October 18, 2023

Dear members of the Canavan community,

Aspa Therapeutics, a BridgeBio company and the sponsor of the CAN*inform* natural history study, would like to extend our appreciation and gratitude for families' participation in CAN*inform*. We are pleased to provide the community with an update on the ongoing study and share how the information has contributed to our understanding of Canavan disease.

The CAN*inform* natural history study began in November 2019. To date, the study has enrolled 59 children in 14 countries.

Group (age) at Enrollment	Number of Participants
0-18 months	18
18-36 months	10
36-60 months	7
More than 60 months	19
Deceased	5

The fundamental goal of the CAN*inform* study is to gain insight into how Canavan disease first presents and how it evolves over time. This information is advancing Canavan disease knowledge among researchers and clinicians and is being applied productively to the CAN*aspire* gene therapy trial. Natural history data from the CAN*inform* study can help identify the most informative ways to assess the effects of treatment and to measure what those effects are. Using the CAN*inform* study as a comparison for the CAN*aspire* clinical trial allows all participants in the CAN*aspire* trial to receive the investigational treatment. No child will receive a placebo.

We are in ongoing dialogue with the FDA about the use of a natural history comparator for CAN*aspire* and are continuing to recruit new participants to CAN*inform*. The more natural history data we can gather, the more informed we'll be regarding how to assess the participants in CAN*aspire*.

From current analyses of CAN*inform* data, several important learnings have emerged:

- Head control, sitting ability, reaching, grasping, and visual tracking – functions flagged by the Canavan community for years - are showing potential as meaningful measures of change in CAN*aspire*.
- N-acetylaspartic acid (NAA) levels in urine are helping to characterize natural differences in NAA levels in patients with Canavan disease. This approach may allow less burdensome measurement of treatment effects in CAN*aspire*.
- The range of *ASPA* gene mutations and the in-depth clinical characterization of participants in the natural history study support CAN*inform* as an appropriate comparator to CAN*aspire*, further reducing the potential need for a placebo.

The selfless contributions of families participating in CAN*inform* are deepening the medical community's understanding of Canavan disease and supporting encouraging progress in the development of future treatment options for children and their families.

With sincere gratitude,

Aspa Therapeutics