CAN*inform*, a Retrospective and Prospective Natural History Study of Canavan Disease: Current Status and COVID-19 Mitigation

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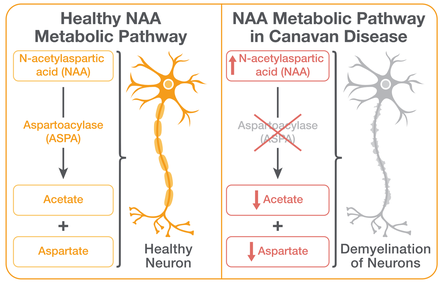
Canavan Disease

Epidemiology and Pathophysiology

- Ultra-rare, fatal autosomal recessive leukodystrophy[1]
- 1:100,000 births/yr – US and EU[2]
- Biallelic loss-of-function mutations in aspartoacylase gene (*ASPA*)[3]
- Aspartoacylase 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

Clinical Features

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

Clinical Development Challenges

- Hampered by too little natural history data
- Informative, clinically meaningful efficacy endpoints need to be identified and confirmed
- Trajectory of change over time not well enough characterized

Genesis of CAN*inform* Natural History Study

- CAN*aspire* Ph 1/2 trial of Aspa's investigational gene therapy for Canavan disease requires a robust body of natural history data for use as a control group and for endpoint selection
- Following FDA and EMA regulatory guidance on natural history studies, designed and initiated CAN*inform*, a rigorous multi-center, retrospective and prospective collection of clinical data on Canavan patients
- Centers in Boston, New York, and Hamburg, GER

Presented at the 49th CNS Annual Meeting October 12-23, 2020

CAN*inform* Natural History Study Design and COVID-19 Mitigation

Original Elements

Retrospective (All Participants)

Systematized extraction of medical and developmental data from patient records

CDC Developmental Milestones ☑☑☐☑ ← → Canavan Disease Rating Scale

Experts in pediatric motor function and development created a detailed extraction plan based on CDC Developmental Milestones and the Canavan Disease Rating Scale (CDRS), and extensively trained the collection team

Prospective (Participant Opt-In)

In-clinic physical, neurological and ophthalmological examinations

In-home developmental and motor function assessments by extensively trained expert Motor Function Raters

Family input and clinician interviews, with strong support from patient advocates, guided scale selection to cover all areas that are most meaningful

Post-COVID Adaptations

No change to medical record data extraction process

Remote medical examinations via telemedicine

Revised developmental and motor function assessments by expert Motor Function Raters via remote video, after extensive additional training on new scales and video/remote assessment process (see table below)

Conduct of remote pilot feasibility study:
- US pilot with 3 families nearing completion
- German site will lead pilot with 3 families
- Caregiver & rater feedback incorporated after each pilot visit
- Full rollout initiated when pilots complete

CANinform Natural History Study **Now Enrolling**

Assessment of Disease Progression (3 Years)
- Motor and Cognitive Development
- Biochemical and Laboratory
- Neurological and Diagnostic
- Parent/Caregiver

Comparison Data and Clinical Endpoint Selection

CANaspire Gene Therapy Study **Planned for 2021**

Safety, Dose Finding, PD, and Clinical Efficacy
Ph 1/2 FIH trial of AAV9 gene therapy for Canavan disease

Anticipated Gene Therapy Approval

CAN*inform* is the foundation of the CAN*aspire* treatment trial:

- CAN*inform* natural history data guide selection of clinical endpoints and provide a comparator group (planned instead of placebo)
- Remote CAN*inform* assessments carry over to CAN*aspire* for consistency and comparability

Post-COVID Remote Assessments

Goal was to use scales that could be performed and recorded via brief video, and that covered the same domains as the original scales

Development/Motor	Added for Remote
*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	AIMS: *Alberta Infant Motor Scale*
CDRS: *Canavan Disease Rating Scale*	IMP: *Infant Motor Profile*
Impact on Family	Response to Sensory Stimuli
Vineland 3: *Adaptive Behavior Scales, Expanded Interview Form*	
PedsQoL-FIM: *Pediatric Quality of Life Inventory (Family Impact Module)*	
Canavan Disease Questionnaire	

*Discontinued original assessments.
We hope to resume in-person visits on CANinform, if safe for families and study staff.

CAN*inform* Study Status

CAN*inform* Enrollment by Cohort (as of 10 Sept 2020)	
Cohort 1 (<18 mo)	6
Cohort 2 (18 mo to 3 yrs)	5
Cohort 3 (>3 to 5 yrs)	5
Cohort 4 (>5 yrs)	8
Cohort 5 (deceased)	3
Total	**23**

- CAN*inform* natural history study opened in November 2019
- Current enrollment = 23
- All CAN*inform* sites continue to enroll
- Remote assessments have been implemented for ongoing prospective data collection

Summary and Next Steps

- CAN*inform* retrospective and prospective Canavan disease natural history study currently enrolling in the US and Germany (clinicaltrials.gov/ct2/show/NCT04126005)
- COVID-19 drove identification and implementation of remote CAN*inform* assessments permitting continued, robust prospective collection of patient natural history data
- Remote assessments will carry over to the CAN*aspire* gene therapy trial for consistency/comparability as well as mitigation of future COVID constraints
- US opening of CAN*aspire* gene therapy trial anticipated in 2021

References: 1) Bokhari 2020 https://www.ncbi.nlm.nih.gov/books/NBK430816/ 2) Orphanet 2019 3) Matalon 2018 NCBI Bookshelf 4) Matalon 1998 *Eur J Paediatr Neurol* 5) Bley et al. The Natural History of Canavan Disease: 23 New Cases and Comparison with Patients from Literature (in review) 6) NORD 2019 7) Traeger 1998 *Pediatr Neuro*