Transpher A, an open-label, multicenter, single-dose, dose-escalation, Phase 1/2 Clinical Trial of gene transfer of ABO-102 in Sanfilippo Syndrome type A (Mucopolysaccharidosis IIIA): Safety, tolerability, biopotency and neurocognitive data

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4. Abeona Therapeutics Inc.

Sanfilippo Syndrome (MPS III)

A group of four clinically indistinguishable lysosomal enzyme deficiencies that result in accumulation of the glycosaminoglycan (GAG) heparan sulfate (HS)

- Global incidence varies by regions and it is estimated 0.17-2.35 per 100,000 births*
- MPS IIIA is the most frequent subtype, caused by a deficiency in N-Sulfoglucosamine Sulfohydrolase (SGSH)

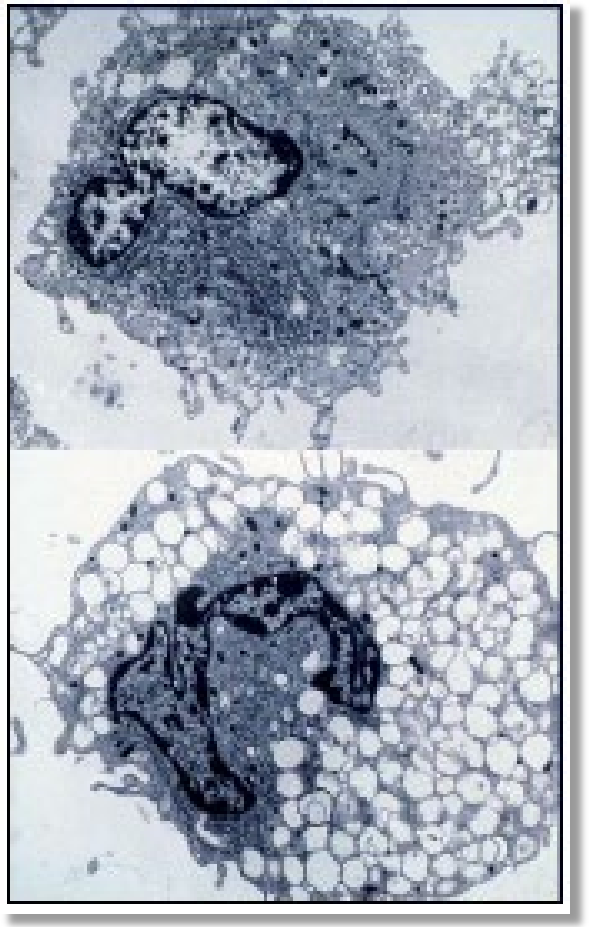
Disease manifest as early as 12-24 months involving:

- *Central nervous system features predominate (gray > white matter)*
  - Slowing and then regression of development, first speech/cognitive then gross motor
  - Impulsivity, hyperactivity, sleep disturbance, aggressive behavior, seizures
  - Relentless loss of skills progressing to dementia
- *Somatic features are milder than other MPS disorders*
  - Coarse facial features/hirsutism, frequent otitis media, airway compromise, Umbilical hernia, hepatosplenomegaly, mild dysostosis multiplex/short stature, heart valve thickening

No approved treatments available

- 70% of children with MPS III do not reach age 18 years of age

Normal cell



Cell with
lysosome deficiency

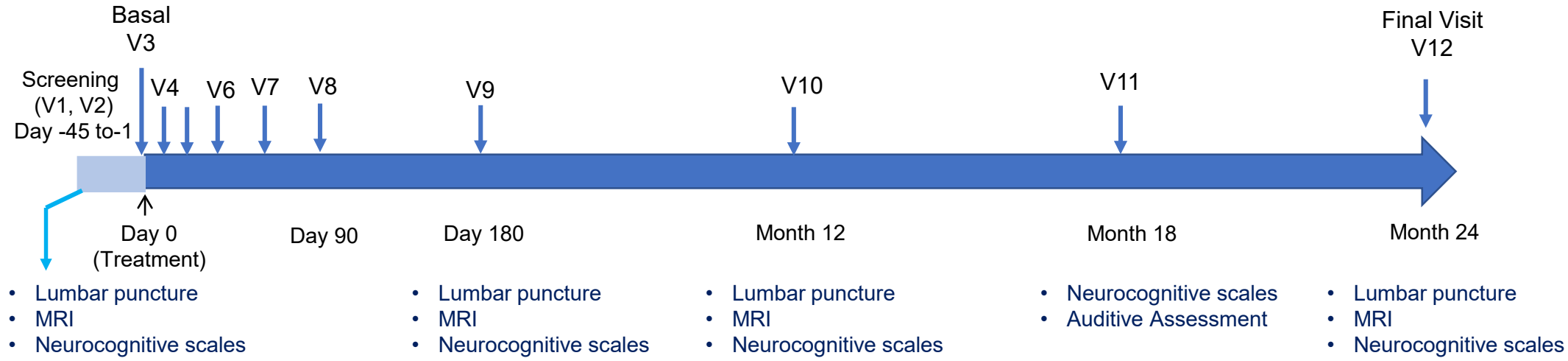
* Zelei et al. 2018. Orphanet Journal of Rare Diseases

Transpher A: Phase 1/2 Clinical Trial for MPS IIIA with scAAV9.U1.hSGSH

Intravenous Dosing	• **Cohort 1**: 5 x 10^{12} vg/kg (n=3) • **Cohort 2**: 1 x 10^{13} vg/kg (n=3) • **Cohort 3**: 3 x 10^{13} vg/kg (n= 9 to 16)
Inclusion Criteria	• 6 mo - 2 yrs of age or older than 2 years with a Developmental Quotient (DQ) ≥ 60 (using the Bayley Scale) • Confirmed Diagnosis of MPS IIIA by genetic and enzymatic determinations
Primary Endpoint	• Age Equivalent Developmental score compared with Natural History Study data assessed by the MSEL • Product safety
Secondary Endpoints	• Change from baseline in biomarkers after treatment: CSF, plasma and urine • Change from baseline in Liver, spleen and brain volume by MRI • Neurocognitive function as measured by Mullen Scales of Early Learning or Bayley Scales of Infant and Toddler Development • Adaptive functioning, by Vineland Adaptive Behavior Scale (caregiver report) • Change from baseline in the Sanfilippo Behavior Rating Scale [Time Frame: Month 6, 12, 18, 24] • Change from baseline in Pediatric Quality of Life Inventory (PedsQL™) total score [Time Frame: Month 6, 12, 18, 24] • Change from baseline in parent quality of life, using the Parenting Stress Index, 4th Edition (PSI-4) short form [Month 12, 24]

Clinical Trial Design and Schedule of Visits

Study Duration	24 months (followed by a Long-term follow up study for additional 3 years)
Administration	Single intravenous administration in 15-45 minutes. Hospital for 2 days. Steroids for the first 2 months (1 mg/kg prednisone or prednisolone)
Comparator Group	Natural History Studies
Visit schedule	Screening, basal, Days 7, 14, 30, 60, 90, 180, Months 12, 18 and 24



Enrollment and Safety Update

26 patients have been screened as of May 2020:

- 10 patients have failed screening
- 15 patients have been treated (Cohort 1=3; Cohort 2=3; Cohort 3=9)
- 1 patient screened and scheduled for dosing

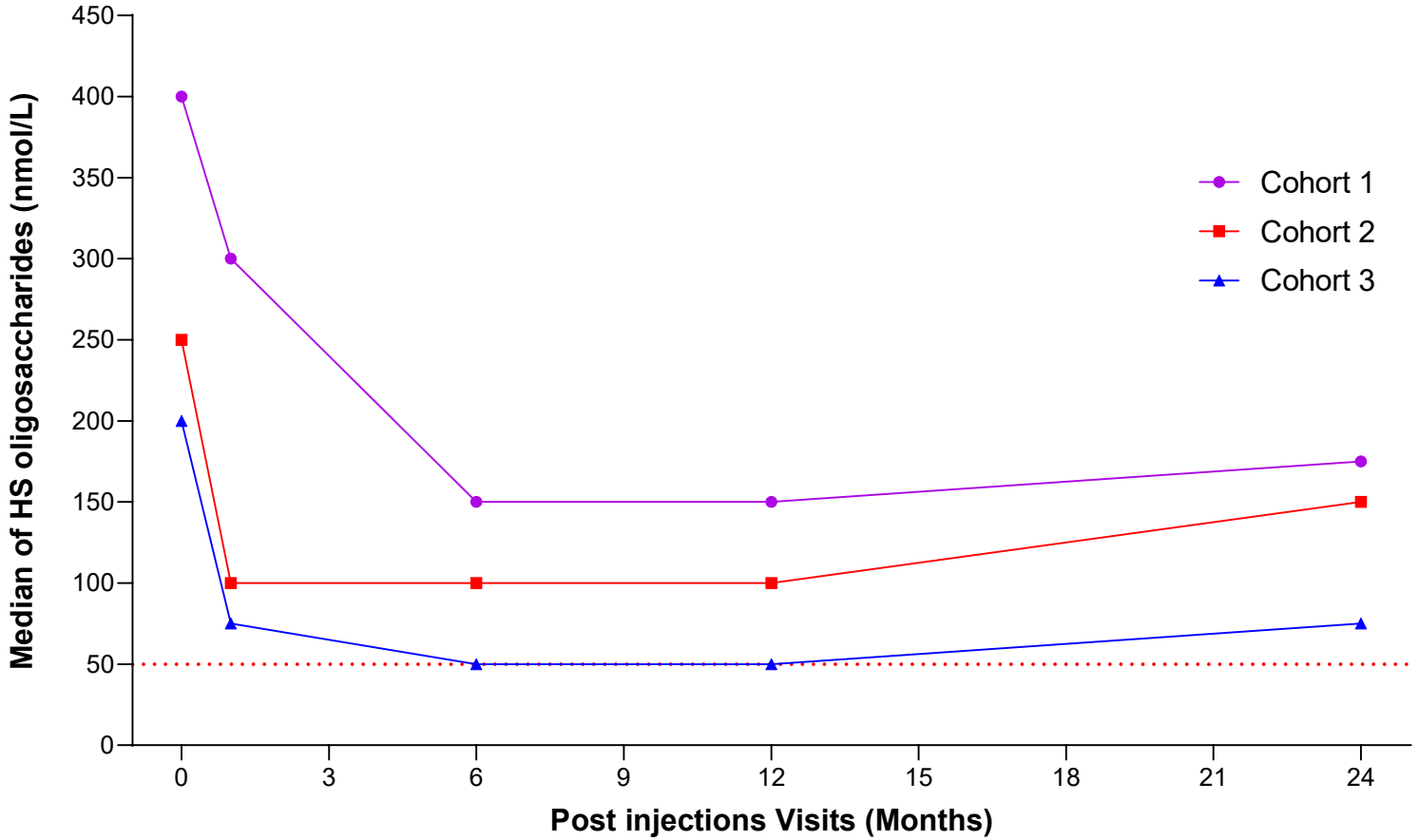
Mean follow up as of April 2020 (n=14)

- Cohort 1: 46 months
- Cohort 2: 38 months
- Cohort 3: 26 months

ABO-102 has been well tolerated

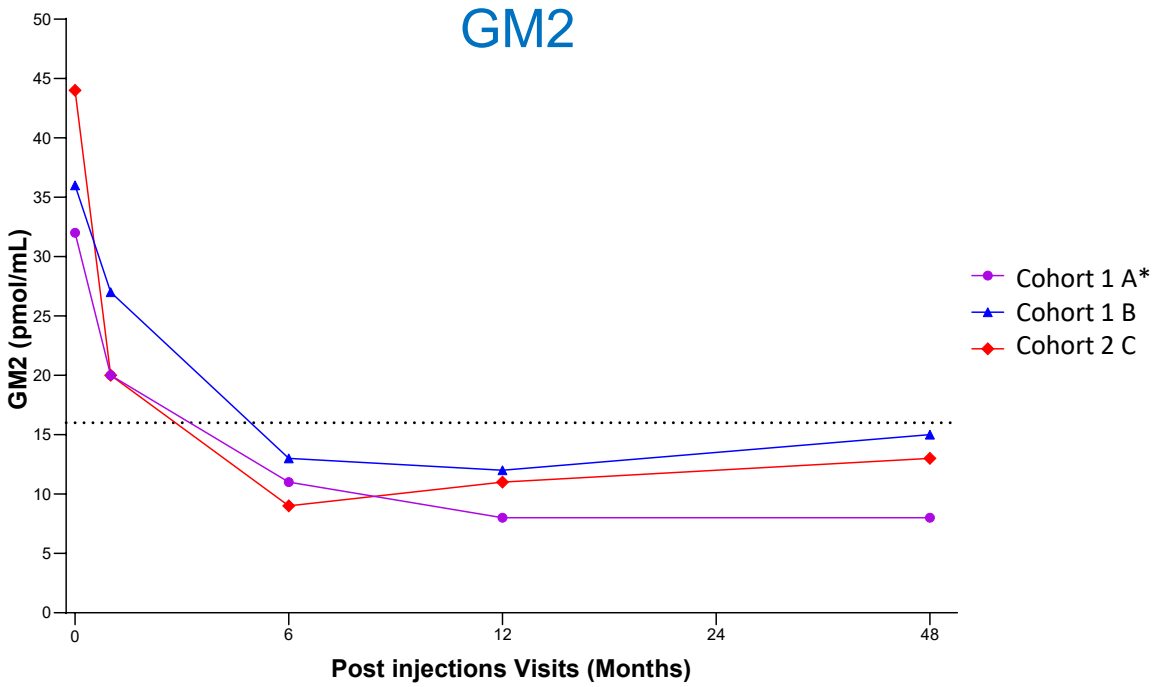
- No infusion-related adverse events
- No drug-related SAEs
- Drug-related AEs have been Grade 1 or 2 and all resolved
  - Subclinical, transient ALT and AST elevations, without accompanying changes in GGT or bilirubin.
  - ELISpots have been negative with the exception of low and transient positive responses to AAV9 capsid peptides in 8 out of 14 patients
  - Mild and transient thrombocytopenia in 4 patients, not clinically significant (lowest level 69K)

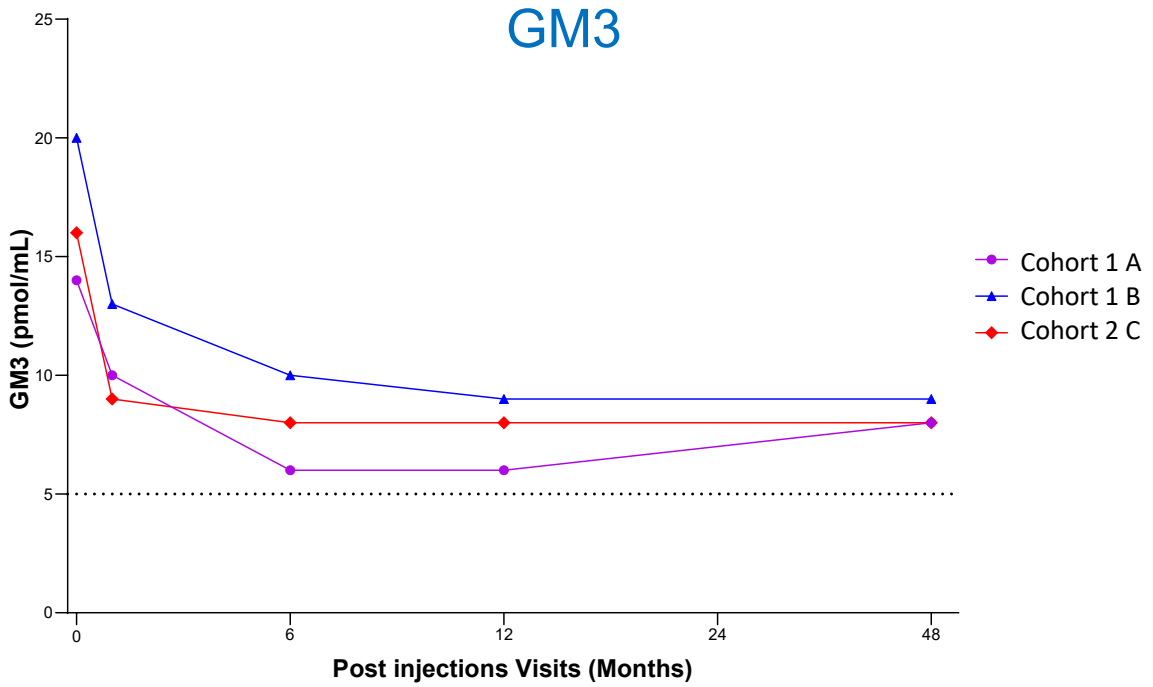
Rapid, Dose-dependent, and Sustained Reduction in CSF Heparan Sulfate Post Treatment



No Patients	Screening	Month 1	Month 6	Month 12	Month 24
Cohort 1	3	3	3	2	2
Cohort 2	3	3	3	3	3
Cohort 3	8	8	8	8	4

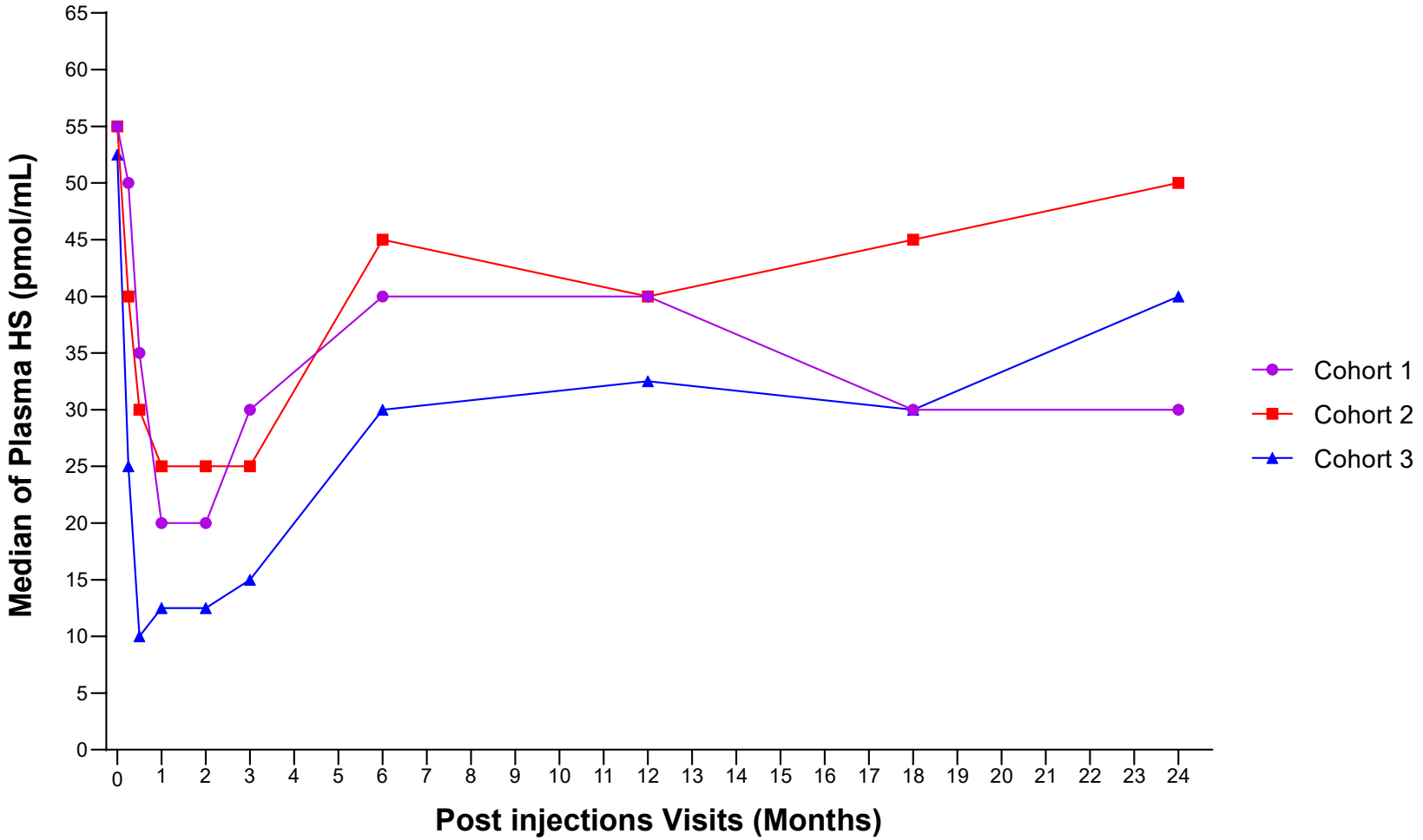
Reduction in CSF ganglioside (GM2 and GM3) Levels Post Treatment





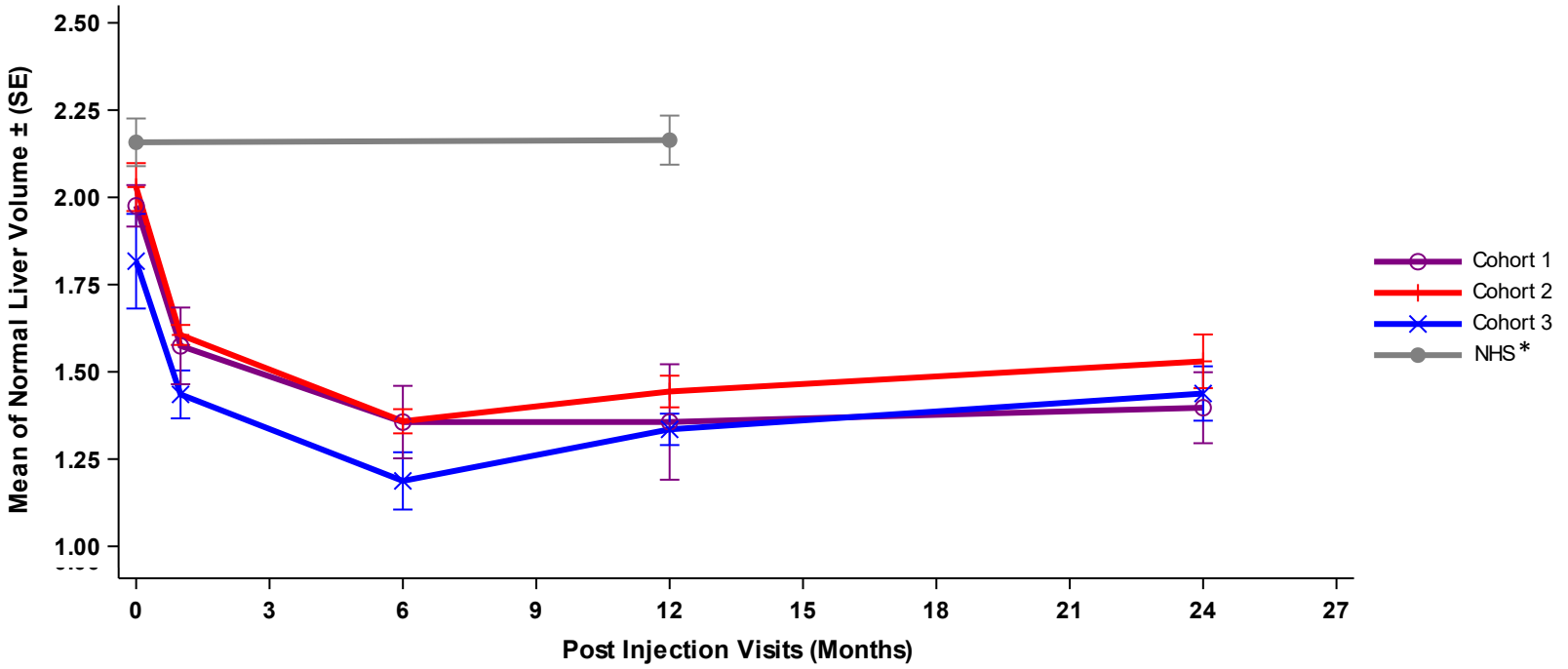
* Data from the first three subjects analyzed (A and B from Cohort 1 and C from Cohort 2)

Reduction in Plasma Heparan Sulfate Levels



No Patients	Screening	Day 7	Day 14	Month 1	Month 2	Month 3	Month 6	Month 12	Month 18	Month 24
Cohort 1	3	3	3	3	3	3	3	3	3	3
Cohort 2	3	3	3	3	3	3	3	3	3	3
Cohort 3	6	5	5	8	8	8	8	8	6	3

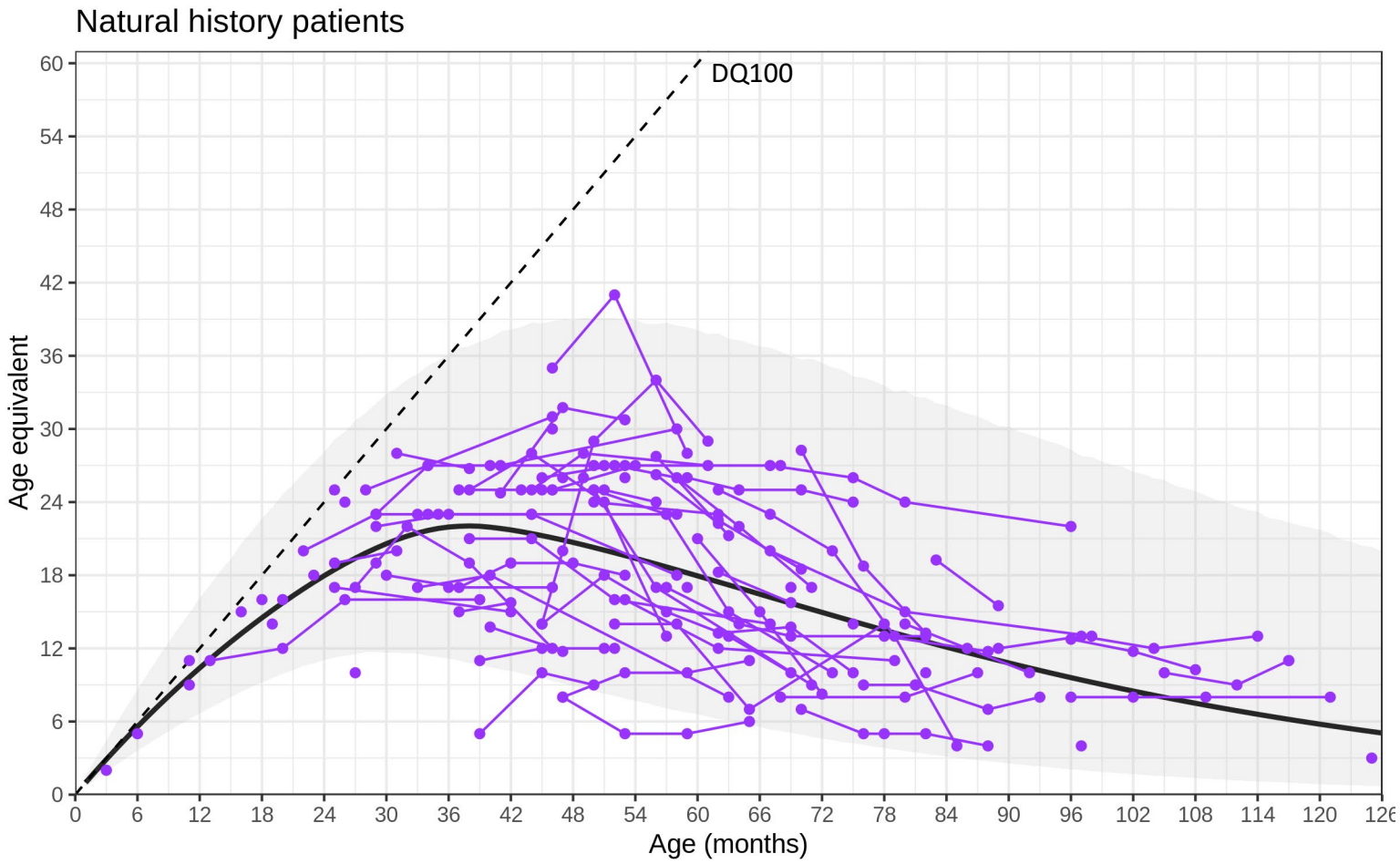
Durable, Dose-dependent Reduction in Liver Volume Post Treatment



No Patients	Screening	Month 1	Month 6	Month 12	Month 24
Cohort 1	3	3	3	3	3
Cohort 2	3	3	3	3	3
Cohort 3	7	8	8	8	2

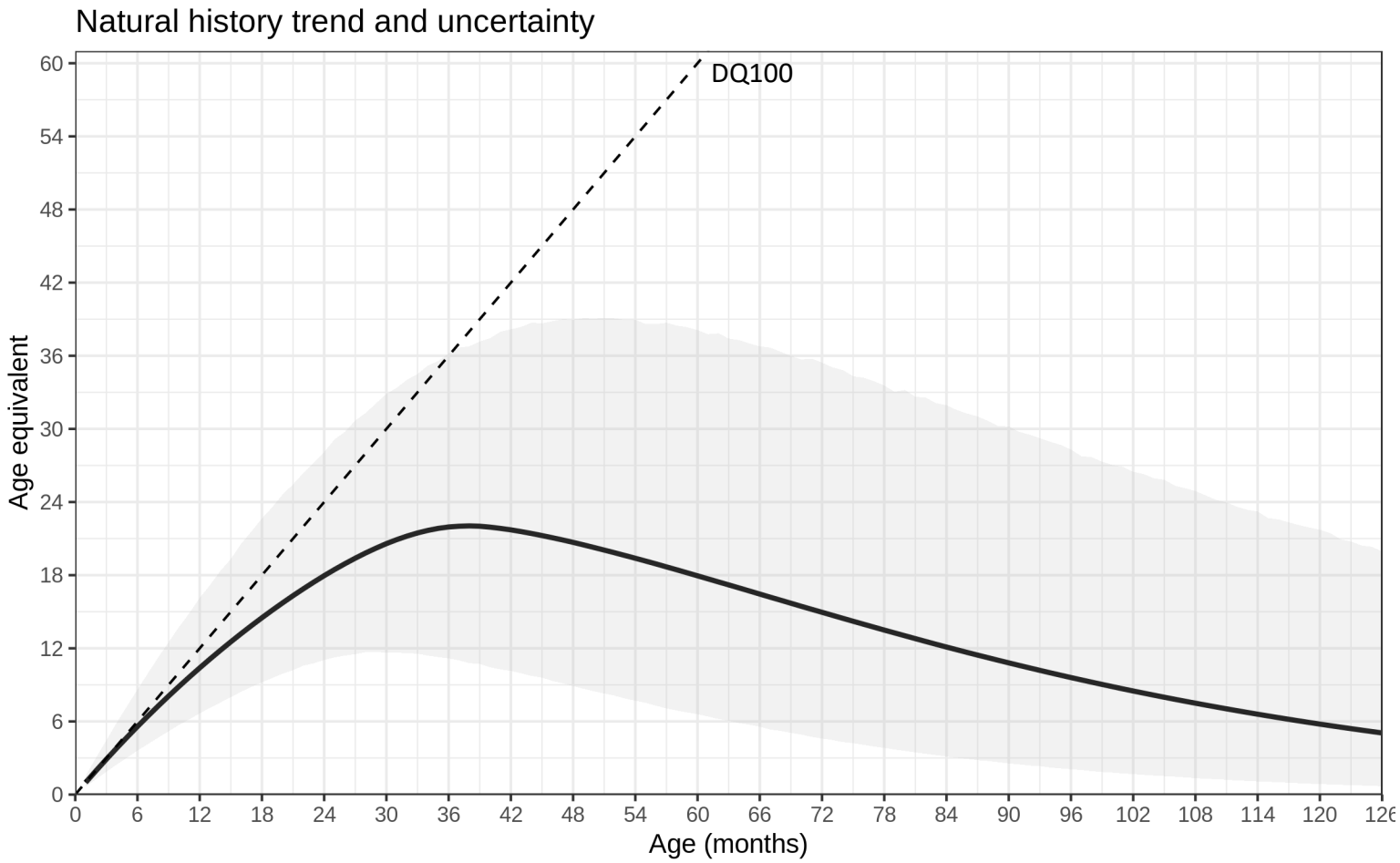
*Truxal et al, 2016, Mol Genet Metab

Natural-History Disease Progression Model



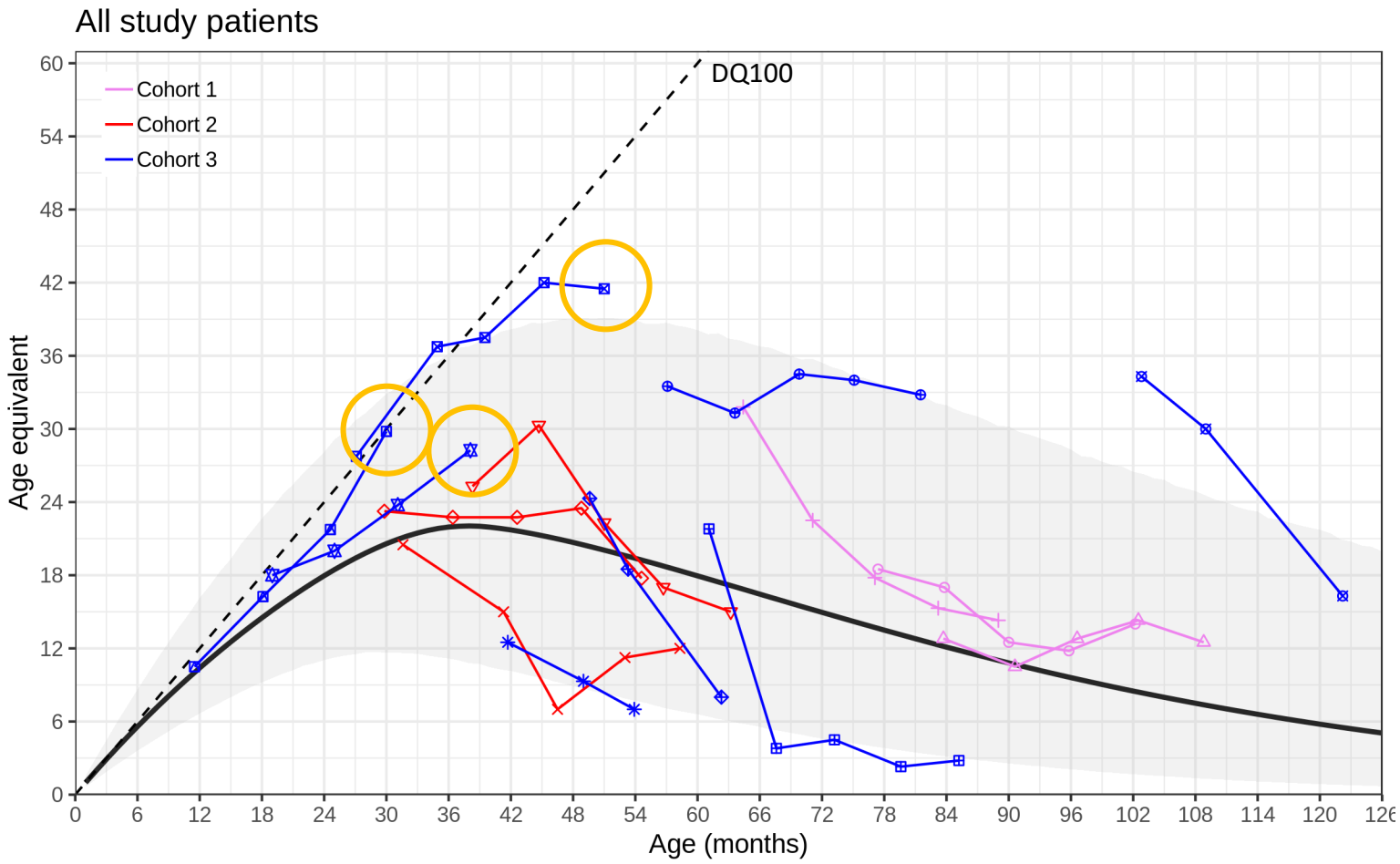
Truxal *et al, Mol Genet Metab,* 2016
Berman *et al, J Inherit Metab Dis* 2014
Shapiro *et al, J Pediatrics*, 2016
Wijburg *et al,* WORLD Symposium, 2018

Natural-History Disease Progression Model



The black solid line is the typical developmental pattern for children with MPS IIIA according to Natural History Data
The gray shaded area is a 95% credible interval, incorporating variability from patient-to-patient differences and measurement error.
The black dotted line shows the expected development for children without disease

Mullen's Cognitive Age Equivalent Post Treatment vs. Natural-History Disease Progression Model



The black solid line is the typical developmental pattern for children with MPS IIIA according to Natural History Data
The gray shaded area is a 95% credible interval, incorporating variability from patient-to-patient differences and measurement error.
The black dotted line shows the expected development for children without disease

Summary: Phase 1/2 Study Data (N=15) with ABO-102 (scAAV9.U1.hSGSH)

Well-tolerated with no treatment-related SAEs and no clinically significant AEs 15-45 months post-dosing (n=14)

- Follow-up: Cohort 1 (n=3; 44.5-48 months), Cohort 2 (n=3; 36.5-39 months), Cohort 3 (n=8; 18-33 months)

Evidence of clinical benefit

- Preservation of neurocognitive development in the three young patients treated before 30 months of age in cohort 3 (18-24 months of follow-up)
- Rapid and sustained, dose-related reduction in disease-specific biomarkers
  - CSF levels of heparan sulfate reduced to lower limit of quantitation
  - CSF gangliosides (GM2 and GM3) reduced significantly, within normal range in the case of GM2
  - HS levels in the CSF provide evidence of CNS enzyme activity following ABO-102 administration (HS or GM2/GM3 don't cross the blood-brain barrier)
- Sustained decrease in liver volume, with up to 24 months of follow-up in Cohorts 1, 2 and 3

Acknowledgments

We thank all the patients and families and the MPS community for their participation in and support of this study

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- Kelly McNally, PhD
- Krista Cope
- Tabatha Simmons PhD

Women's and Children's Hospital
ADELAIDE

- **Nick Smith, MD, PhD**
- Mark Pertini, MD
- Louise Jaensch, CRN
- Maria Fuller, PhD

Complexo Hospitalario Universitario de Santiago de Compostela

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- Michael Snyder
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- Ruth Fuentes

Transpher B, an open-label, multicenter, single-dose, dose-escalation, Phase 1/2 Clinical Trial of gene transfer of ABO-101 in Sanfilippo Syndrome type B (Mucopolysaccharidosis IIIB)

María José de Castro, K M Flanigan, B Héron, M L Couce, K V Truxal, K L McBride, C Ravelli, T R Simmons, K A McNally, F Rinaldi, K Giraudat, L Lopez, M Tajes, M T Oreiro, R Chans, M Fuller, A B del Campo, J Ruiz

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Abeona Therapeutics Inc.

Sanfilippo Syndrome (MPS III)

A group of four clinically indistinguishable lysosomal enzyme deficiencies that result in accumulation of the glycosaminoglycan (GAG) heparan sulfate (HS)

- Global incidence varies by regions and it is estimated 0.17-2.35 per 100,000 births*
- MPS IIIB is the second subtype in frequency and it is caused by a deficiency in N-Acetyl-Alpha-Glucosaminidase (NAGLU)

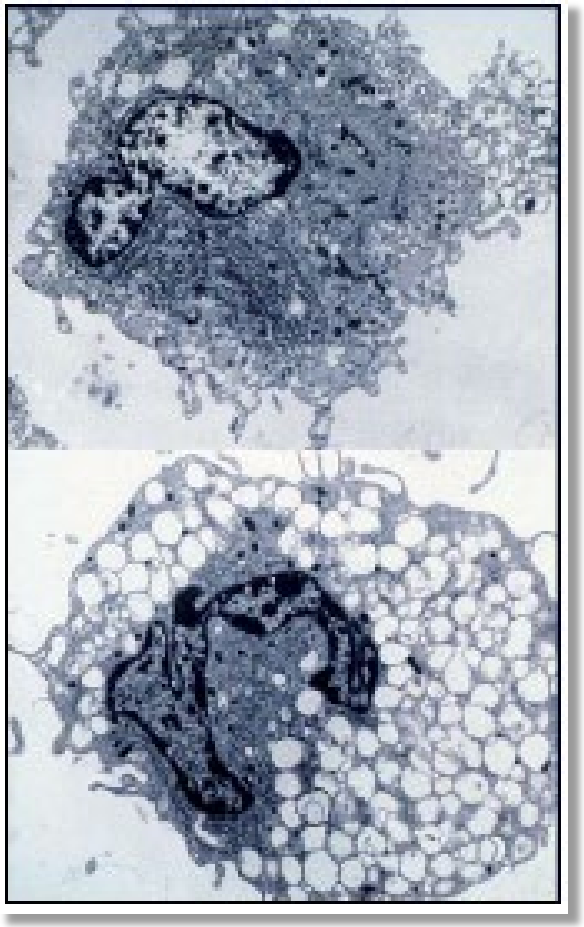
Disease manifest as early as 12-24 months involving:

- *Central nervous system features predominate (gray > white matter)*
  - Slowing and then regression of development, first speech/cognitive then gross motor
  - Impulsivity, hyperactivity, sleep disturbance, aggressive behavior, seizures
  - Relentless loss of skills progressing to dementia
- *Somatic features are milder than other MPS disorders*
  - Coarse facial features/hirsutism, frequent otitis media, airway compromise, Umbilical hernia, hepatosplenomegaly, mild dysostosis multiplex/short stature, heart valve thickening

No approved treatments available

- 70% of children with MPS III do not reach age 18 years of age

Normal cell



Cell with
lysosome deficiency

* Zelei et al. 2018. Orphanet Journal of Rare Diseases

Transpher B phase 1/2 Clinical Trial for MPS IIIB with rAAV9.CMV.hNAGLU

Intravenous Dosing	• **Cohort 1**: 1 x 10^{13} vg/kg (n=2) • **Cohort 2**: 5 x 10^{13} vg/kg (n=5) • **Cohort 3**: 1 x 10^{14} vg/kg (n= up to 5)
Inclusion Criteria	• 6 mo - 2 yrs of age or older than 2 years with a Developmental Quotient (DQ) ≥ 60 (using the Bayley Scale) • Confirmed Diagnosis of MPS IIIB by genetic and enzymatic determinations
Primary Endpoint	• Age Equivalent Developmental score compared with Natural History Study data • Product safety
Secondary Endpoints	• Change from baseline in biomarkers after treatment • Change from baseline in Liver, spleen and brain volume by MRI • Neurocognitive function as measured by Mullen Scales of Early Learning or Bayley Scales of Infant and Toddler Development • Adaptive functioning, by Vineland Adaptive Behavior Scale (caregiver report) • Change from baseline in the Sanfilippo Behavior Rating Scale [Time Frame: Month 6, 12, 18, 24] • Change from baseline in Pediatric Quality of Life Inventory (PedsQL™) total score [Time Frame: Month 6, 12, 18, 24] • Change from baseline in parent quality of life, using the Parenting Stress Index, 4th Edition (PSI-4) short form [Time Frame: Month 12, 24]

Clinical Trial Design and Schedule of Visits

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Administration	Single intravenous administration in 15-45 minutes. Hospital for 2 days. Steroids for the first 2 months (1 mg/kg prednisone or prednisolone)
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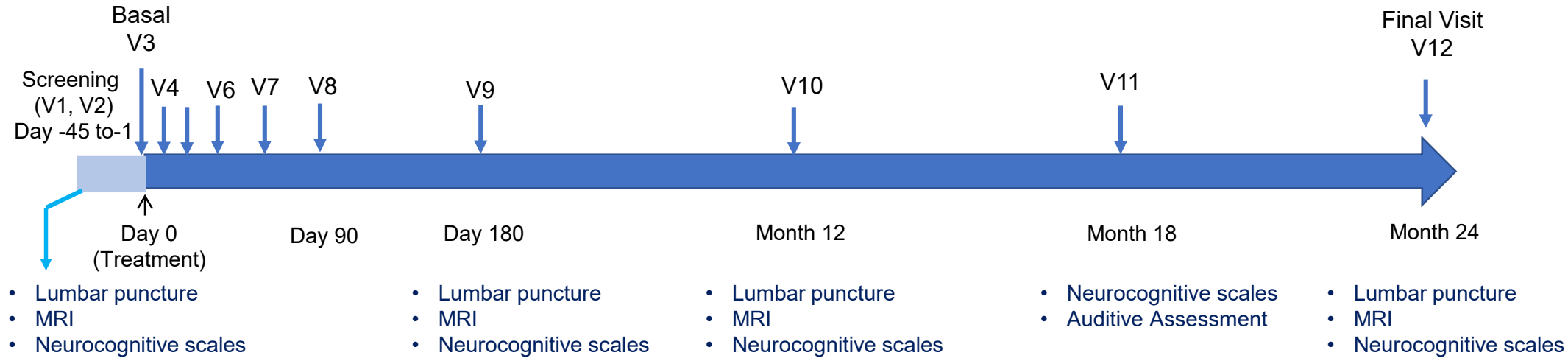


Enrollment

13 patients have been screened:

- 3 patients have failed screening
- 9 patients have been treated (Cohort 1=2; Cohort 2=5; Cohort 3=2)
- 1 patient pending dosing

Two pairs of siblings have been enrolled and treated

- A 5.3 year old girl in Cohort 1 and her 4 months old sister in Cohort 2 (under a protocol waiver)
- A 3.7 year old boy and his 1.75 year old sister in Cohort 2

Safety Update

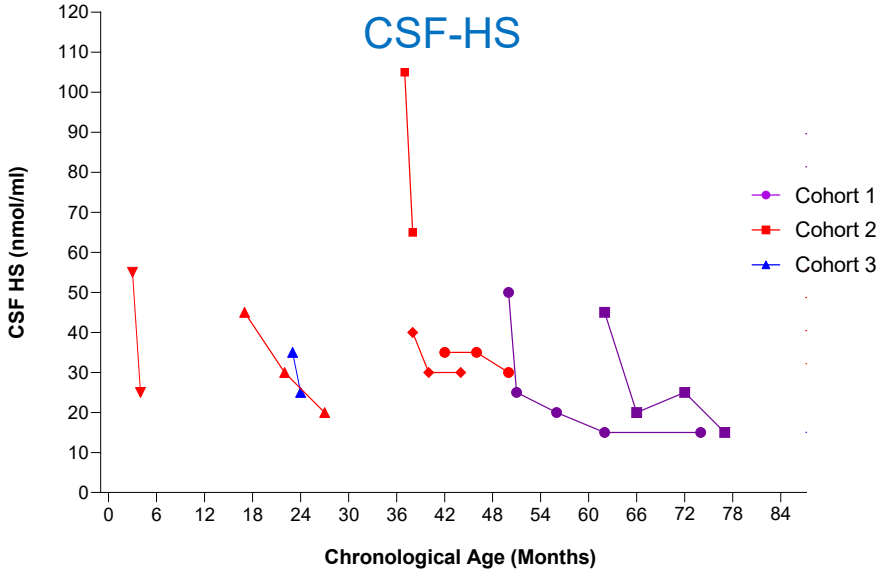
Mean follow up as of April 2020

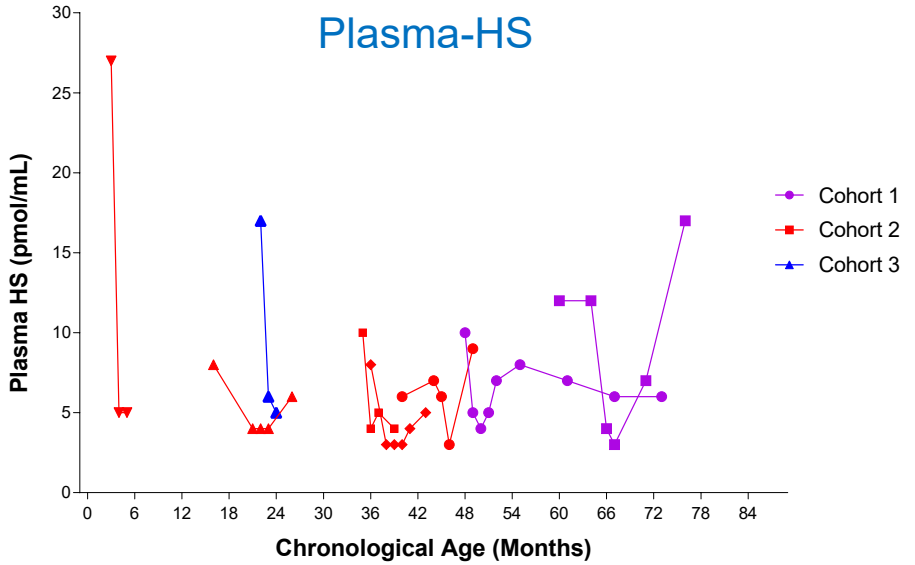
- Cohort 1: 22 months
- Cohort 2: 9 months
- Cohort 3: 1.8 months

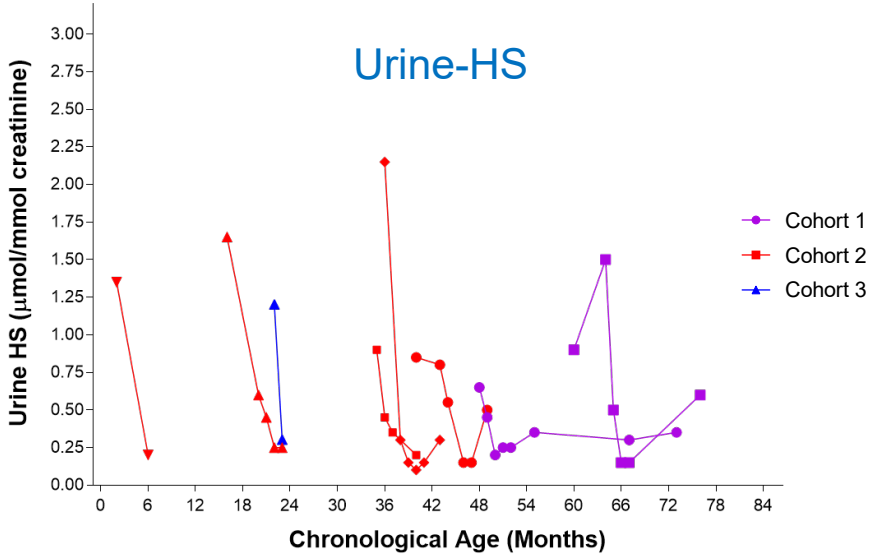
ABO-101 has been well tolerated

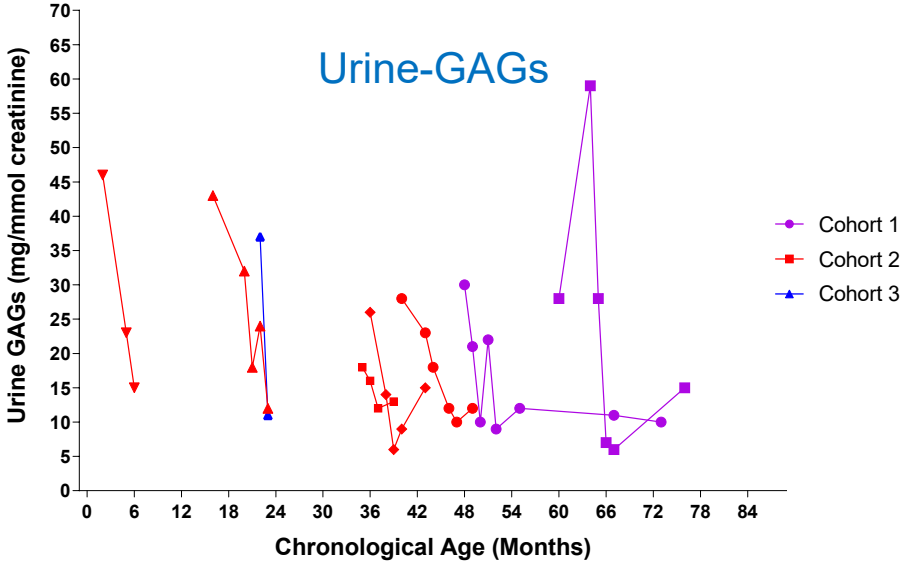
- No infusion-related adverse events
- No drug-related SAEs
- Drug-related AEs include
  - Subclinical, transient ALT and AST elevations, without accompanying changes in GGT or bilirubin
  - Mild and transient decrease in WBC and absolute lymphocyte counts in 2 subjects
  - AEs: grade 1/2 vomiting (n=5 subjects), anorexia n=2 subjects (associated with fever n=1), asthenia and vomiting (n=1)
  - ELISpot to AAV9 capsid peptide pools have been negative in all subjects, except in one subject in Cohort 1 that was positive at Month 12 but negative again at Month 18

Improvement in Disease Biomarkers in CSF, Plasma, Urine

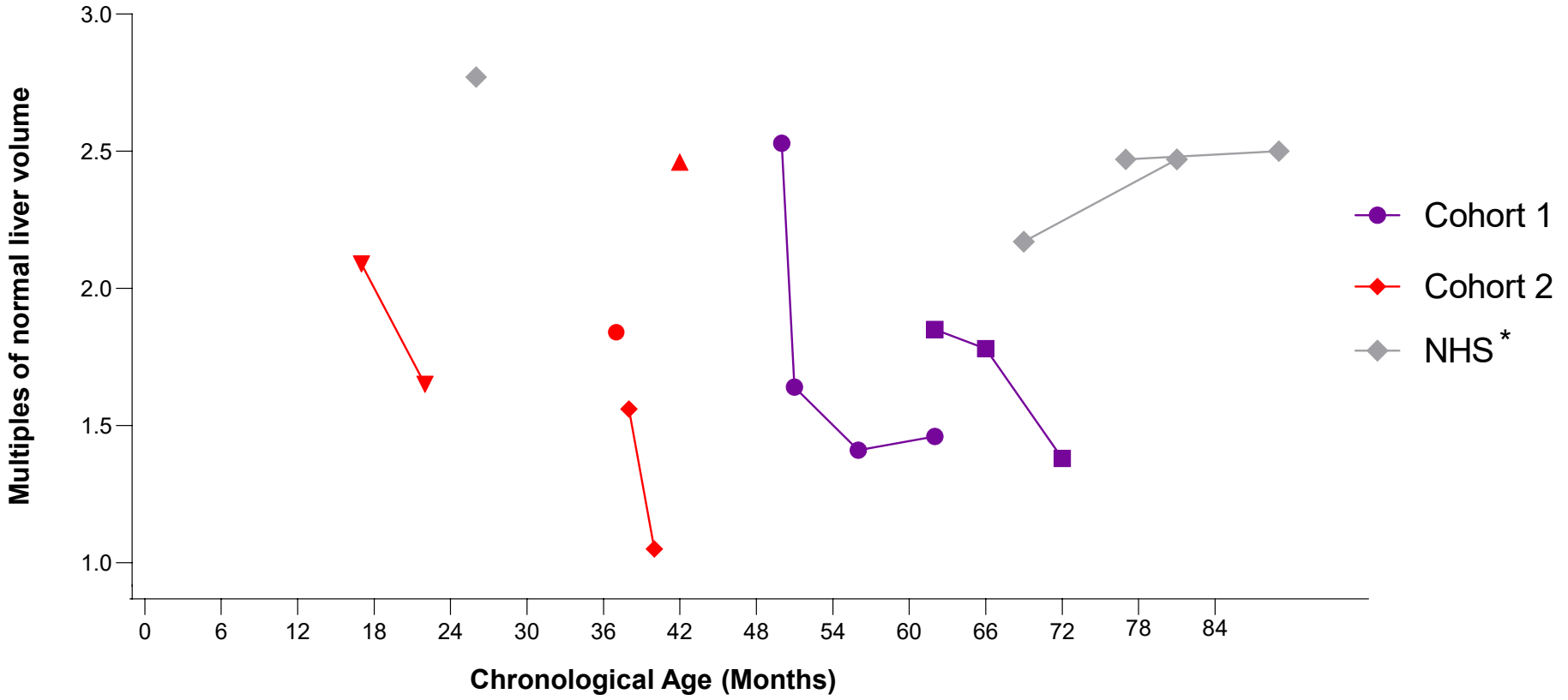






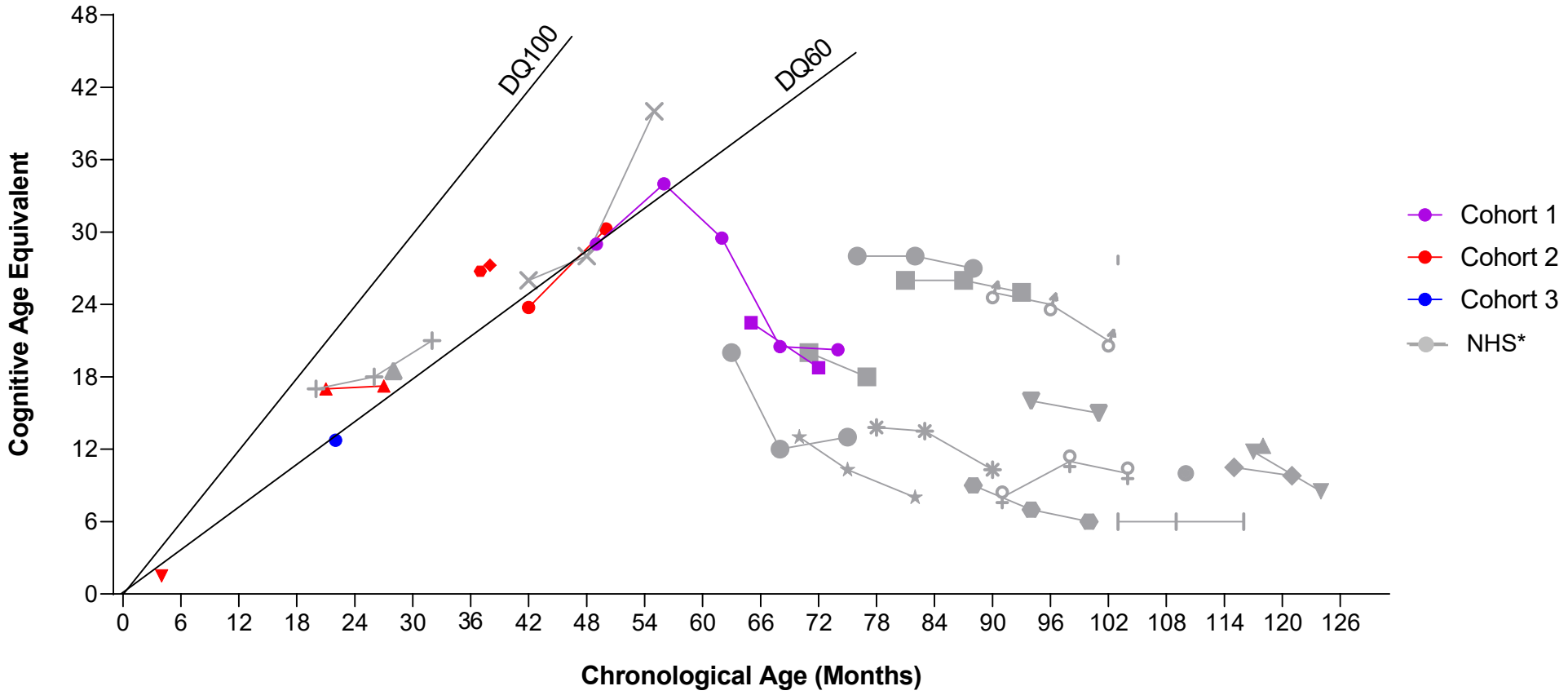


Reduction in Liver Volume Post Treatment



*Truxal et al, 2016, Mol Genet Metab; Whitley et al, 2018, J Pediatr

Mullen's Cognitive Age Equivalent Post-Treatment vs. Natural History



*Truxal et al, 2016, Mol Genet Metab; Whitley et al, 2018, J Pediatr

Summary: Phase 1/2 Study Data (N=9) with ABO-101

Well-tolerated with no treatment-related SAEs and no clinically significant AEs or laboratory abnormalities

- Follow-up: cohort 1 (n=2; 15 to 29 months); cohort 2 (n=5; 5.2 to 12 months); cohort 3 (n=2; 0.7 to 2.9 months)

Clear biologic effect post treatment

- Decreased CSF HS levels (maintained up to 12 months)
- Reduction in plasma and urine HS and GAGs
- Reduction in liver volume
- Limited follow-up duration to date preclude adequate assessment of neurological outcomes

Active enrollment in cohort 3 ($1E^{14}$ vg/kg)

Acknowledgments

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