CAN*aspire* Trial of Systemic AAV9-mediated Gene Therapy for Canavan Disease: Biomarker, Imaging and Clinical Findings

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Author Disclosures and Disclaimer

Florian Eichler:

- PI of in vivo gene therapy trial in Canavan disease sponsored by Aspa Therapeutics, a subsidiary of BridgeBio Pharma
- Co-PI of ex vivo lentiviral gene therapy trial in cerebral adrenoleukodystrophy sponsored by bluebird bio
- Co-PI of in vivo gene therapy trial in GM2 sponsored by Sio Therapeutics
- Site-PI of trials in late onset GM2 sponsored by Sanofi Therapeutics and in Alexander Disease sponsored by Ionis Therapeutics
- Consultant to Autobahn, Poxel, Takeda, SwanBio Therapeutics, UpToDate and Taysha Gene Therapies
- Founder of SwanBio Therapeutics

Alex Fay: No disclosures

Amanda Nagy: No disclosures

Genevieve Laforet, Chrissy Burton, Rachel Williams, Adam Shaywitz: full-time employees and stockholders of BridgeBio Pharma

Paul Harmatz: No disclosures

Eric Mallack: No disclosures

Bernard Kinane: No disclosures

Elise Townsend: SME and consultant to Aspa Therapeutics, a subsidiary of BridgeBio Pharma, and Biogen

Michael Kiefer: receives financial compensation as an independent contractor for Aspa Therapeutics

Beth Leiro: SME and consultant for Aspa Therapeutics, a subsidiary of BridgeBio Pharma

Annette Bley: PI of Canavan disease natural history study CVN-101 (sponsored by Aspa Therapeutics), PI of PeriNAA-research project (sponsored by the German Government BMBF)

BBP-812 is under investigation and has not been approved by the FDA or any other regulatory authority

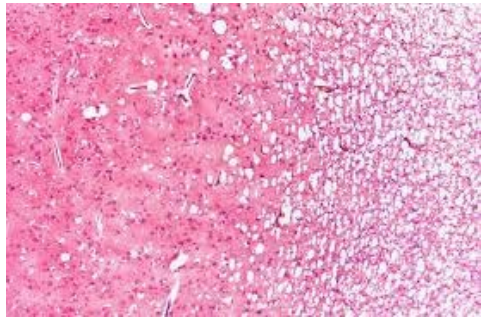
Canavan Disease Overview

Canavan Disease → **Aspartoacylase Deficiency** → **Demyelination of Neurons** → **Clinical Features**

Ultra-rare (1:100,000)

Autosomal recessive leukodystrophy (brain white matter disorder)

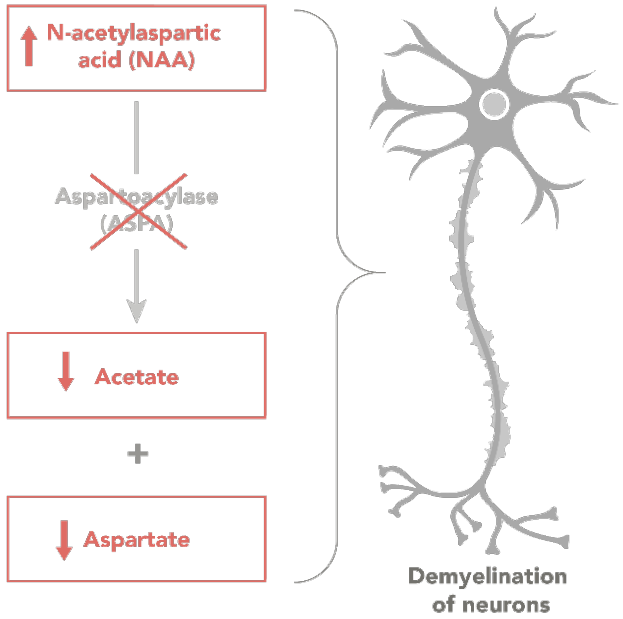
Caused by loss-of-function mutations in *ASPA*



Spongiform leukodystrophy

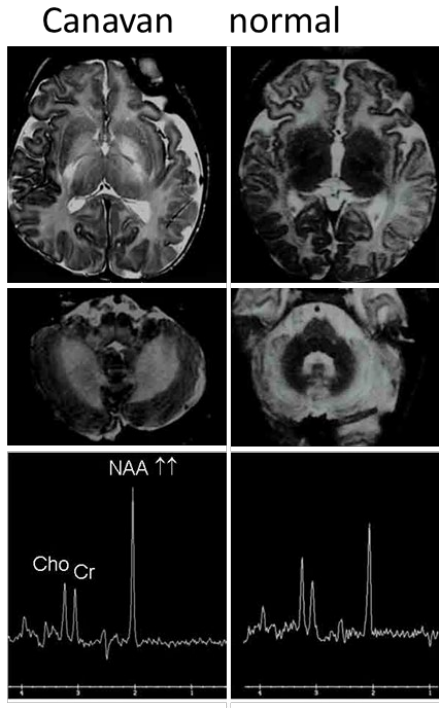
NAA buildup in brain, CSF, urine

Decreased acetate and aspartate production



failure to properly build and maintain CNS myelin

visible early in brainstem and cerebellar peduncles



Accelerated head growth

Poor head control

Nystagmus, abnormal visual tracking

Hypotonia, delayed motor development

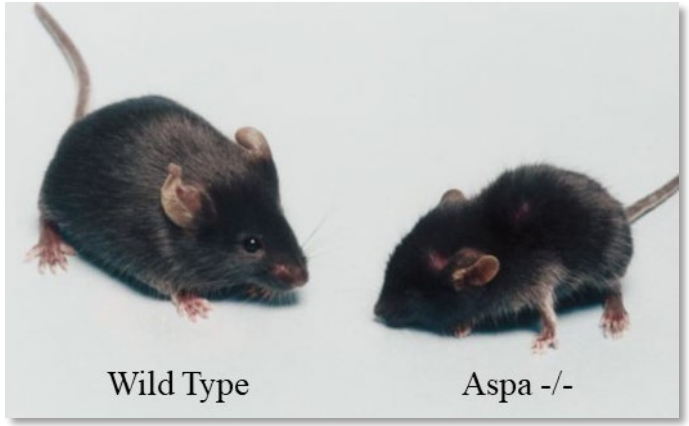
Seizures

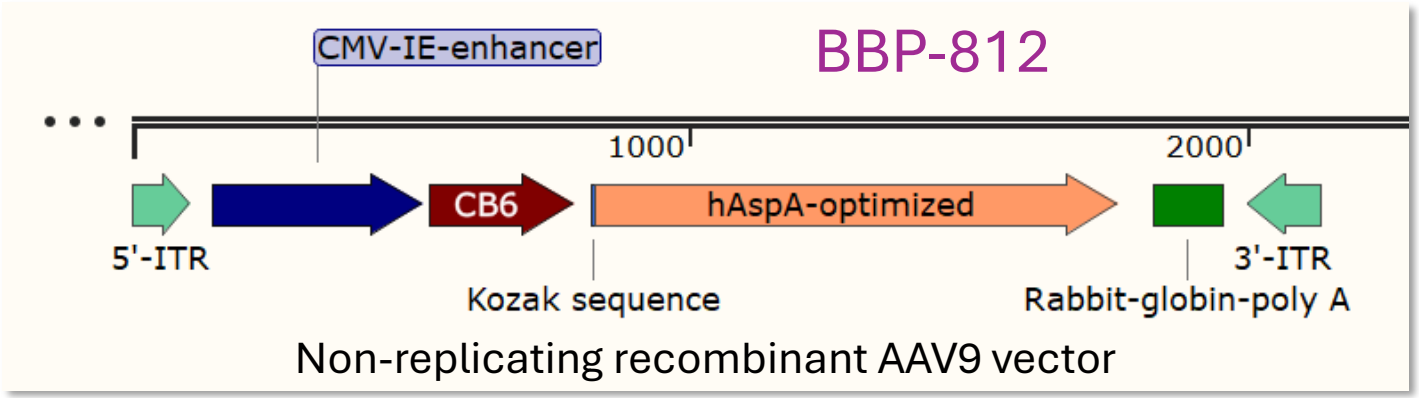
Fatal in childhood or adolescence

Matalon R et al. GeneReviews (Internet). 1999 Sep 16, 2018 Sep 13

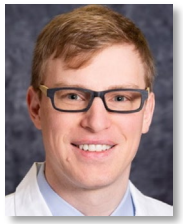
Caregiver permission granted for use of photo

BBP-812: Non-clinical Evidence Supporting Systemic AAV9-*ASPA* Administration in Canavan Disease





- *Aspa* -/- mouse model recapitulates key features of Canavan disease, including **NAA buildup**
- IV AAV9 *ASPA* gene therapy with BBP-812 led to dose-dependent improvements in NAA levels, histopathology and motor function
- Complete normalization of NAA and motor function at highest dose level

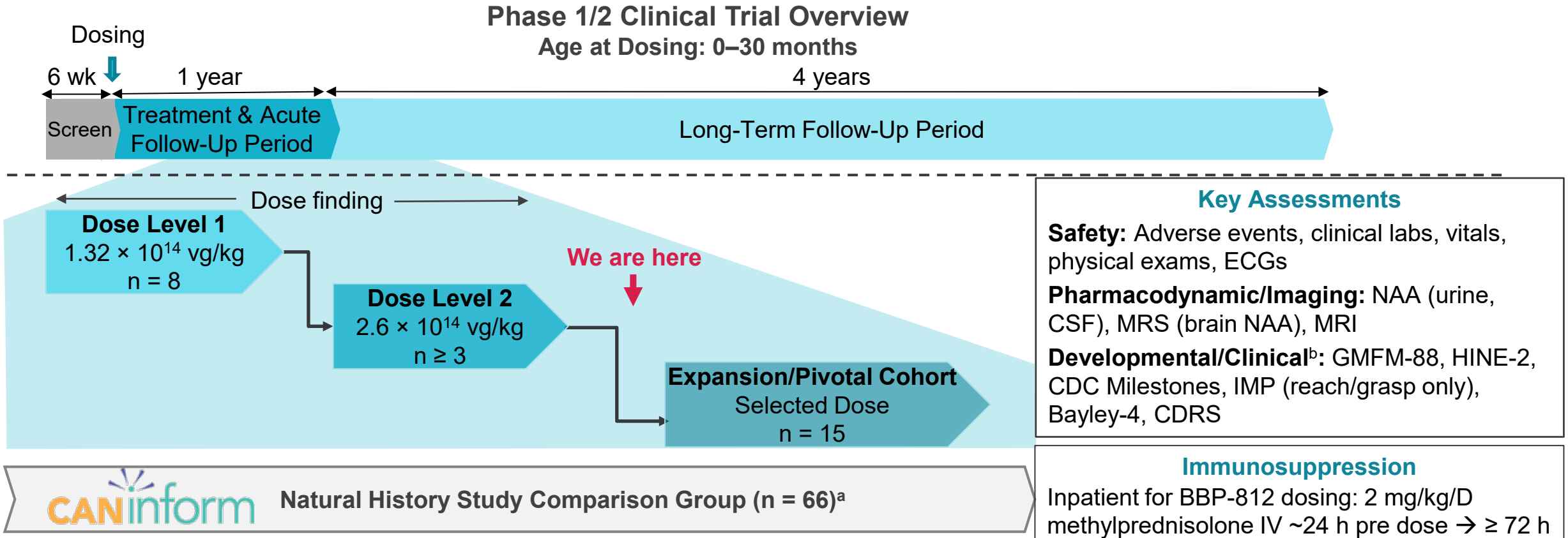


University of Massachusetts Medical School

Horae (红瑞) Gene Therapy Center

Gessler DJ et al. JCI Insight. 2017 Feb 9;2(3):e90807.

CANaspire CVN-102 Open-Label Gene Therapy Trial with CANinform CVN-101 Natural History Study as a Comparator



Key Assessments

Safety: Adverse events, clinical labs, vitals, physical exams, ECGs

Pharmacodynamic/Imaging: NAA (urine, CSF), MRS (brain NAA), MRI

Developmental/Clinical[b]: GMFM-88, HINE-2, CDC Milestones, IMP (reach/grasp only), Bayley-4, CDRS

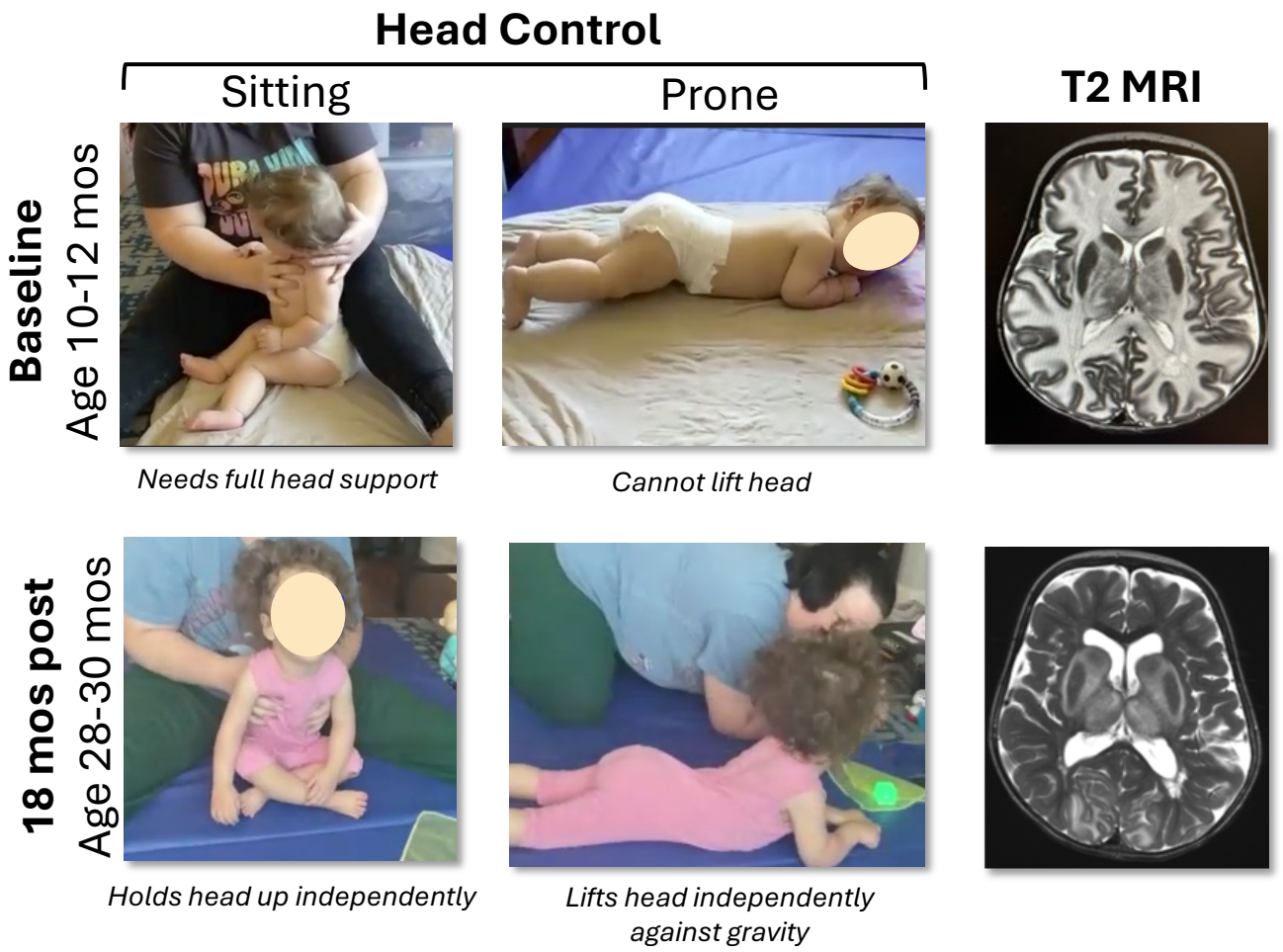
Immunosuppression

Inpatient for BBP-812 dosing: 2 mg/kg/D methylprednisolone IV ~24 h pre dose → ≥ 72 h post dose (until discharge)
Outpatient: 2 mg/kg/D prednisolone PO x 3 mos followed by taper

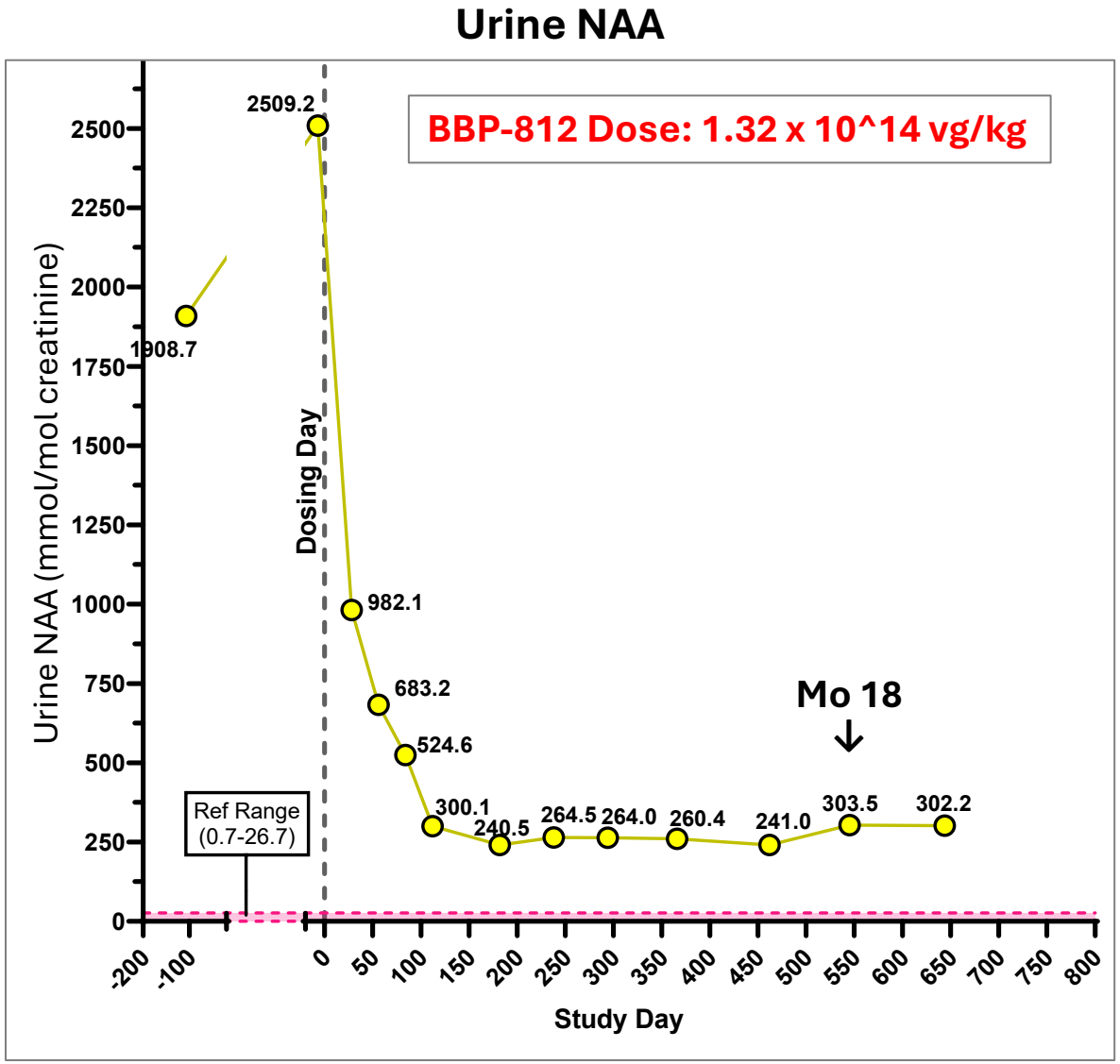
[a]As of October 2, 2024
[b]Key functional endpoints
CDC, Centers for Disease Control and Prevention; CDRS, Canavan Disease Rating Score; CSF, cerebrospinal fluid; ECG, electrocardiogram; GMFM, Gross Motor Function Measure; HINE-2, Hammersmith Infant Neurological Examination Section 2; IMP, Infant Motor Profile; kg, kilogram; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartic acid; vg, vector genomes; wk, week; mos, months

CAN*aspire*: NCT04998396 CAN*inform*: NCT04126005

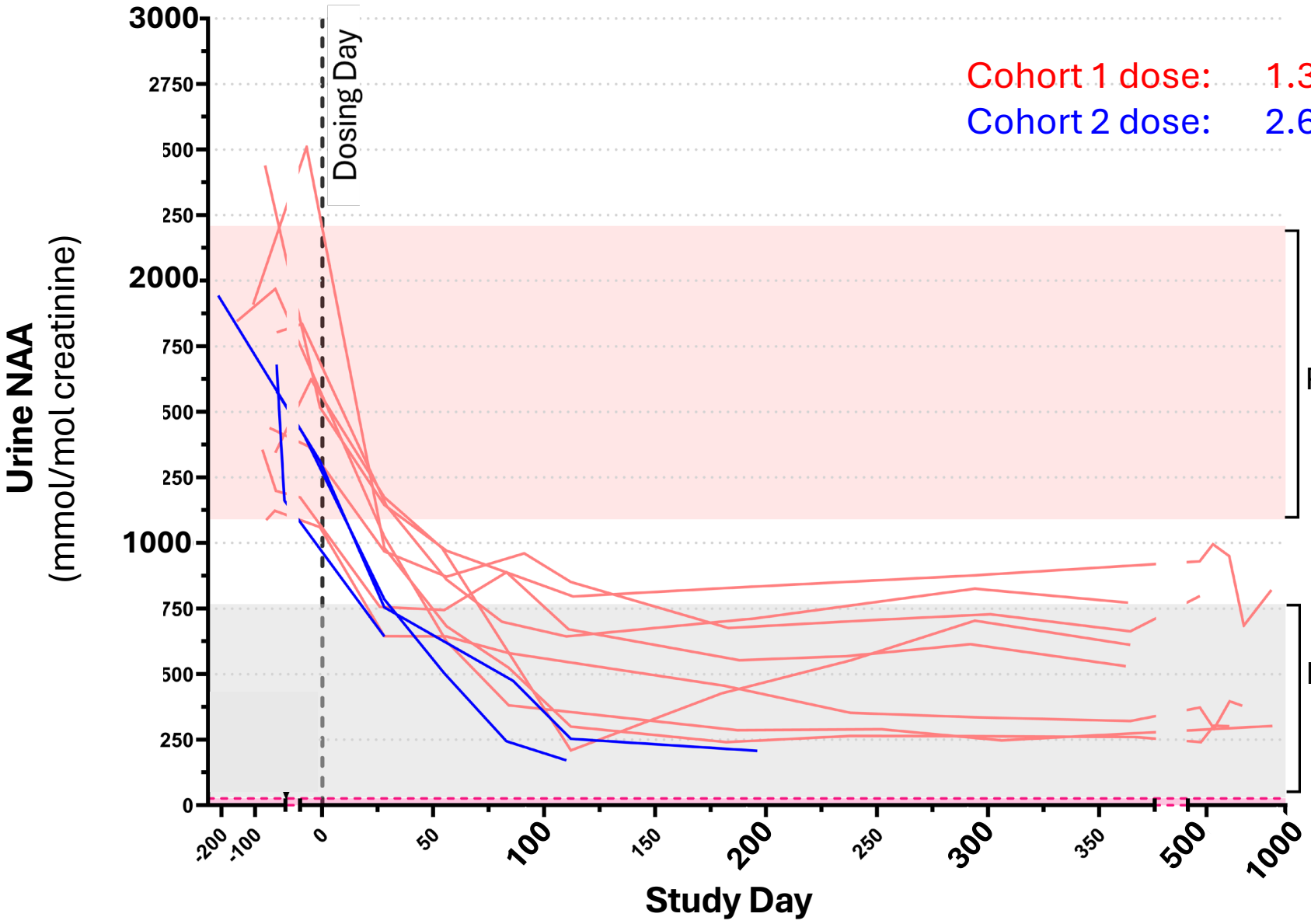
Improvements in Motor Function, Myelination, and Biomarker Levels: Example from a Participant 18 Months Post Dosing



Illustrative of one participant's experience. This participant is not an outlier.



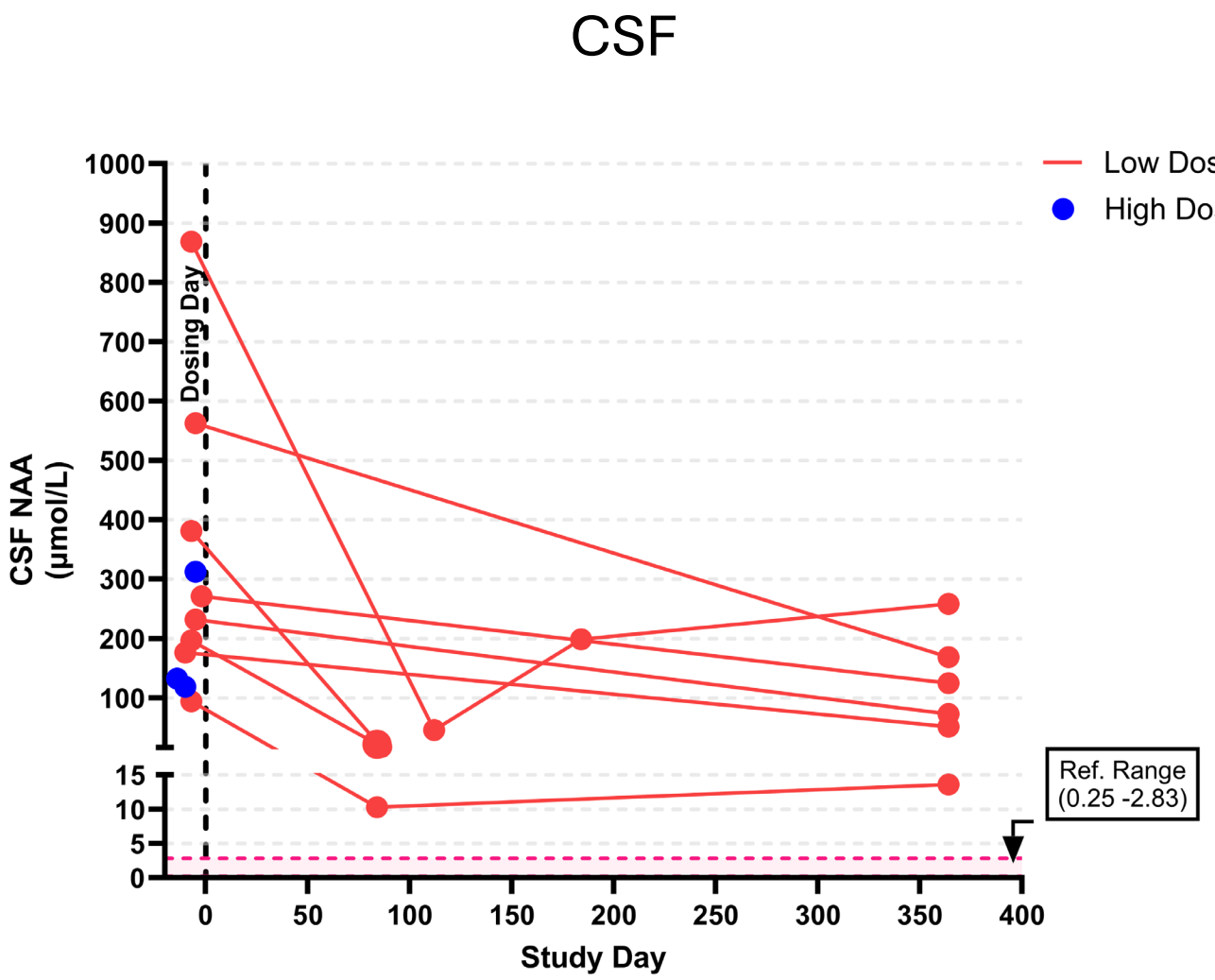
BBP-812 Reduces Urine NAA in All Participants



Participant	Age range at dosing, months
A	28-30
B	18-20
C	20-22
D	10-12
E	16-18
F	8-10
G	16-18
H	24-26
I	16-18
J	10-12
K	12-14

NAA, N-acetylaspartic acid; vg, vector genome.

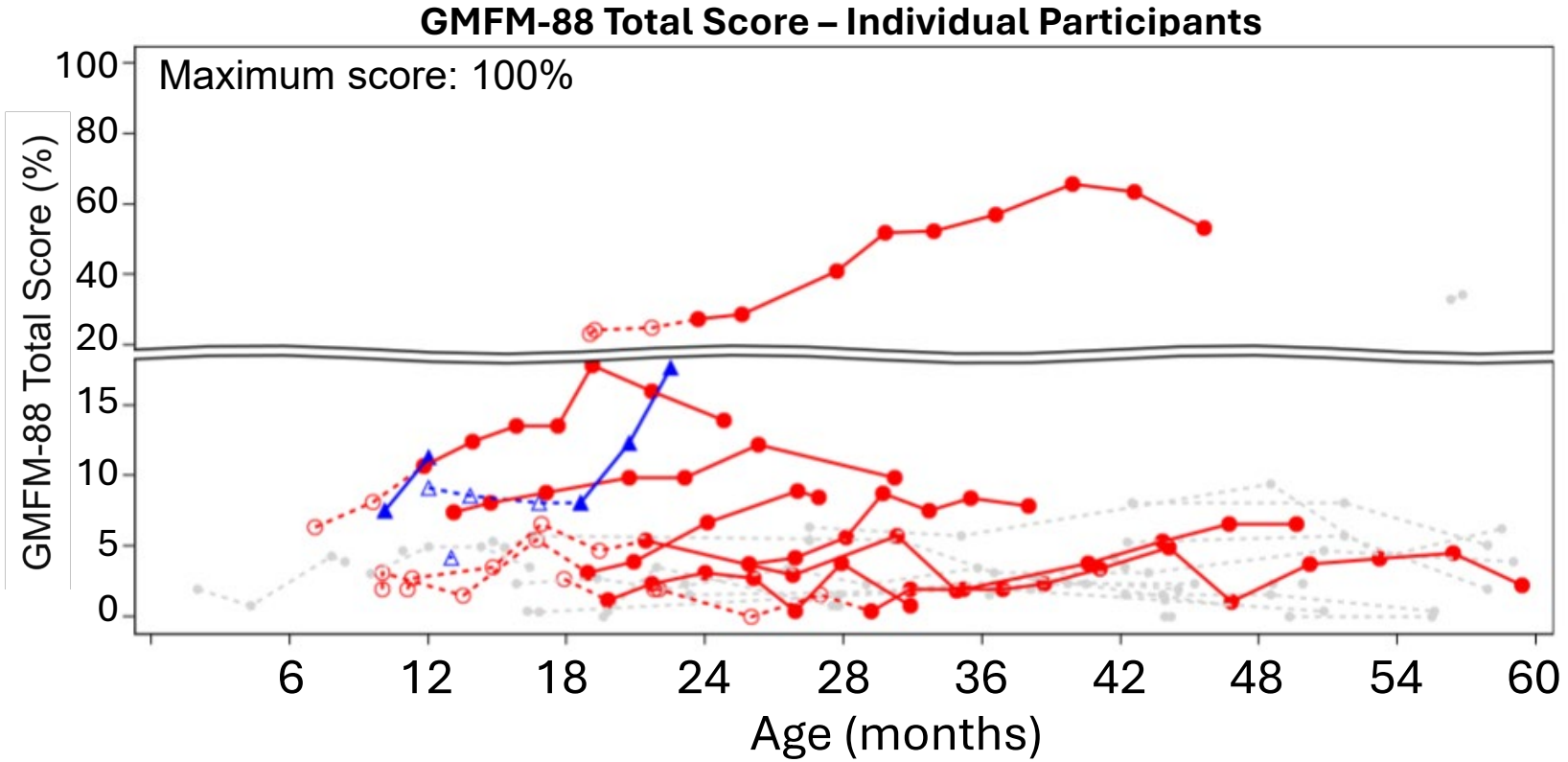
Decreased NAA in Cerebrospinal Fluid Seen in All Participants Post-BBP-812

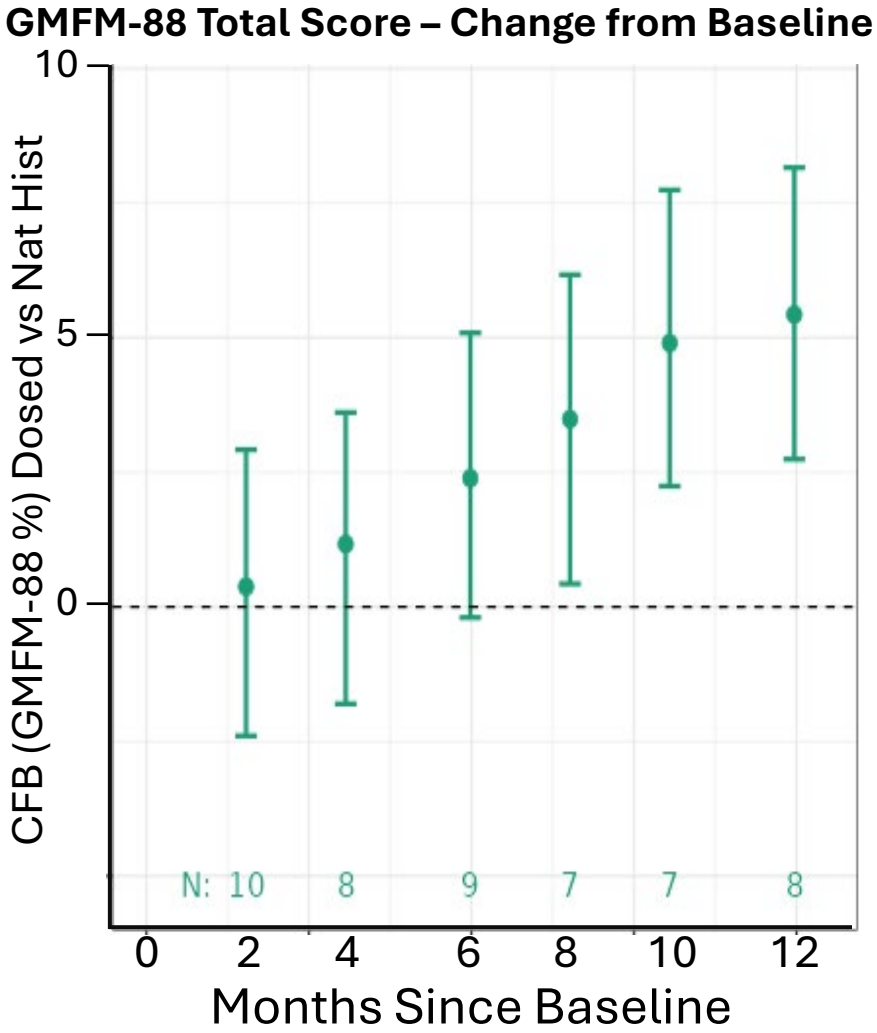


Gross Motor Function Measure-88 (GMFM-88)

- Designed and validated to assess gross motor function in children with cerebral palsy
- 88 items grouped into 5 dimensions
  - A: lying and rolling
  - B: sitting (includes head control)
  - C: crawling and kneeling
  - D: standing
  - E: walking, running, and jumping
- Items scored on a 0–3 scale
- Total score: Weighted total of dimension scores (%) – Max = 100%
- Skills are typically mastered by age 5 in children without motor impairments

Improvements in GMFM-88 in CD Patients Dosed with BBP-812 vs Natural History





Gray: CVN-101 Natural History Study
N= 28 prospective natural history participants; excludes 7 participants with genotypes associated with a mild phenotype who would be ineligible for the interventional trial.

Red and Blue: CVN-102 Interventional Trial
Open symbols/dashed lines = pre dose (screening, baseline)
Solid symbols/solid lines = post dose
Cohort 1: 1.32E14 vg/kg **Cohort 2: 2.6E14 vg/kg**

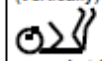
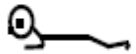
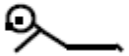
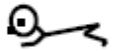
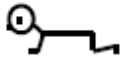
Y-axis: difference in change from baseline (CFB) between natural history study and interventional trial (point estimates and 95% confidence intervals)
X-axis: months since baseline. N = the number of interventional trial participants at each time point.

GMFM, Gross Motor Function Measure

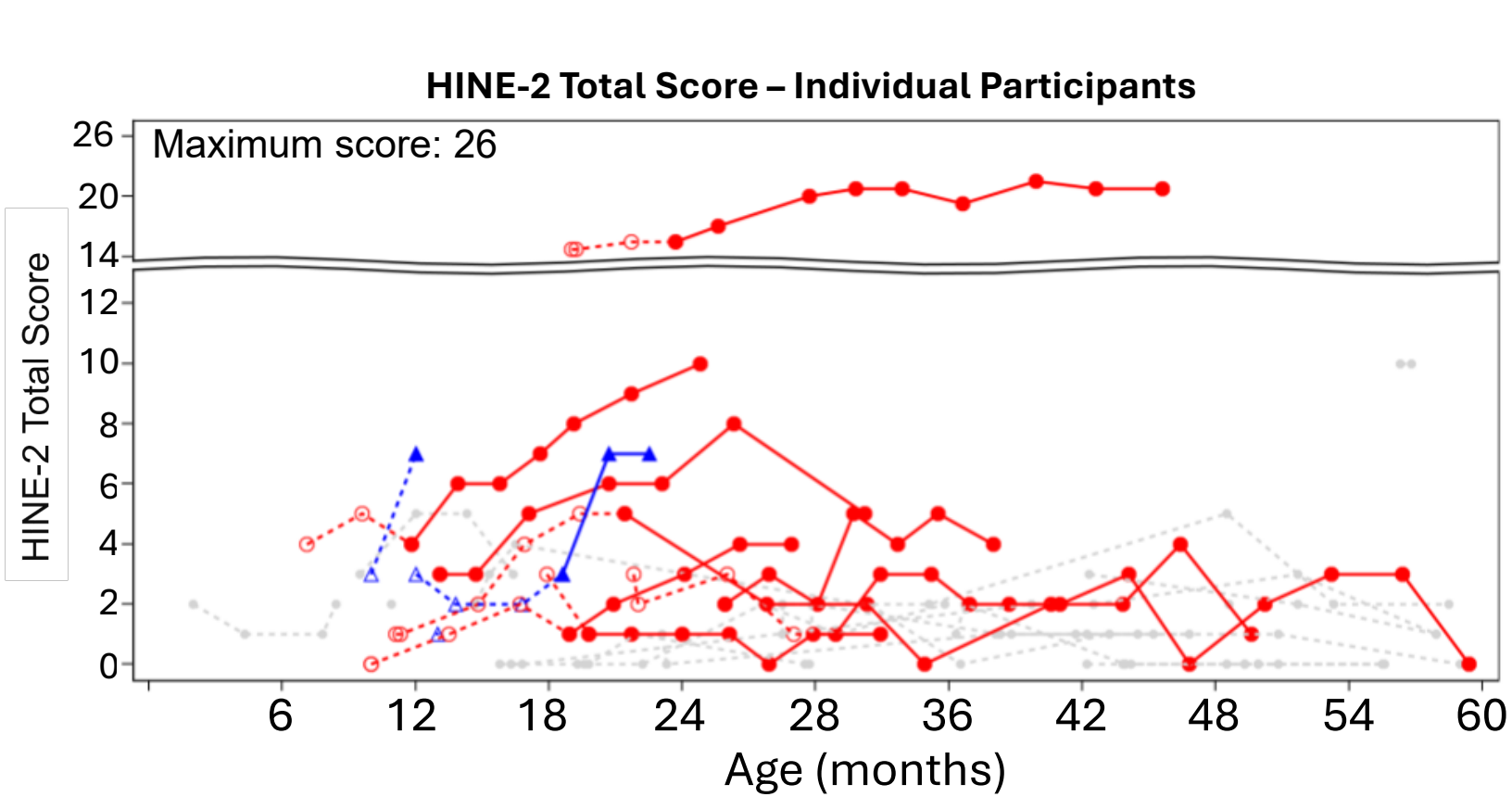
Hammersmith Infant Neurological Examination – Section 2 (HINE-2)

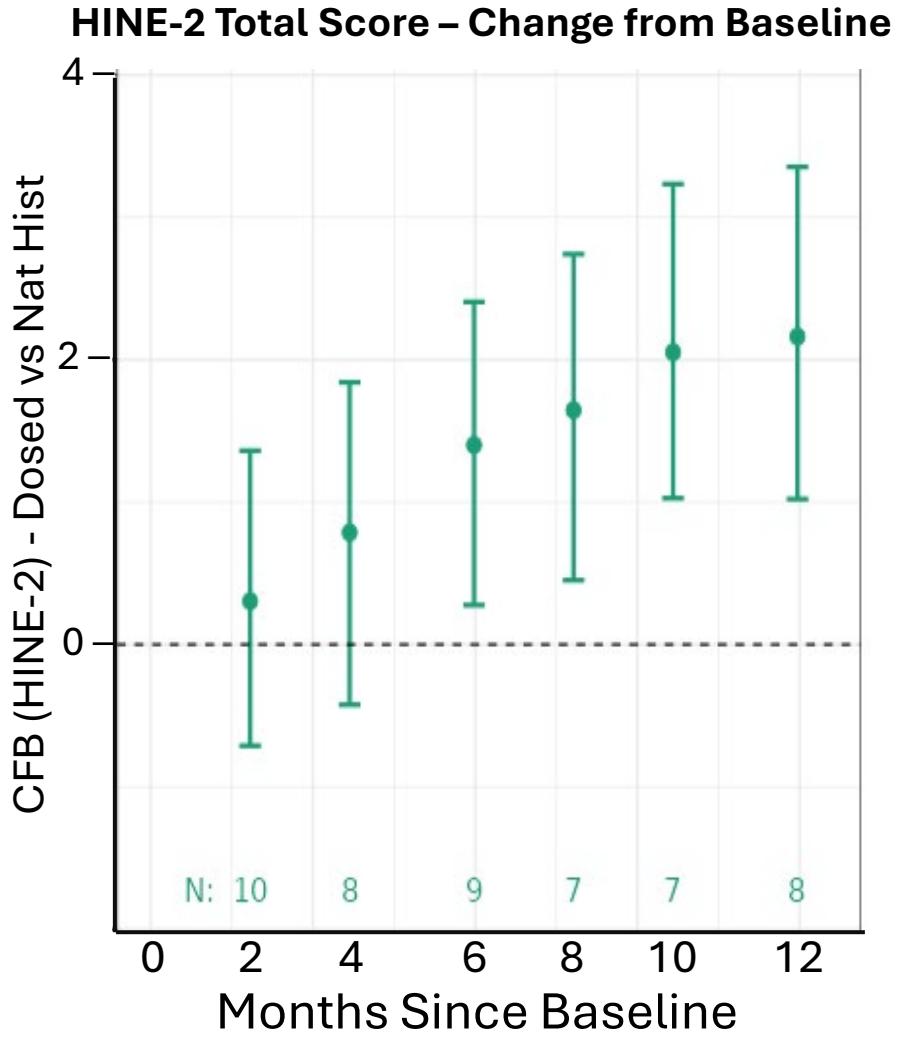
- Indexes 8 motor milestones scored on a scale of 0 (absence of activity) to 2, 3, or 4 points (depending on the item)

Maximum total score = 26

Head control	**Head control**	Unable to maintain head upright normal to 3m	Wobbles normal up to 4m	Maintained upright all the time normal from 5m		
Sitting	**Sitting**	Cannot sit	With support at hips  normal at 4m	Props  normal at 6m	Stable sit  normal at 7-8m	Pivots (rotates)  normal at 9m
Voluntary grasp	**Voluntary grasp – note side**	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Kicking	**Ability to kick in supine**	No kicking	Kicks horizontally but legs do not lift	Upward (vertically)  normal at 3m	Touches leg  normal at 4-5m	Touches toes  normal at 5-6m
Rolling	**Rolling - note through which side(s)**	No rolling	Rolling to side normal at 4m	Prone to supine normal at 6 m	Supine to prone normal at 6 m	
Crawling	**Crawling - note if bottom shuffling**	Does not lift head	On elbows  normal at 3m	On outstretched hands  normal at 4m	Crawling flat on abdomen  normal at 8m	Crawling on hands and knees  normal at 10m
Standing	**Standing**	Does not support weight	Supports weight normal at 4m	Stands with support normal at 7m	Stands unaided normal at 12m	
Walking	**Walking**		Bouncing normal at 6m	Cruising (walks holding on) normal at 12m	Walking independently normal by 15m	

Improvements in HINE-2 in CD Patients Dosed with BBP-812 vs Natural History





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Y-axis: difference in change from baseline (CFB) between natural history study and interventional trial (point estimates and 95% confidence intervals)
X-axis: months since baseline. N = the number of interventional trial participants at each time point.

GMFM, Gross Motor Function Measure

All Participants Have Shown Post-Dosing Improvements in Clinically Meaningful Motor Skills

BBP-812 Dose (x 10^{14} vg/kg)	Participant	Age Range at Dosing (M)	Length of Follow-up (M)	Visual Tracking	Head Control	Rolling	Weight-bearing on Legs	Sitting	Control/ Use of Hands*
1.32	A	28-30	33						
	B	18-20	30						
	C	20-22	27						
	D	10-12	21						
	E	16-18	18						
	F	10-12	18						
	G	16-18	15	Improved on CDRS @M12 (no M15 data)					
	H	24-26	15						
2.6	I	16-18	8.5						
	J	10-12	4						

*Brings hands to midline; reach/grasp

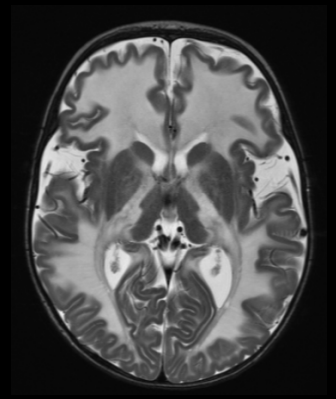
Progress since dosing

Maintenance of baseline skill

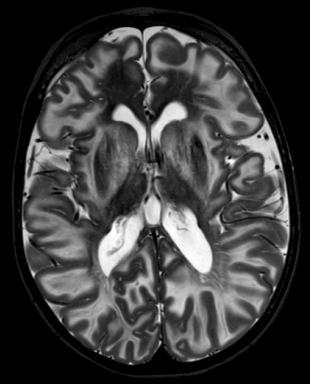
Skill absent at baseline and unchanged

Skill regression from baseline

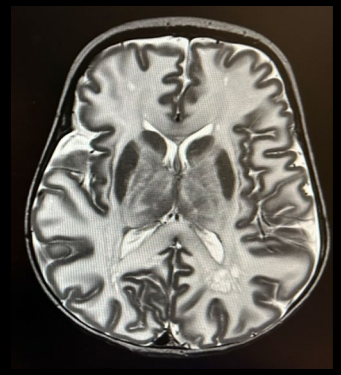
Improvements in Myelination Post BBP-812 Administration (1.32E14 vg/kg)



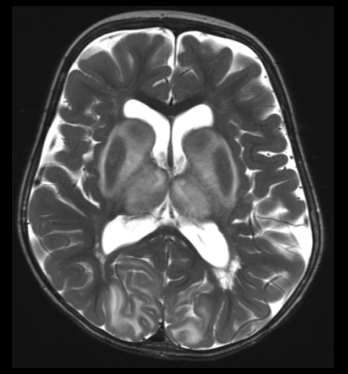
Pre-dosing
Age 18-20 mos.



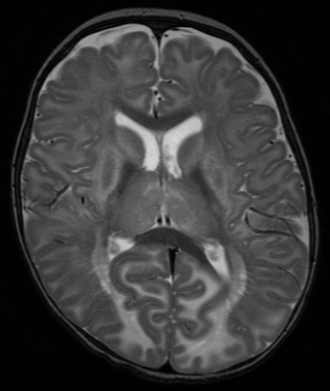
30 mos. post



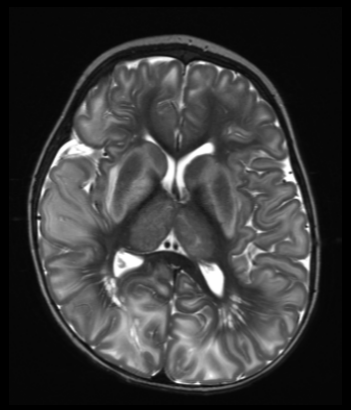
Pre-dosing
Age 10-12 mos.



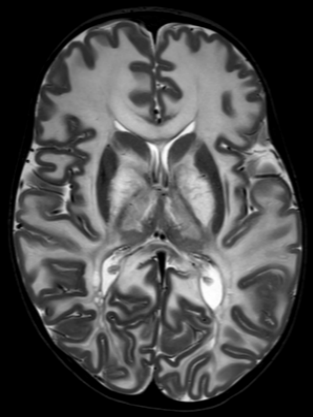
18 mos. post



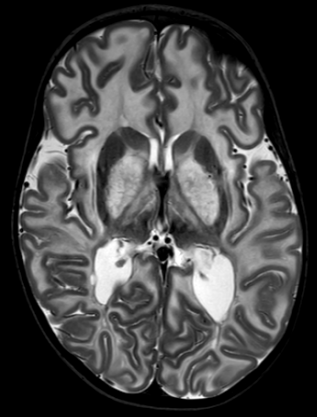
Pre-dosing
Age 8-10 mos.



12 mos. post

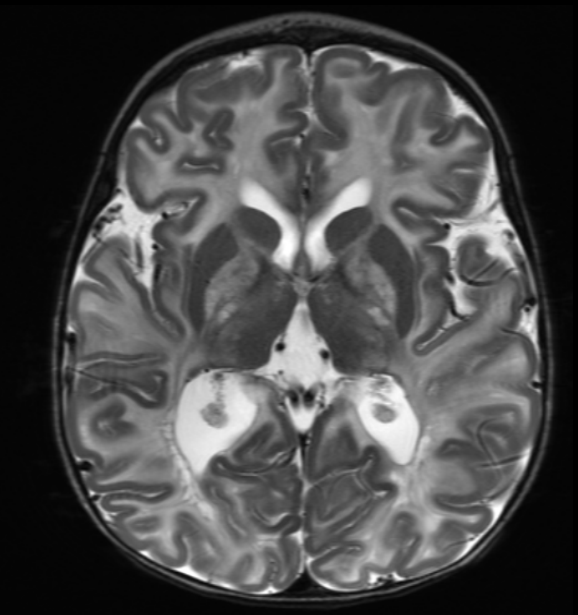


Pre-dosing
Age 16-18 mos.

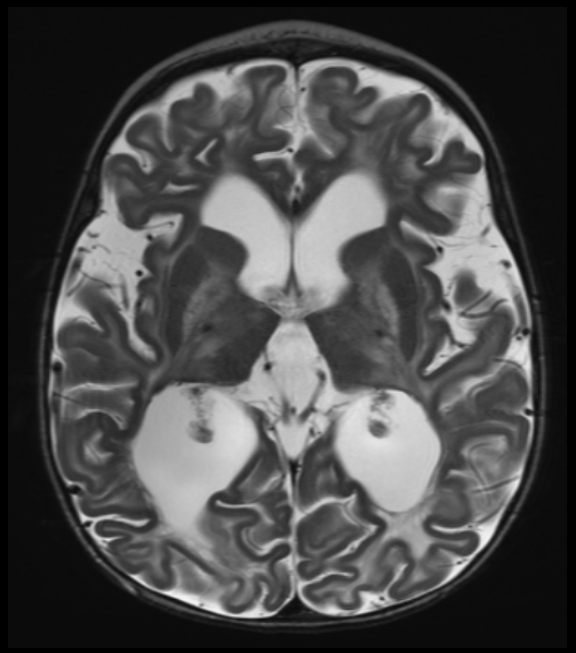


12 mos. post

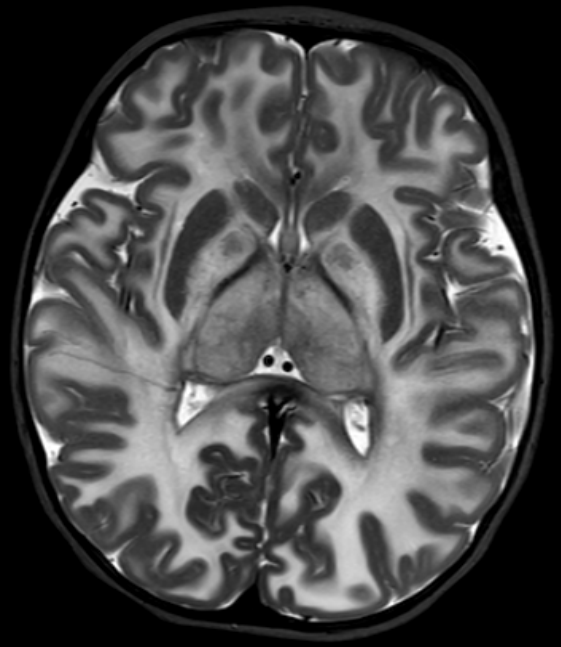
Improvements in Myelination Post BBP-812 Administration (2.6E14 vg/kg)



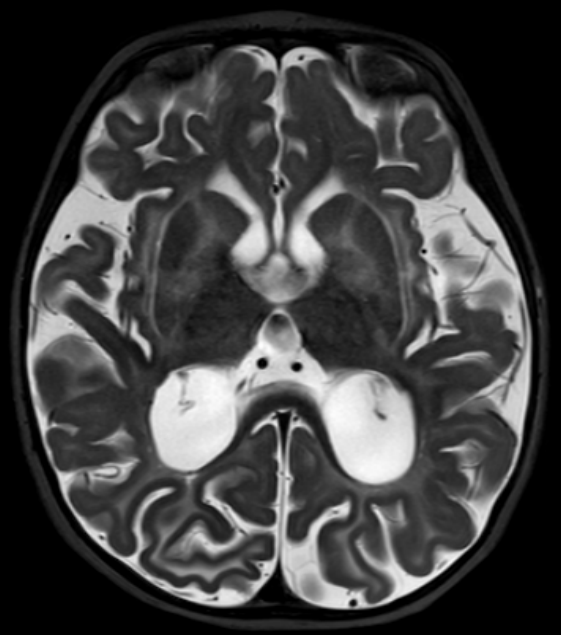
Pre-dosing
Age 16-18 mos.



3 mos. post



Pre-dosing
Age 8-10 mos.



3 mos. post

Summary

- CVN-101 natural history:
  - Robust comparison group for CVN-102
  - Children with Canavan disease have profound and persistent motor deficits
- Pharmacodynamics of BBP-812:
  - Rapid and marked NAA decreases urine, CSF and brain (MRS) consistent with expression of active ASPA enzyme
  - High dose (2.6E14 vg/kg) associated with lower urine NAA levels
- Safety of BBP-812:
  - Generally well-tolerated at 1.32E14 vg/kg and 2.6E14 vg/kg
  - Safety profile manageable and generally consistent with other systemically administered AAV gene therapy products
- Clinical efficacy of BBP-812:
  - All participants have shown improved performance in at least one clinically meaningful motor skill
  - Most participants have shown improved myelination on T2-weighted MRI
  - Emerging evidence of earlier and more robust improvements in myelination and motor function at high dose
  - More data and longer follow-up are needed to fully characterize potential clinical benefit