Systemic AAV9-mediated Gene Addition for Canavan Disease (CAN*aspire* Trial): Managing Immune Responses, Lowering N-acetylaspartate and Impacting Disease Severity

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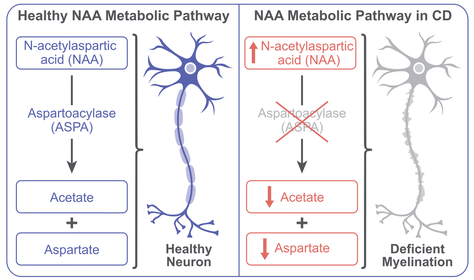
Canavan Disease (CD)

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
- Results in failure to develop and maintain myelination in brain



ASPA Enzyme Deficiency and NAA Accumulation Lead to Deficient Myelination in CD

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*inform* CD Natural History Study

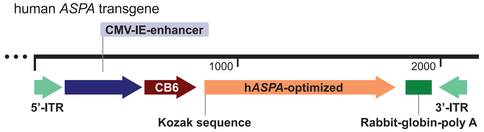
- Rigorous retrospective and prospective natural history study; includes any patient with CD, living or deceased
- Serves as control group and supports clinical endpoint selection for CAN*aspire* gene therapy clinical trial
- Same motor function raters and assessment scales used in CAN*inform* and CAN*aspire*

CAN*aspire* Phase 1/2 FIH Study of BBP-812 for the Treatment of CD

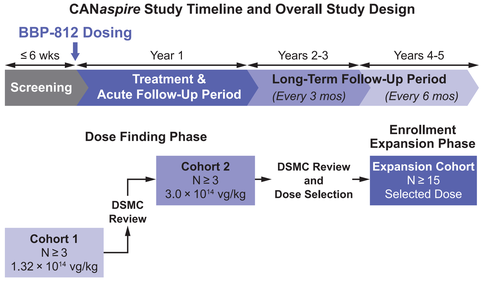
Study sites: Mass General Brigham, NY Presbyterian/Weill-Cornell Medicine, Benioff Children's Hospital/UCSF

Objective: Evaluate the safety, PD, and clinical activity of BBP-812 for treatment of CD

BBP-812 is a systemically administered, non-replicating, rAAV serotype 9 (AAV9) gene therapy vector containing an expression cassette for the human *ASPA* transgene



CAN*aspire* Study Timeline and Overall Study Design



CAN*aspire* Key Inclusion Criteria:

- Age ≤ 30 months at dosing
- Stable health in the opinion of the Investigator
- Biochemical, genetic, and clinical diagnosis of CD

CAN*aspire* Key Exclusion Criteria:

- Positive for total anti-AAV9 antibodies
- Prior gene therapy or other therapy involving AAV
- High-dose immunosuppressant therapy
- Significantly progressed CD
- *ASPA* genotype known to be associated with mild CD phenotype

CAN*aspire* Assessments

Safety: AEs, laboratory tests, PE, ECG

Efficacy:

- **Pharmacodynamic:** NAA levels in urine, CSF, brain (MRS)
- **Imaging:** Structural MRI, DTI, ASL, MRS
- **Functional:** Characterization of potential BBP-812 treatment effects on clinically meaningful motor/developmental skills
  - » **Canavan Disease Rating Scale (CDRS):**[5] Investigator-rated severity of impairment in 11 CD concepts of interest
  - » **CDC Developmental Milestone Checklist:**[7] Caregiver and rater reports based on US CDC checklist of typical milestones from 2-18 mos
  - » **Motor/Developmental Scales:** Administered remotely by video and in person (COVID conditions permitting) by trained physiotherapist raters

Functional Assessments and Caregiver-reported Outcomes in CAN*aspire* (Screening; Baseline; Months 2, 4, 6, 8, 12; Q3M for 4Y)

Five key motor/developmental constructs were identified as the most clinically meaningful, relevant, and informative for CD based on input from caregivers, clinical/motor function experts, and the CAN*inform* natural history data:

1. Head control in the upright position (4)
2. Sitting ability (5)
3. Reach and grasp (6)
4. Visual fixation and tracking
5. Supported standing/weightbearing

Development/Motor
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
Added for Remote Video Assessments Post COVID-19
AIMS: Alberta Infant Motor Scale
IMP: Infant Motor Profile
Response to Sensory Stimuli: Assessment of ability to respond to auditory and visual stimuli

CAN*aspire* Cohort 1 Demographics and CD History

Pt ID	Sex	Age at Diagnosis (months)	Age at Treatment (months)	*ASPA* Mutation	*ASPA* Mutation
001	M	9	29	p.Asn54Lys	p.Asn54Lys
002	M	5	20	p.Ala305Glu	p.Ser108Leufs*2
003	F	11	22	p.Glu285Ala	p.Ile16Thr
004	F	6	11	p.Ala305Glu	p.Ala305Glu
005	M	4	18	p.Gly27Arg	p.Gly27Arg
006	M	6	10	p.Glu285Ala	p.Arg168Cys
007	F	8	17	p.Ala305Glu	p.Ala305Glu
008	M	14	26	p.Ala305Glu	p.Gly27Arg

CAN*aspire* Safety Data

- 8 participants have received BBP-812 IV at a dose level of 1.32×10^{14} vg/kg
- IV infusions of BBP-812 have been generally well-tolerated
- Treatment-related nonserious adverse events have been mild or moderate
- All but 2 SAEs have been assessed as unrelated to BBP-812
  - » Transient decerebrate posturing reported as possibly related by investigator but considered not or unlikely related by Sponsor and DSMC

Treatment-Emergent Serious Adverse Events (as of 03 Oct 2023)

Pt ID	Adverse Event	CTCAE Grade	Relationship to Study Drug
002	Seizure exacerbation	3 – Severe	Unlikely Related
	G-tube placement	3 – Severe	Not Related
	Subdural Hemorrhage with mass effect requiring decompression surgery	3 – Severe	Possibly Related
004	Vomiting, decreased PO intake, irritability	3 – Severe	Unlikely Related
005	Irritability	3 – Moderate	Not Related
	Choking Episode	3 – Severe	Unlikely Related
006	Transient decerebrate posturing	2 – Moderate	Possibly Related
008	Urinary Tract Infection	3 – Severe	Unlikely Related

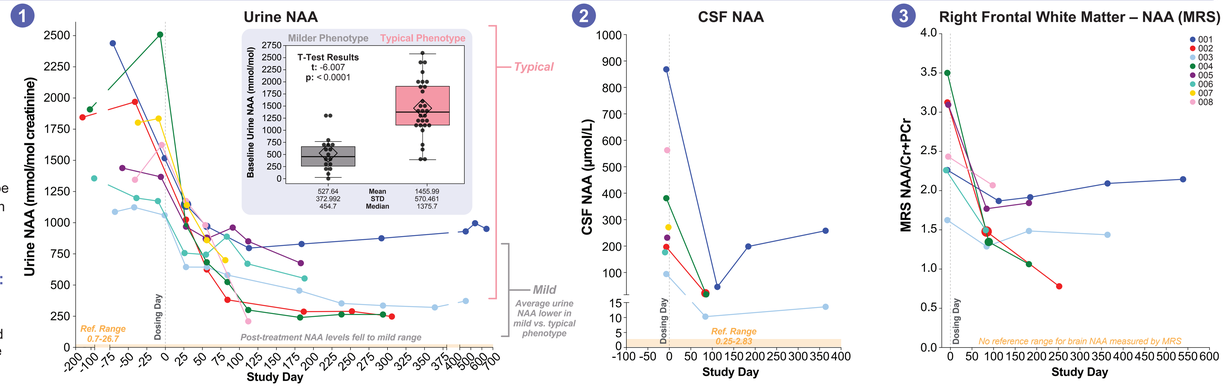
CAN*aspire* Preliminary Efficacy

Pharmacodynamics:

- NAA reductions in urine (1), CSF (2), and brain (MRS) (3) provide evidence of restored ASPA enzymatic activity in compartments of interest.
- Lower NAA is associated with milder disease (1 inset)
  - » Some literature and data from the CAN*inform* natural history study suggest that lower NAA levels are associated with a milder CD phenotype
  - » It is not known whether an intervention that lowers NAA will make existing severe CD milder; more clinical data are needed

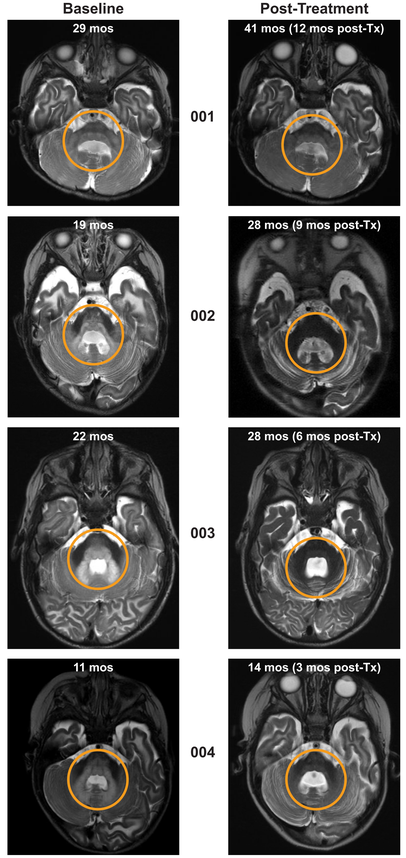
Management of Immune Responses:

- Prophylaxis: 2.0 mg/kg/D prednisolone × 3 mos → gradual taper
- No thrombotic microangiopathy observed to date; eculizumab available for reactive use as needed



CAN*aspire* Imaging

Evidence of improved myelination post-BBP-812 treatment.
All images are T2 MRI sequences obtained on 3T scanner.



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Abbreviations: CSF, cerebrospinal fluid; CTCAE, Common Terminology Criteria for Adverse Events; G-tube, gastrostomy tube; CMV, cytomegalovirus; DSMC, Data and Safety Monitoring Committee; FIH first-in-human; IE, immediate-early; ITR, inverted terminal repeat; MRS, magnetic resonance spectroscopy; NH, natural history; PE, physical examination; PO, by mouth; Pt ID, Participant identification number; RFWM, right frontal white matter; RSV, respiratory syncytial virus; SAE, serious adverse event; Tx, treatment; 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.

CAN*aspire* Preliminary Functional Data: Motor Rater Assessments

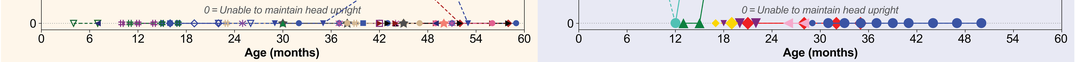
CANinform Natural History Study

Results from all prospective natural history participants (n = 28) assessed remotely and in person; CVN-101 participants shown have not been explicitly matched to baseline characteristics of CVN-102 participants

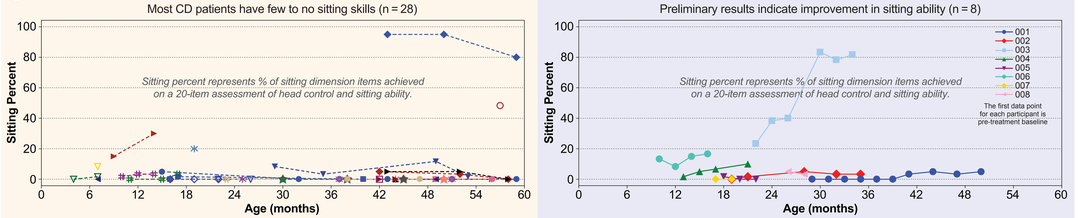
CANaspire Gene Therapy Study

Results from all BBP-812-treated patients (n = 8)

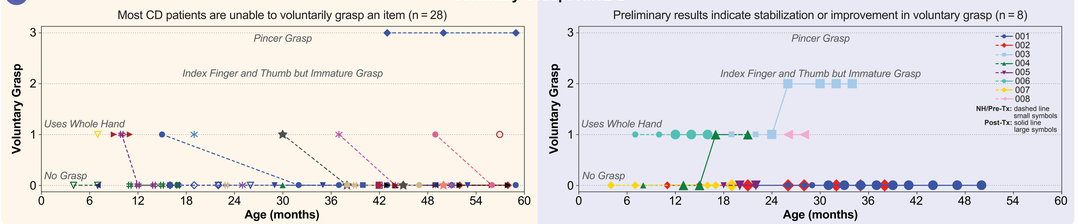
4 Head Control: HINE-2



5 Sitting Ability: GMFM-88 Sitting Dimension



6 Voluntary Grasp: HINE-2



Summary

- Eight children with CD aged 9.6-29 mos have been treated with BBP-812 at 1.32×10^{14} vg/kg
- All eight have shown post-tx decreases in urine, CSF, and brain NAA indicative of ASPA enzymatic activity
  - » Decreases have persisted as long as ~2 years, the maximum follow-up time point to date
  - » Urine NAA levels fell to the range associated with milder CD phenotypes
- Preliminary evidence of:
  - » Improved myelination on T2 MRI
  - » Improved head control, sitting ability, and voluntary grasp
  - » Achievement of ambulation with a mobility aid in one participant
- Safety: BBP-812 has been generally well-tolerated
  - » All but 2 SAEs have been assessed as unrelated to BBP-812
- More data and longer follow-up are needed to determine safety, tolerability, and clinical benefit

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