#223

CAN*aspire*, a First-in-Human Phase 1/2 Controlled Open-Label Study of BBP-812, a Recombinant AAV9-h*ASPA* Vector for the Treatment of Canavan Disease

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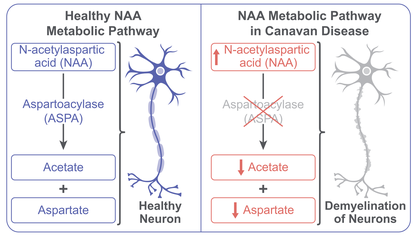
CANaspire Gene Therapy Study

Canavan Disease

Epidemiology and Pathophysiology

- Ultra-rare, fatal autosomal recessive leukodystrophy[1]
- 1:100,000 births/year – US and EU[2]
- *ASPA*[3] mutations lead to lack of aspartoacylase (ASPA) activity
- ASPA deficiency prevents breakdown of N-acetylaspartate (NAA) into aspartate and acetate[3]
- Results in failure to develop and maintain myelination in brain[3]



ASPA Enzyme Deficiency and NAA Accumulation Lead to Demyelination in Canavan Disease

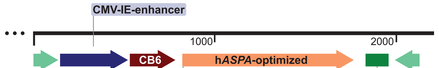
Disease Features

- Profound neurodevelopmental delay[3] with global cognitive, language, and motor impairment[4]
- Fatal; 73% reach the age of 10 years[5]
- Care is supportive/palliative,[6,7] no approved treatments

CAN*aspire* Gene Therapy Study

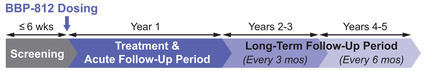
- The objective of the CAN*aspire* gene therapy study (CVN-102, NCT04998396) NCT04is to evaluate the safety, pharmacodynamic, and clinical activity of BBP-812 for treatment of Canavan disease
- BBP-812 is a non-replicating, recombinant AAV serotype 9 (AAV9) gene therapy vector containing an expression cassette for the human *ASPA* transgene

scAAV9-CB6-h*ASPA*opt Vector Design

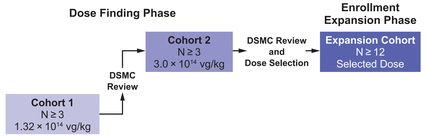


- Study center at Massachusetts General Brigham in Boston, MA

Study Timeline



Study Design



Abbreviations: CMV, cytomegalovirus; DSMC, Data and Safety Monitoring Committee; IE, immediate-early; ITR, inverted terminal repeat; RFWM, right frontal white matter; vg, vector genomes.

References: 1) Bokhari 2020 https://www.ncbi.nlm.nih.gov/books/NBK430816. 2) Orphanet (https://www.orpha.net/consor/cgi-bin/OC_Exp.php?&Expert=141). 3) Matalon 2018 NCBI Bookshelf. 4) Matalon 1998 *Eur J Paediatr Neurol*. 5) Bley et al. Orphanet J Rare Dis 2021 16:227. 6) Traeger 1998 *Pediatr Neuro*. 7) Zubler et al. Evidence-Informed Milestones for Developmental Surveillance Tools. *Pediatrics*. 2022;149(3):e2021052138.

Eligibility Criteria

Key Inclusion Criteria:

- Age ≤ 30 months at dosing
- Stable health in the opinion of the Investigator
- Biochemical, genetic, and clinical diagnosis of Canavan disease:
  - » Elevated urinary NAA
  - » Biallelic mutation of the ASPA gene
  - » Active clinical signs of Canavan disease

Key Exclusion Criteria:

- Positive for total anti-AAV9 antibodies
- Prior gene therapy or other therapy involving AAV
- High-dose immunosuppressant therapy
- Significantly progressed Canavan disease:
  - » Continuous/constant decerebrate or decorticate posturing
  - » Recurrent status epilepticus
  - » Seizures unresponsive to ≥ 3 anticonvulsants

Assessments

Safety

- Adverse events
- Laboratory tests
- Physical examinations
- ECGs

Efficacy

- Pharmacodynamic: NAA levels in
  - » Urine
  - » Cerebrospinal fluid (CSF)
  - » Brain by magnetic resonance spectroscopy (MRS)

Function:

The same assessments are being performed by the same raters from the CAN*inform* natural history study (CVN-101, CNS 2022 Poster #160)

- **Canavan Disease Rating Scale (CDRS)**[5]
  - » Records signs, symptoms and developmental skills typically seen in children with Canavan disease, scored by investigator on a scale from 0-2
- **CDC Developmental Milestone Checklist**[7]
  - » Based on checklist of expected developmental milestones published by the US Centers for Disease Control
  - » Sample of typical milestones from 2-18 months
  - » Developmental skills across all domains rated by trained physiotherapist raters as Absent or Present
- **Motor/Developmental Scales**
  - » Administered remotely by video and in person (COVID conditions permitting) by trained physiotherapist raters

Functional and Medical Assessments

Development/Motor
*TIMPSI: *Test of Infant Motor Performance Screening Items*
GMFM-88: *Gross Motor Function Measure, 88 Items*
*Bayley 4: Bayley Scales of Infant Development
HINE-2: *Hammersmith Infant Neurological Examination, Section 2*
CDC Developmental Milestone Checklist
Disease Severity
CDRS: *Canavan Disease Rating Scale*
Impact on Family
Vineland 3: *Adaptive Behavior Scales, Expanded Interview Form*
PedsQoL-FIM: *Pediatric Quality of Life Inventory (Family Impact Module)*
Canavan Disease Questionnaire
Medical
Physical Examinations
Neurological Examinations
Opthalmologic Examinations
Laboratory Tests

*In-person only

Added for Remote
AIMS: *Alberta Infant Motor Scale*
IMP: *Infant Motor Profile*
Response to Sensory Stimuli

Cohort 1 Demographics and Canavan Disease History

Part.	Sex	Race / Ethnicity	Age at Informed Consent	ASPA Mutation	Age of Canavan Diagnosis
1	M	Asian, not Hispanic/Latino	27 months	p.Asn54Lys, homozygous pathogenic variant	9 months
2	M	White, not Hispanic/Latino	18 months	p.Ala305Glu p.Ser108Leufs*2	5 months
3	F	White, not Hispanic/Latino	20 months	p.Glu285Ala p.Ile16Thr	11 months

Safety

- To date, 3 participants have received BBP-812; all received the starting dose of 1.32×10^{14} vg/kg
- IV infusions of BBP-812 have been generally well-tolerated
- Treatment-related adverse events have been mild or moderate
- No treatment-related serious adverse events reported
- The data and safety monitoring committee (DSMC) has reviewed cumulative safety data and endorsed continued enrollment and dosing of participants
- Current DSMC-recommended immune prophylaxis regimen:
  - » 2 mg/kg/day IV methylprednisolone (2.5 mg/kg/day prednisolone equivalent) starting 1 day prior to BBP-812 dosing, continued through inpatient dosing stay
  - » After discharge, prednisolone oral formulation:
    - – 2 mg/kg/day through Day 28 (1 month)
    - – 1.5 mg/kg/day through Day 49 (Week 7)
    - – 1 mg/kg/day through Day 77 (Week 11)
    - – Labs permitting, begin tapering for ≥ 6 weeks, with ≤15% taper per week

Treatment-Emergent Adverse Effects

System Organ Class Preferred Term	n (%)	Treatment-Related[†] n (%)
Investigations		
Transaminases increased	3 (100)	2 (66.7)
Blood and lymphatic system disorders		
Lymphopenia	2 (66.7)	2 (66.7)
Thrombocytopenia	2 (66.7)	2 (66.7)
Gastrointestinal disorders		
Vomiting	2 (66.7)	2 (66.7)
Stomatitis	1 (33.3)	0
General disorders & admin. site conditions		
Pyrexia	2 (66.7)	2 (66.7)
Face oedema	1 (33.3)	0
Infections and infestations		
COVID-19	1 (33.3)	0
Metabolism and nutrition disorders		
Feeding disorder	1 (33.3)	1 (33.3)
Nervous system disorders		
Infantile spasms	1 (33.3)	0
Seizure	1 (33.3)	0
Psychiatric disorders		
Irritability	1 (33.3)	1 (33.3)
Skin and subcutaneous tissue disorders		
Hirsutism	1 (33.3)	0
Vascular disorders		
Hypotension	1 (33.3)	1 (33.3)

[†]Possibly or Probably Related to Study Drug

Treatment-Emergent Serious Adverse Event (Unrelated to Study Drug)

System Organ Class Preferred Term	n (%)
Nervous system disorders	
Seizure	1 (33.3)

Acknowledgments: Many thanks to everyone whose contributions made this work possible — the patients and families who generously participated in this study; our expert team of motor function raters; site staff at MGB; Veristat clinical, data management, and biostatistics teams; Valis Biosciences Clinical Trials Science and Technology Solutions; Kennedy-Krieger Biochemical Genetics Laboratory; Aspa clinical and patient advocacy teams; and our advocacy partners: Canavan Foundation, Canavan Research Illinois, and the National Tay-Sachs and Allied Diseases Association.

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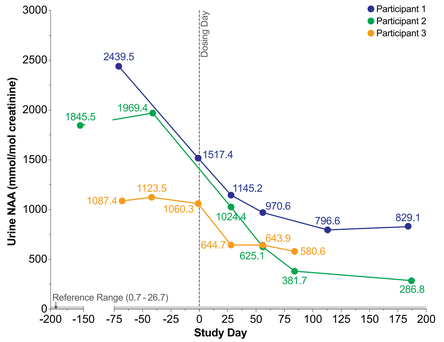
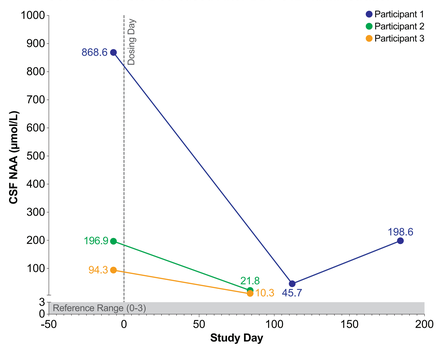
Preliminary Efficacy

- NAA reductions seen in urine, CSF, and brain MRS support restoration of ASPA enzymatic activity in compartments of interest
- NAA levels can be variable but observed degree of NAA reduction was greater than expected from available natural history data
- Although CSF NAA decreased by 77 to 95% 3-6 months after dosing, concentrations were not reduced to non-Canavan levels
- Some literature suggests that lower NAA levels are associated with milder Canavan phenotype
  - » More participants and longer follow-up are needed to determine the relationship between restoring ASPA activity/lowering NAA and clinical improvement

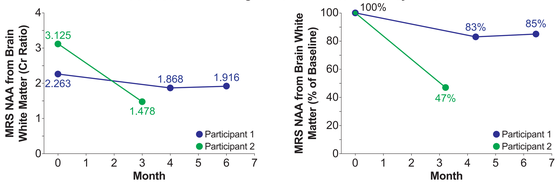
Urine NAA Levels Decreased After BBP-812 Administration



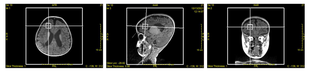
CSF NAA Levels Decreased After BBP-812 Administration



Decreased NAA in Right Frontal White Matter by MRS

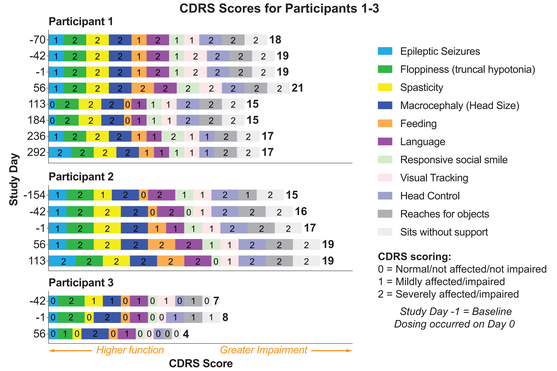


Voxel Placement, Participant 1, Baseline, Right Frontal White Matter (RFWM)



Preliminary Functional Data

CDRS Scores for Participants 1-3



- Participant 1:
  - » Stable improvement (≥2 consecutive improved [i.e. lower] scores vs baseline) seen in:
    - – Visual tracking beginning at Month 4
    - – Head control beginning at Month 8
- Participant 2:
  - » Stable overall except for:
    - – Feeding difficulties: began worsening leading up to dosing
    - – Epileptic seizures: recent exacerbation noted at Month 4 visit (associated with systemic infection and decreased compliance with oral anti-epileptic regimen)
- Participant 3:
  - » 4-point improvement in total CDRS score at Month 4 (first post-dosing assessment) vs baseline
  - » Driven by reductions from 1 (mildly affected/impaired) to 0 (normal/not affected/not impaired) for truncal hypotonia, head control, reaching, and sitting

Summary and Next Steps

- CAN*aspire* continues to recruit globally, enroll, and dose participants
- Expanding study sites: Massachusetts General Brigham, Boston, MA, USA is currently open, with activation of additional US sites pending
- Positive preliminary results from 3 dosed participants:
  - » Safety:
    - – No treatment-related serious adverse events reported
    - – DSMC safety reviews have supported continued enrollment and dosing
  - » Preliminary efficacy:
    - – Pharmacodynamic data: Evidence of ASPA enzymatic activity based on substrate reduction with decreased NAA in urine and CNS in all 3 dosed participants
  - » Functional data: 2 of 3 participants showed decreased total CDRS scores starting 2-4 months after treatment
- Preliminary safety and efficacy data to date are encouraging; more participants and longer follow-up are needed to fully determine safety, tolerability, and clinical benefit

clinicaltrials.gov
treatcanavan.com
aspatx.com