Total GAG measured by validated 1,9-dimethylene blue (DMB) colorimetric assay, dermatan sulfate and heparan sulfate measured by validated mass spectrometry assay*

Data cut-off date: 10 JAN 2019

SB-318-1502: Summary of Results

- SB-318 was administered to 3 subjects with attenuated MPS I at a dose of up to 5e13 vg/kg and was generally well-tolerated
- No adverse events related to the study drug were reported
- Increases in leukocyte IDUA activity were observed in all three treated subjects at both the 1e13 and 5e13 vg/kg dose
- Plasma IDUA activity was not significantly changed from pre-treatment values
- Analysis of liver biopsy tissue obtained at week 24 is planned to assess for evidence of genome editing
- ERT withdrawal is planned under a protocol-specified schedule with monitoring of safety, IDUA/GAG biochemical markers, and functional measures

Acknowledgements

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