#160

CAN*inform*, a Retrospective and Prospective Natural History Study of Canavan Disease: Status and Initial Analyses

Florian Eichler[1], Elise Townsend[1], Beth Leiro[2], Mike Kiefer[1], Anzalee Khan[3], Christian Yavorsky[3], Kathleen Kirby[2], Chrissy Burton[2], Stacy Maciel[1], Genevieve Laforet[2], Adam Shaywitz[2], John Balser[2], Annette Bley[4]

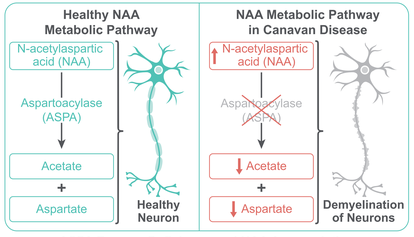
[1]Department of Neurology, Massachusetts General Hospital, Massachusetts, USA; [2]Aspa Therapeutics, California, USA; [3] Valis Bioscience, California, USA; [4]Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

CANinform Natural History 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

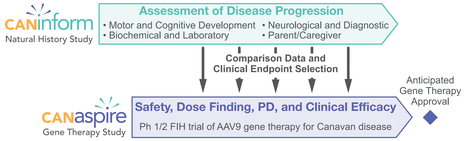
- Profound neurodevelopmental delay[3] with global cognitive, language, and motor impairment[4]
- Fatal; 73% reach the age of 10 years[5]
- Care is supportive/palliative,[6,7] no approved treatments

Clinical Development Challenges

- Paucity of natural history data; disease trajectory not well characterized
- Need to identify informative, clinically meaningful efficacy endpoints

CAN*inform* Natural History Study

- Rigorous retrospective and prospective Canavan disease natural history study (CVN-101, NCT04126005)
- Intended to support CAN*aspire* gene therapy clinical trial with control group and clinical endpoint selection (CVN-102, CNS 2022 Poster #23)



- Opened in November 2019; centers in Boston, MA and Hamburg, GER

CAN*inform* Study Status

- Current enrollment (as of 19 Aug 2022) = 48 participants from 16 countries

CAN*inform* Enrollment by Cohort	n	%
Total Number Enrolled	**48**	100
Cohort (at entry)		
1 (0 to 18 mo)	9	18.7
2 (18 to 36 mo)	10	20.8
3 (36 to 60 mo)	7	14.6
4 (>60 mo)	17	35.4
5 (deceased)	5	10.4

- Available retrospective CDRS Data: 41 participants (3/41 higher-functioning outliers)
  - » 9 participants have all 11 CDRS items in the same age window
- Available retrospective CDC Milestone Data: 41 participants (3/41 higher-functioning outliers)
- Prospective Motor Function Rater Data: 28 participants

CAN*inform* Natural History Study Design and Methods

Retrospective (All Participants)

- Systematized extraction of disease-related and motor/developmental data from patient records
- Experts in pediatric motor function and development followed a detailed extraction plan using two different tools to document the presence or absence of Canavan disease key concepts of interest:
  - » **Canavan Disease Rating Scale (CDRS)**[5]
    - – Records signs, symptoms and developmental skills typically seen in children with Canavan disease, rated on a scale from 0-2

0 Normal function	1 Mild Impairment	2 Severe Impairment

11 Scoring Categories

• Epileptic Seizures	• Responsive social smile
• Floppiness	• Visual tracking
• Spasticity	• Head control
• Macrocephaly	• Reaches for objects
• Feeding	• Sits without support
• Language	

Minimum Score = 0 (appropriate for age) **Maximum Score = 22 (severely affected)**

  - » **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 as Absent or Present

Prospective (Participant Opt-In)

- In-clinic physical and neurological examinations (COVID-19 conditions permitting)
- Motor function assessments by extensively trained expert physiotherapist raters (remote post-COVID-19)

Developmental and Motor Scales (Adapted Post-COVID-19 for Remote Testing by Video)[8]

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

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

**Original in-person assessments discontinued post-COVID in the US; German site continued to conduct all assessments in person*

- The same assessments are being performed by the same raters in the CAN*aspire* gene therapy trial (CVN-102)
- Assessment scales selected with input from families, patient advocates, and clinicians to assess the most clinically meaningful developmental skills across multiple domains

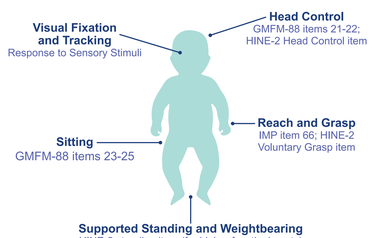
CAN*inform* Preliminary Analyses and Findings

Approach and Principles

- Use visual representations of retrospective and prospective data to assess:
  - » Quantity and quality of data:
    - – Overall data density
    - – Coverage of relevant ages, focused on data up to and including 60 months of age:
      - ■ >30 through 42 months: maximum age at the 12-month primary endpoint for participants dosed at ≤30 months in the CAN*aspire* gene therapy trial
      - ■ >42 through 60 months: covers an additional 1½ years of long-term follow-up in the CAN*aspire* gene therapy trial
  - » Patterns in developmental and disease parameters over time
- Ideal characteristics for selection of informative endpoints:
  - » Early onset
  - » Universal/near universal occurrence
  - » Relative consistency across patients by age
  - » Neither at floor nor at ceiling
  - » Clinical meaningfulness

Emerging Motor/Development Expert Endpoint Recommendations

- Determined by:
  - » Review of CVN-101 natural history study data
  - » Consultation with motor raters gathering their observations and clinical sense
- Several motor constructs have arisen as:
  - » Most relevant to Canavan disease consistent with CDRS concepts of interest
  - » Most likely to capture clinically meaningful improvement for children treated at ≤30 months of age in the CAN*aspire* gene therapy trial
    - – Head control in the upright position
    - – Sitting ability (prop sit with hand support, hands-free sitting)
    - – Reach and grasp function
    - – Visual fixation and tracking
    - – Standing/weight-bearing (for high-functioning outliers)



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 data extraction specialists and motor function raters; site staff at MGB and UKE; Veristat clinical, data management, and biostatistics teams; Valis Biosciences Clinical Trials Science and Technology Solutions; Aspa clinical and patient advocacy teams; and our advocacy partners: Canavan Foundation, Canavan Research Illinois, and the National Tay-Sachs and Allied Diseases Association.

Mass General Brigham | UKE HAMBURG | clinicaltrials.gov | treatcanavan.com | aspats.com

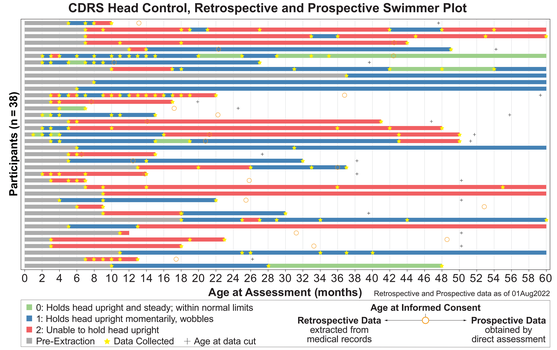
Presented at the Child Neurology Society Annual Meeting San Francisco, CA, USA October 8-12, 2022

By-Participant Characteristics and Data Density Examples of Two Promising Assessments: Head Control & Reach and Grasp

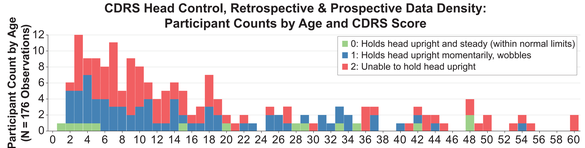
Head control

- Clinically meaningful: critical skill needed to advance to sitting and for self-feeding
- Deficit evident early, occurs universally, and readily measured
- Defined scoring criteria

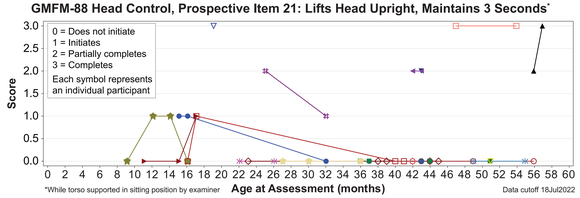
CDRS Head Control, Retrospective and Prospective Swimmer Plot



CDRS Head Control, Retrospective & Prospective Data Density: Participant Counts by Age and CDRS Score



GMFM-88 Head Control, Prospective Item 21: Lifts Head Upright, Maintains 3 Seconds*



*While torso supported in sitting position by examiner

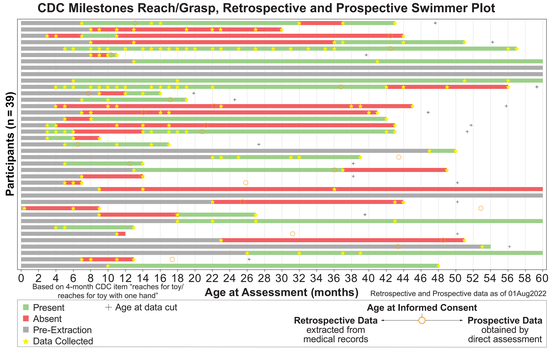
Head Control: Data Features and Implications for Use as a Clinical Endpoint

- Favorable data density at early ages
- Most natural history participants are at floor so evidence of clinical efficacy would require improvement in function
- Participants with a CDRS Score of 0 (Holds head upright and steady / within normal limits) at any time during age interval:
  - » >30 through 42 months: 2/13 participants
  - » >42 through 60 months: 2/11 participants
- GMFM-88: Only 3 natural history participants could complete the activity at any age (≤60 mos)
- Head control findings were consistent across CDRS retrospective and prospective and GMFM-88 prospective natural history data

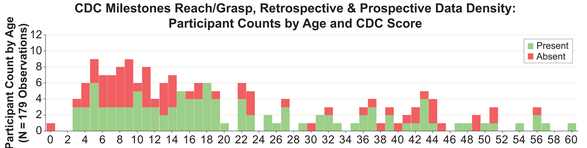
Reach and Grasp

- Clinically meaningful: critical ability for quality of life, e.g., self-feeding
- Skill often acquired at a basic level, though delayed (less floor effect)
- Defined scoring criteria

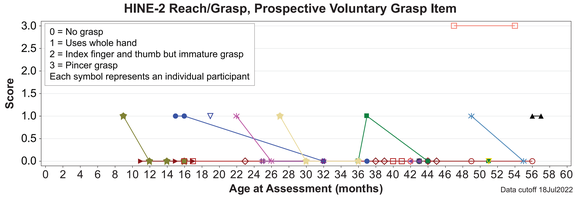
CDC Milestones Reach/Grasp, Retrospective and Prospective Swimmer Plot



CDC Milestones Reach/Grasp, Retrospective & Prospective Data Density: Participant Counts by Age and CDC Score



HINE-2 Reach/Grasp, Prospective Voluntary Grasp Item



Reach and Grasp: Data Features and Implications for Use as a Clinical Endpoint

- Participants with a CDC 4-month skill "Reach for Toy/Reach for Toy with One Hand" present at any time during age interval:
  - » >30 through 42 months: 7/13 participants
  - » >42 through 60 months: 10/16 participants
- HINE-2: Some participants had low-level voluntary grasp ability
- Because the CAN*aspire* gene therapy trial doses children up to the age of 30 months, it is important to follow skills that are above the floor during the follow-up period
  - » Look for maintenance of skill when present
  - » Look for acquisition of skill when absent

Summary and Next Steps

- CAN*inform* has continued to collect retrospective and prospective natural history data with remote adaptations in response to the pandemic
- CAN*inform* is beginning to shape our understanding of the most informative and clinically meaningful endpoints for Canavan patients in the CAN*aspire* gene therapy trial
- A more detailed interim analysis of CAN*inform* data is planned to inform ultimate endpoint selection

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. *Pediatrics*, 2022;149(3):e2021052138. 8) Kiefer et al. Transitioning from in-person to remote motor assessment of children with Canavan disease. Abstract presented at 2022 Autumn Conference of the International Society for CNS Clinical Trials and Methodology Sept 8-9, Boston, MA.