STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	An Open-label Safety, Pharmacokinetic, and Efficacy Study of Miglustat for the Treatment of CLN3 Disease in Patients 17 Years of Age and Older
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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AUC	Area Under the Curve
BMI	Body Mass Index
CLN3	Juvenile Batten Disease
Cmax	Maximum Plasma Concentration
Cmin	Minimum Plasma Concentration (at Steady State)
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
HbA1c	Hemoglobin A1c
HDL	High-Density Lipoprotein
HEENT	Head, Ears, Eyes, Nose, Throat
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ICH	International Council for Harmonization
LDL	Low-Density Lipoprotein
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCL	Neuronal Ceroid Lipofuscinosis
NIH CC	National Institutes of Health Clinical Center
OCT	Optical Coherence Tomography
OD	Right Eye
OS	Left Eye
PI	Principal Investigator

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Abbreviation	Description
PK	Pharmacokinetic(s)
PT	Preferred Term
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
T1/2	Elimination Half-Life
TCH	Texas Children's Hospital
TEAE	Treatment-Emergent Adverse Event
TESAE	Serious Treatment-Emergent Adverse Event
TID	Three Times Daily
TLF	Tables, Listings, Figures
Tmax	Time to Cmax
UBDRS	Unified Batten Disease Rating Scale
ULOQ	Upper Limit of Quantification
VS	Vital Signs
WHODD	World Health Organization Drug Dictionary

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1 PURPOSE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol Batten-1-01: An Open-label Safety, Pharmacokinetic, and Efficacy Study of Miglustat for the Treatment of CLN3 Disease in Patients 17 Years of Age and Older.

This SAP should be read in conjunction with the study protocol, case report form (CRF), and any other applicable study documents. This version of the SAP is based on the protocol Batten-1-01, v5.0 dated 06Feb2024 and CRF, v4.0 dated 12Feb2024. Changes to these documents may result in subsequent changes to the SAP. The final, sponsor-approved version of the SAP must occur prior to database lock.

1.1 Changes to the Planned Analyses

The following changes from the protocol were made in this SAP:

1. Adverse Event summaries are presented by system organ class (SOC), high level group term (HLGT) and preferred term (PT) as per Sponsor request, instead of presenting by SOC and PT. HLGT is added to provide more information.
2. According to the protocol, Medical Dictionary for Regulatory Activities (MedDRA; dictionary Version 21.1) and World Health Organization (WHO) Drug Dictionary Version SEP 2018 B3 GLOBAL will be used for coding of adverse events, medical history and medications. In practice, the most recent versions of MedDRA and WHODD available ahead of database lock will be used for coding.

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2 INTRODUCTION

The Sponsor has identified a novel therapy that it believes holds particular promise for the treatment of juvenile Batten disease (CLN3). The Sponsor's product, Batten-1 is oral miglustat.

CLN3 disease is an ultra-rare, genetic, lysosomal storage disease that primarily affects the nervous system and is fatal. Children with CLN3 disease develop normally, even excelling in school until ages 4 to 7 years, when progressive vision loss becomes noticeable. Concomitantly, or shortly thereafter, parents report personality changes and behavioral issues. Typically, within 2–3 years after symptom onset, total vision loss occurs, and seizures begin. This is followed by declining speech, progressive loss of motor coordination, and cardiac involvement. Psychosis, hallucinations and/or dementia can appear anytime during the disease. Eventually, children become wheelchair-bound, then bedridden, and die in their late teens or early twenties.

2.1 Trial Description

This is an open label study in 6 subjects in 2 centers to assess the safety, pharmacokinetics (PK), and efficacy of the maximum tolerable dose (MTD) of oral miglustat (100 mg once daily [QD] to 200 mg 3 times daily [TID]) in subjects ≥ 17 years of age with CLN3 disease.

The study sites are Texas Children's Hospital (TCH) and National Institutes of Health Clinical Center (NIH CC).

- Screening visit, screening confirmation and the end-of-study visit for follow-up safety assessments will be conducted by the TCH. Eligibility will be confirmed by TCH after all inclusion/exclusion criteria are assessed; screening confirmation decision will be communicated to subjects via telephone call by TCH. TCH will also review all subject safety data throughout the duration of the study. TCH will also confirm remotely the final enrollment after NIH baseline (V2).
- Baseline, every 6 months visit and end-of-treatment visit for efficacy assessments will be conducted at NIH CC.
- Additional safety assessments will be performed at the Local Health Center /Subject's Home and at the NIH CC as per protocol.
- Patients will have their last efficacy visit at National Institutes of Health (NIH) at week 78 and their last on-treatment visit at Texas Children's Hospital (TCH), and will continue to be treated until they can be switched to an early access program.

The study includes a dose-titration period of 9 weeks. Subjects will be assigned to miglustat at Week 1 and dosing will be escalated weekly as presented in Table 1-1 of the protocol.

Treatment with miglustat will begin at a dose of 100 mg QD. If the initial dose of miglustat is well tolerated, then the dose will be increased weekly until the MTD for a subject is reached. The dose increment is 100 mg. If needed for tolerability reasons, a dose may be repeated for 1 or more weeks prior to increasing. If a dose is not tolerated (based on the occurrence of treatment-emergent adverse events (TEAEs) and at the discretion of the TCH Principal Investigator (PI)), the dose may be adjusted downward to the previous dose. Dose increases may resume if there is time left in the titration scheme and at the discretion of the TCH PI; otherwise, this lower dose

becomes the subject's MTD. If a subject has not reached the maximum dose (600 mg/d) by Week 8, the Week 8 dose will be subject's MTD.

Once the dose titration and PK sampling period are completed, subjects will continue their MTDs during the maintenance period. Temporary or permanent dose reductions of miglustat for tolerability are permitted at any time during the maintenance period of the study.

An early access program is planned for subjects who wish to continue the treatment. This early access program will be described in a separate protocol.

2.2 Study Sample Size Determination

A total of six subjects will be enrolled in the study. Due to the ultra-rare nature of CLN3 disease, sample size is based on subject availability and not a statistical determination.

2.3 Treatment Assignment and Binding

This is an open-label study. All subjects will receive miglustat.

2.4 Schedule of Assessments and Procedures

See section 1.3 Schedules of Activities of the protocol for a tabular representation of the schedule of assessments.

3 OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 1 below.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of the Batten-1 treatment regimen over the study period	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs); • Changes from baseline in clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiogram (ECG) findings, slit lamp evaluation, vital signs (heart rate and blood pressure) as well as physical and neurological examinations
Secondary	
• To assess the pharmacokinetics (PK) of miglustat in subjects with CLN3 disease	• Week 1 first dosing: Maximum plasma concentration (Cmax), Time to Cmax (Tmax), area under the concentration-time curve calculated to the last observable concentration at time t (AUC 0-t), area under the concentration-time curve extrapolated to infinity (AUC 0-∞), elimination half-life (T1/2) • Week 9 - Repeated dose (steady state): Cmin, Cmax, Tmax, AUC 0-8hr
• To assess the effect of the Batten-1 treatment regimen on the longitudinal progression of clinical symptoms of CLN3 disease	• Unified Batten Disease Rating Scale (UBDRS) • Seizure frequency (diaries) • Vineland Adaptive Behavior Scales, Version 3 (Communication, Daily Living Skills, Socialization, and Motor Skills domains) • Ophthalmic assessments including visual acuity, visual fields (if feasible), and optical coherence tomography (OCT) • Magnetic resonance imaging (MRI)
Exploratory	
• To assess potential biomarkers of CLN3	• Measure biomarkers in cerebrospinal fluid (CSF), blood and urine and CSF concentration of miglustat

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4 ANALYSIS POPULATIONS

The **Safety Population** will consist of all subjects who enroll in the study and receive at least 1 dose of study medication.

The **PK Population** will consist of subjects who received at least 1 dose of study drug and had a full PK sample set drawn per protocol for that day.

PK Population is used for all PK analyses. PK analyses are performed by [redacted] PK group, described in PK Analysis Plan, and reported in PK Analysis Report. PK analyses are not in scope of this SAP.

The **Efficacy Population** will consist of the subjects who received at least 1 dose of study medication and had at least 1 follow-up efficacy assessment, defined as at least one post-baseline Unified Batten Disease Rating Scale assessment.

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5 STATISTICAL METHODS

5.1 Primary Endpoints

The primary endpoints pertain to subject safety and will be summarized for the Safety Population. Details on primary endpoints analyses are provided in sections below.

5.1.1 Adverse Events

Non-treatment emergent adverse events (AEs) will be collected from the time the subject screened into the study (date of signature of informed consent) until first administration of study drug.

Thereafter, all AEs are **treatment-emergent adverse events** (TEAEs) and will be recorded until the end of study visit has been performed. In all outputs, AEs with start date(time) on or after the study drug start date(time) will be considered as TEAEs (i.e., TEAE designation will be programmatically derived based on dates; eCRF checkbox for TEAE will not be used). In case it is impossible to determine whether an AE is treatment-emergent or not (i.e., AE occurs on day 1 but time is unknown), the AE will be considered a TEAE.

Partial start dates of AEs will be imputed according to section 8.1 for the determination of non-treatment emergent and treatment-emergent designations.

AEs will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA) latest version available before the database lock. National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used for the grading of AEs by the investigators.

For summary tables, AEs with relatedness "Definite", "Probable", and "Possible" will be considered as "Related", AEs with relatedness "Unrelated" and "Unlikely" will be considered "Not Related" and AEs with relatedness "Not Applicable" will be reported as such. AEs with missing relatedness assessment will be considered as "Related" for summary tables and will be footnoted in applicable tables; listings will present relatedness data as collected (i.e., missing).

AEs with missing seriousness assessment will be considered as "Serious" for summary tables; listings will present seriousness data as collected (i.e., missing). Should AEs with missing seriousness be present at time of reporting, these will be footnoted in applicable serious adverse event tables.

AEs with missing severity assessment will be considered as "Grade 3" for summary tables; listings will present severity data as collected (i.e., missing). Should AEs with missing severity be present at time of reporting, these will be footnoted in applicable adverse event tables.

An overall summary of AEs will be produced, including counts and percentages of subjects with any incidence of:

1. AEs (including non-treatment emergent AEs),
2. TEAEs,

3. Non-serious TEAEs,
4. Serious TEAEs (TESAEs),
5. Related TEAEs,
6. Related serious TEAEs,
7. TEAEs by maximum CTCAE grade,
8. CTCAE Grade 3 or above TEAEs,
9. CTCAE Grade 3 or above related TEAEs,
10. TESAEs leading to death,
11. TEAEs leading to treatment discontinuation,
12. TESAEs leading to treatment discontinuation,
13. Related TEAEs leading to treatment discontinuation
14. TEAEs leading to study discontinuation.

Summaries of AEs by MedDRA system organ class (SOC), high level group term (HLGT) and preferred term (PT) will be sorted by overall incidence of SOC, HLGT and PT and will include the following:

1. TEAEs,
2. TEAEs leading to treatment discontinuation,
3. TESAEs,
4. TEAEs by maximum CTCAE grade,
5. TEAEs by closest relatedness.

When calculating the incidence of AEs, each subject will be counted only once within a MedDRA category (e.g., overall, SOC, HLGT, or PT). When AEs are summarized within levels of another AE assessment (e.g., relatedness or CTCAE grade), subjects will be counted once at the worst level of the assessment within the MedDRA category (e.g., closest relatedness or highest CTCAE grade).

With the exception of summary tables by maximum CTCAE grade and closes relatedness, event counts will be included in all TEAE tables in addition to subject counts.

Adverse event duration (days) will be calculated as:

$$\textit{Adverse Event End Date} - \textit{Adverse Event Start Date} + 1$$

Adverse event duration will only be calculated for events with complete start and end dates available (i.e., imputed, partial and missing values will not be used for duration calculation); duration will only be included in listings.

AE data will be listed. Additionally, an SAE listing will be created.

5.1.2 Clinical Laboratory Tests

Hematology, biochemistry, and urine results will be reported using standard units as provided by central laboratory; no further standardization is applied by [redacted].

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Lab values below lower limit of quantification (LLOQ) will be imputed as ½ LLOQ. Lab values above upper limit of quantification will (ULOQ) will be imputed as 1.1 * ULOQ.

The following clinical laboratory evaluations will be reported:

1. **Hematology**: hemoglobin, hematocrit, erythrocytes, leukocytes, differential white blood cell count, thrombocytes.
2. **Biochemistry**: creatinine, total bilirubin (direct and indirect if values were above normal ranges), hemoglobin A1c (HbA1c), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, creatinine kinase, sodium, potassium, cholesterol (total, HDL, LDL), triglycerides, creatinine clearance.
3. **Urine**: glucose, nitrate, pH, hemoglobin, leukocytes, specific gravity, protein, ketones.
4. **Other tests**: HIV, hepatitis B, hepatitis C.
5. **Pregnancy test**: urine/serum.

Observed values and changes from baseline for hematology and biochemistry will be summarized at each scheduled post-baseline visit. Baseline will be defined as last value collected before first study drug administration (both dates and times will be compared); both data collected at scheduled and unscheduled visits will be included in baseline derivation.

Additionally, shift tables from baseline to each scheduled post-baseline visit will be added for select laboratory parameters: thrombocytes, and creatinine kinase. Lab values will be classified as low, normal, and high for the purpose of shift table creation.

Urinalysis overall interpretation (Abnormal – Clinically Significant / Abnormal – Not Clinically Significant / Normal) will be presented by visit in a frequency table. Urinalysis results by parameter will only be listed.

Laboratory data will be listed.

5.1.3 12-Lead Electrocardiogram

Electrocardiogram (ECG) results collected through the study include:

1. PR interval (msec),
2. QRS duration (msec),
3. RR interval (msec),
4. QT interval (msec),
5. QTcF (msec),
6. Overall interpretation (Normal / Abnormal – Not clinically relevant / Abnormal - Clinically relevant).

QTcF will be presented as collected on eCRF (i.e., no derivations done by [redacted] biostatistics).

Observed values and changes from baseline for continuous ECG parameters will be summarized at each scheduled post-baseline visit; overall interpretation results will only be listed.

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When triplicate values are collected at given visit, the average of the triplicate will be calculated and presented for that visit; in case less than three values are reported, the average will be calculated over non-missing values. Baseline for ECG is based on averaging the last pre-dose triplicate (not the last individual measurement pre-dose).

All ECG data will be listed (including the individual triplicate measurements as well as the average results).

5.1.4 Slit Lamp Evaluation

Slit lamp evaluation results collected through the study include:

1. Ocular cataracts performed (Yes / No) and result, if performed (Normal / Abnormal),
2. Ocular opacity performed (Yes / No) and result, if performed (Normal / Abnormal).

Slit lamp evaluation results will be presented by visit in a frequency table.

Slit lamp evaluation data will be listed.

5.1.5 Vital Signs and Body Measurements

Vital signs (VS) and body measurements results collected through the study include:

1. Height (cm; only collected at screening),
2. Weight (kg),
3. BMI (kg/m^2),
4. Systolic blood pressure (mm Hg),
5. Diastolic blood pressure (mm Hg),
6. Heart rate (beats per minute).

For screening visit, BMI auto-calculated in the eCRF will be used. For other visits where weight is measured, BMI will be calculated by [redacted] biostatistics as:

Weight at Given Visit in kg / (Baseline Height in m)^2.

Observed values and changes from baseline for VS and body measurements parameters (excluding height) will be summarized at each scheduled post-baseline visit. Baseline will be defined as last value collected before first study drug administration (both dates and times will be compared); both data collected at scheduled and unscheduled visits will be included in baseline derivation.

For weight, percent change from baseline will additionally be included in the summary tables.

VS data will be listed.

5.1.6 Physical Examination

The following body systems are assessed through the study:

1. General appearance, skin, neck (including thyroid),
2. HEENT (head, ears, eyes, nose, throat),

3. Cardiovascular,
4. Respiratory,
5. Abdomen,
6. Lymph nodes,
7. Extremities,
8. Nervous system,
9. Musculoskeletal.

For each of the body systems, the result is assessed as Normal / Abnormal – Clinically significant / Abnormal – Not clinically significant.

Physical examination results will be summarized by body system and visit in a frequency table.

Physical examination data will be listed.

5.1.7 Neurological Examination

Neurological examination results collected through the study include:

1. Visual impairment assessment performed and result, if performed,
2. Mental status assessment performed and result, if performed,
3. Cranial nerves function assessment performed and result, if performed,
4. Motor function assessment performed and result, if performed,
5. Sensory function assessment performed and result, if performed,
6. Cerebellar function assessment performed and result, if performed.

For each assessment performed, the result is assessed as Normal / Abnormal.

Neurological examination results will be presented by visit in a frequency table.

Neurological examination data will be listed.

5.2 Secondary Endpoints

All efficacy summaries described below will be analyzed using the Efficacy Population; listings will use All Screened Subjects.

5.2.1 Unified Batten Disease Rating Scale (UBDRS)

The UBDRS assessment consists of several domains with individual questions within each domain. The assessments will be collected at the visits as shown in the protocol schedule of events. UBDRS domains measured, corresponding questions and relevant imputation rules are described in Table 2 below. Subscales of Physical Assessment domain are also derived and described in Table 2.

Table 2. UBDRS Domains/Subscales and Analysis Methods

Domain	Contributing Questions	Method of Summarization	Imputation Rules
Physical Assessment	1, 1A, 2, 3, 4A, 4B, 5A, 5B, 6, 7A, 7B, 8A, 8B, 9A, 9B, 10A, 10B, 11, 12, 13, 14A, 14B, 15, 16, 17, 18, 19, 20	Sum of scores of individual questions divided by number of questions (28).	Missing or not done individual question values will be imputed with the worst possible value (i.e., 4) for summaries
Modified Physical Assessment Subscale	1, 1A, 3, 4A, 4B, 5A, 5B, 6, 9A, 9B, 11, 12, 13, 14A, 14B, 19	Sum of scores of individual questions divided by number of questions (16).	As for Physical Assessment domain
Physical Assessment 5-item Subscale	1, 11, 12,13, 19	Sum of scores of individual questions divided by number of questions (5).	As for Physical Assessment domain
Physical Assessment 2-item Subscale	1, 12	Sum of scores of individual questions divided by number of questions (2).	As for Physical Assessment domain
Seizure Assessment	23-34	Sum of scores of individual questions divided by number of questions (12).	Missing or not done individual question values will be imputed with the worst possible value for summaries: 1. Questions 23, 25, 26, 27, 29 – 6, 2. Questions 24, 28, 30 – 5, 3. Questions 31, 32 – 3. 4. Question 33 – 2, 5. Question 34 – 1.
Behavioral Assessment (Past Month)	36A, 36B, 37A, 37B, 38A, 38B, 39A, 39B, 40A, 40B, 41A, 41B, 42A, 42B, 43A, 43B, 44A, 44B, 45	Sum of scores of individual questions divided by number of questions (19).	Missing or not done individual question values will be imputed with the worst possible value for summaries: 1. Question 45 – 1, 2. All other questions – 3.
Capability Assessment Given Actual Vision	52-56	Sum of scores of individual questions divided by number of questions (5).	Missing or not done individual question values will be imputed with the worst possible value for summaries: 1. Questions 52-55 – 3, 2. Question 53 – 2.
Clinical Summary	61-67	Each question (including 6 CGIs*** and one assessment of change) will be presented separately.	Missing or not done individual question values will be imputed with the worst possible value for summaries (5). Question 61 (Assessor's global impression of change since last assessment) value "Not applicable (never seen before)" will not be imputed.

* NCL history domain of UBDRS (completed by first rater) will be summarized with baseline disease history data

(see datils in section 5.7).

** Capability assessment assuming normal vision is not assessed in this study.

*** CGI = Clinician Global Impression.

Domain scores, subscale scores and individual question scores (only for Clinical Summary domain which does not have domain score), and their respective changes from baseline will be summarized at each scheduled post-baseline visit. Baseline will be defined as last value collected before first study drug administration; both data collected at scheduled and unscheduled visits will be included in baseline derivation. For Clinical Summary domain question 61 (Assessor's global impression of change since last assessment), only observed values (not change from baseline) are presented.

UBDRS data (including both individual and domain scores) will be listed.

5.2.2 Seizure Frequency

Seizure frequency will be collected in subject diaries and all seizures reported in the diaries will also be reported as AEs on the adverse events eCRF page.

For the purpose of summarizing seizures, the more granulated information from AE pages will be used. Each AE with preferred term including the word "seizure" will be considered a seizure for the purpose of this analysis.

For each subject the number of seizures per the following 3-month intervals will be calculated:

1. Pre-treatment,
2. Baseline to month 3 (study days 1 to 90; both inclusive),
3. 4 to 6 months (study days 91 to 180; both inclusive),
4. 7 to 9 months (study days 181 to 270; both inclusive),
5. 10 to 12 months (study days 271 to 360; both inclusive),
6. 13 to 15 months (study days 361 to 450; both inclusive),
7. 16 to 18 months (study days 451 to 540; both inclusive),
8. After 18 months (study day 541 and onwards),
9. Entire study duration (all previous combined).

Qualifying AE start days will be compared with the study days above to determine in which time interval the seizure occurred. For study day 1, treatment start time and AE start time will additionally be compared. In case of missing or partial AE start dates, imputation rules provided in section 8.1 will be used for determining the interval in which the seizure occurred.

Summary statistics of seizure counts for all subjects in the Efficacy Population will be provided by time interval. Individual seizure counts by time interval will be provided in a listing.

5.2.3 Vineland Adaptive Behavior Scales, Version 3

Vineland Adaptive Behavior Scales data will be collected and analyzed by NIH.

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For the purpose of this SAP, Vineland Adaptive Behavior Scales data will only be listed.

5.2.4 Ophthalmic Evaluation

The following ophthalmic evaluation data is collected in the eCRF throughout the study:

1. Visual acuity evaluation performed and result (Normal / Abnormal), if performed,
2. Visual fields evaluation performed and result (Normal / Abnormal), if performed,
3. Optical Coherence Tomography (OCT) evaluation performed and result (Normal / Abnormal), if performed,
4. Intraocular pressure in the left eye (OS) (mm Hg),
5. Intraocular pressure in the right eye (OD) (mm Hg).

Categorical ophthalmic evaluation results will be presented by visit in a frequency table.

Observed values and changes from baseline for intraocular pressure variables will be summarized at each scheduled post-baseline visit. Baseline will be defined as last value collected before first study drug administration; both data collected at scheduled and unscheduled visits will be included in baseline derivation.

Ophthalmic evaluation data collected in the eCRF will be listed.

NIH is collecting and analyzing additional ophthalmic data. That data is only listed for the purpose of this SAP.

5.2.5 MRI Assessments

Volumetric assessments using MRI are collected and analyzed by NIH.

For the purpose of this SAP, MRI data will only be listed.

5.3 Exploratory Endpoints

Biomarkers are collected in blood, urine, and cerebrospinal fluid. Biomarker data is collected and analyzed by NIH.

For the purpose of this SAP, biomarker data will only be listed.

5.4 PK Analysis

A specific PK Analysis Plan was prepared by [redacted] PK group describing all analysis of PK endpoints. PK analyses are not in the scope of this SAP.

5.5 Subject Disposition

A tabulation of subject disposition will be provided for all screened subjects and will include:

1. Number of subjects screened,

2. Number (%) of screen failures,
3. Number (%) of subjects enrolled,
4. Number (%) of subjects treated,
5. Number (%) of subjects in each analysis population,
6. Number (%) of subjects who completed the treatment,
7. Number (%) of subjects who did not complete the treatment, and reasons for doing so,
8. Number (%) of subjects who completed the study,
9. Number (%) of subjects who terminated the study early, and reasons for doing so.

Screened subject is defined as any subject with informed consent date. **Screen failure** is defined as any subject who answered "NO" to "Did the subject satisfy all the enrollment criteria?" on "Enrollment" eCRF page. **Enrolled subject** is defined as any subject who answered "Yes" to "Did the subject satisfy all the enrollment criteria?" on "Enrollment" eCRF page.

A disposition listing will be created to support the information in the disposition table.

Listings of inclusion/exclusion criteria and enrollment criteria will also be created.

5.6 Protocol Deviations

Protocol deviations are defined as activities on a study that diverge from the approved protocol.

Prior to database lock, the Sponsor will produce the final protocol deviation file in collaboration with the data monitoring group; this file will include a description of the protocol deviation, the occurrence date, the categorization as minor / major. This file will be finalized prior to hard database lock.

Protocol deviations data will be listed separately for major and minor deviations.

5.7 Demographics and Baseline Characteristics

Demographics information will be summarized using descriptive statistics for the Safety Population and will include:

1. Age (years) at time of informed consent (as continuous variable),
2. Sex (Male / Female),
3. Ethnicity (Hispanic or Latino / Not Hispanic or Larino / Not Reported / Unknown),
4. Race (White / Black or African American / Asian / Native Hawaiian or Other Pacific Islander / American Indian or Alaska Native / Other),
5. Weight (kg; as continuous variable),
6. Height (cm; as continuous variable),
7. Body mass index (BMI; kg/m^2; as continuous variable).

Age at time of informed consent and BMI will be reported as collected on the eCRF. Visit 1 weight, height and BMI are reported for this summary (as height and BMI are only measured at Visit 1).

Demographics and baseline characteristics data (including information on childbearing potential, where applicable) will be listed.

Baseline disease characteristics will be summarized using descriptive statistics for the Efficacy Population and will include baseline information regarding the following:

1. CLN3 mutations: CLN3 variants identified? (Yes / No / Unknown)
    a. Variant 1
    b. Variant 2
2. UBDRS Neuronal Ceroid Lipofuscinosis (NCL) history domain:
    a. 58a. Loss of vision,
    b. 58b. Motor difficulties,
    c. 58c. Cognitive difficulties,
    d. 58d. Behavioral difficulties,
    e. 58e. Seizures,
    f. 58f. Feeding difficulties,
    g. 58g. Sleep disturbances,
    h. 58h. Others.

For both Variant 1 and Variant 2 CLN3 mutations the following data will be summarized:

1. Segregation (Maternal / Paternal / Unknown),
2. DNA change notation,
3. Protein change notation,
4. Zygosity (Homozygous / Heterozygous / Unknown / Other),
5. Classification (Pathogenic / Likely Pathogenic / Likely Benign / Benign / Uncertain Significance),
6. Secondary confirmation performed (Yes / No).

For each of UBDRS NCL history domain questions, the following data will be summarized:

1. Experienced symptoms? (Yes / No / Not Done),
2. Onset age in years,
3. Ranking (order of onset of symptoms, 1-8).

The onset age in years is derived as:

Onset age years (collected in eCRF) + [*Onset age months (collected in eCRF)*] /12,

e.g., if onset age years is entered as 1 and onset age months is entered as 6, then onset age in years will be calculated as 1 + 6/12 = 1.5 (years).

Baseline disease characteristics data will be listed.

5.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the latest version of World Health Organization Drug Dictionary (WHODD) available before the database lock.

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Prior medications are those which have been identified to have been discontinued prior study drug start date (i.e., taken exclusively before treatment start). Concomitant medications are those which have been identified to have been taken at any point on or after the study drug start date. If it is not possible to determine whether a medication is prior or concomitant, it will be assumed to be concomitant.

Partial start and end dates of medications will be imputed according to section 8.1 for the determination of prior and concomitant designations.

The incidence of concomitant medication use will be summarized for the Safety Population by WHODD anatomic therapeutic chemical (ATC) Level 2 classification (i.e., therapeutic main group) and preferred name. A subject will be counted only once at each level of reporting. Prior medication use will only be listed.

Prior and concomitant medication data will be listed.

5.9 Concomitant Procedures

Concomitant procedures will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA) latest version available before the database lock.

Concomitant procedure data will be listed.

5.10 Exposure to and Compliance with Study Drug (Miglustat)

Miglustat administration data will be summarized for the Safety Population by visit and will include the following variables:

1. Was the study drug administered? (Yes / No),
2. Study drug dose / day (mg) (continuous variable),
3. Study drug dose / day (mg) (categorical variable – 100 / 200 / 300 / 400 / 500 / 600).

Miglustat administration data (including supply and accountability) will be listed for the Safety Population.

Note that in initial protocol versions, Trehalose was planned to be administered alongside miglustat. However, the protocol and eCRF were amended before any subject received Trehalose. Therefore, no data will be presented for Trehalose.

5.11 Medical History

Medical history terms will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA) latest version available before the database lock.

A table will be generated to summarize medical history for the Safety Population by SOC and PT. A subject will be counted only once at each level of reporting.

Medical history data will be listed.

5.12 General Aspects for Statistical Analyses

- Categorical variables will be summarized using the number of observations (n), frequency and percentage of subjects. All percentages will be presented as one-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.
- Continuous variables will be summarized using the number of subjects with evaluable data (n), mean, standard deviation (SD), geometric mean (where appropriate), median, minimum and maximum. In general, the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 more decimal places than in the raw data will be presented when reporting the SD.
- Unless stated otherwise, the percentages will be based on the number of non-missing observations. The column header will still contain the number of subjects in the treatment group. Where appropriate, there will be a row for the number of non-missing observations in the table (at each time point, if required) for each variable being summarized.
- All relevant subject data will be included in listings and sorted by treatment group (treated subjects first, followed by screen failures), subject ID, visit/timepoint, and assessment type, as applicable. All listings (except for study drug exposure) will be based on All Screened Subjects.
- Unscheduled or repeat assessments will not be included in summary tables unless specified. All assessments will be included in the subject listings.
- All tables, listings and figures will include footers that identify the name of the program that created the output, together with the date and time on which it was created. Headers will include the total number of pages that the presentation contains and, for each page, the number of the page within the presentation.

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6 INTERIM ANALYSIS

An interim analysis was performed after the six participants were enrolled and completed the titration period for each respective titration scheme. A small number of safety tables was agreed on to summarize the available information at that time and the analysis of PK data collected respectively at Week 1 and Week 9 was performed.

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7 SOFTWARE AND PROGRAMMING SPECIFICATIONS

All datasets, TLFs, and statistical analyses will be generated using SAS, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated datasets, table, listing and figure output will adhere to the following specifications:

7.1 General Programming Specifications

- One SAS program can create several outputs, or a separate SAS program can be created for each output at the statistical programmer's discretion.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format / rtf format.
- Numbering of TLFs will follow ICH E3 guidance.

7.2 Table, Listing, and Figure Format

7.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape-orientated page and a minimum 1-inch margin on the other 3 sides.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (e.g., cm^2, C_{max}).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.

7.2.2 Headers and Footers

- All outputs should have the following header at the top left of each page:

Beyond Batten Disease Foundation
Protocol: Batten-1-01

- All outputs should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) should appear along with program name and location as the last footer on each page.

7.2.3 Display Titles

- Each TLF should be identified by the designation and a numeral (e.g., Table 14.1.1). ICH E3 recommended numbering will be used. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis population should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title (if needed)
Analysis Population

7.2.4 Column Headers

- Column headers should be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects with available data.

7.2.5 Body of the Data Display

7.2.5.1 Table Conventions

- Units will be included where applicable.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
Very Severe	2
Severe	0
Moderate	8
Mild	3

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are required.
- As appropriate, an Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

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- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999 then present as >0.999.
- Unless otherwise specified, tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, drug class, or SOC in descending order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote will note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(continued)" at the top of each subsequent page. The overall summary statistics for the subheading will only be output on the first relevant page.

7.2.5.2 Listing Conventions

- Dates will be printed in SAS® DATE9.format ("DDMMMYYYY": 01JUL2000).
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26 or 11:26:45). Time will only be reported if it was measured as part of the study.
- Units will be included where applicable.

7.2.5.3 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

7.2.5.4 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will be present on all pages of the output. Subject-specific footnotes will be avoided wherever possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing.
- The last 2 lines of the footnote section will be a standard source that indicates the name of the program used to produce the data display, date the program was run, and the listing source (or data source for a listing) (e.g., 'Program: myprogram.sas Listing source: 16.x.y.z').

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8 APPENDICES

8.1 Imputation Rules for Partial Adverse Event and Medication Dates

The algorithms in Table 2 below should be used for missing dates when needed for determining treatment-emergence of adverse events and prior/concomitant designation of medications. All algorithms assume a comparison to study drug start date and/or study drug end date for categorization.

All dates will be considered to be made of three parts: day, month, and year. Note that if day is non-missing but month is missing, day should be considered missing as well in the algorithms below.

Table 3. Imputation Rules for Partial Adverse Event/Medication Dates

AE/Medication Date	Unknown Information	Known Information	Action
Start date	*day, month, year*	none	Set start date to study drug start date.
Start date	*day, month*	*year*	If *year* = year of study drug start date, set the date to study drug start date. If *year* < year of study drug start date, set month and day to December 31st. If *year* > year of study drug start date, set month and day to January 1st.
Start date	*day*	*month, year*	If *year* = year of study drug start date and: • *month* = month of study drug start date, set day to day of study drug start date. • *month* < month of study drug start date, set day to last day of month. • *month* > month of study drug start date, set day to first day of month. If *year* < year of study drug start date, set day to last day of month. If *year* > year of study drug start date, set day to first day of month.

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Should the imputed start date based on the rules above be after a known end date for the AE or medication (an end date with no missing date parts), use the end date instead of the date that would be imputed based on the rules above.			
Medication end date	*day, month, year*	none	If *ongoing* is checked, set the date to study drug end date. If *ongoing* is not checked, do not impute.
Medication end date	*day, month*	*year*	If *year* = year of study drug end date, set the date to study drug end date. If *year* < year of study drug end date, set month and day to December 31st. If *year* > year of study drug end date, set month and day to January 1st.
Medication end date	*day*	*month, year*	If *year* = year of study drug end date and: • *month* = month of study drug end date, set day to day of study drug end date. • *month* < month of study drug end date, set day to last day of month. • *month* > month of study drug end date, set day to first day of month. If *year* < year of study drug end date: set day to last day of month. If *year* > year of study drug end date: set day to first day of month.
Should the imputed end date come before the start date (either fully known or imputed) then use the start date instead of the date that would be imputed based on the rules above.			
Should the imputed end date come after the date of the subject's death or after the subject's End of Study (if applicable), then use the date of death or End of Study date instead.			

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