CLINICAL STUDY PROTOCOL

An Open-label Safety, Pharmacokinetic, and Efficacy Study of Miglustat for the Treatment of CLN3 Disease in Patients 17 Years of Age and Older

Protocol Number:	Batten-1-01
Intervention:	Miglustat
Compound Number:	Batten-1
Indication:	Juvenile Batten (CLN3) Disease
Phase:	1/2
Sponsor:	Beyond Batten Disease Foundation P.O. Box 50221 Austin, TX 78763
Principal Investigators:	
IND Number:	152646
NCT Number:	05174039
Protocol version; date:	Version 5; 6 February 2024

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

SIGNATURE PAGES

Declaration of Sponsor or Responsible Medical Officer

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

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

_____ _____

_____ _____

Declaration of the Investigator

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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, Case Report Forms, and other scientific data.

The study will not begin without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the protocol without the prior written approval of Beyond Batten Disease Foundation, the Regulatory Authority and the IRB, except where necessary to address an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol, including:

- To adhere to the Declaration of Helsinki, and the principles on Good Clinical Practice (GCP), the local laws and applicable regulatory requirements
- To obtain informed consent prior to performing any study procedures
- To use the study drug and all study materials only within the framework of this clinical study
- To comply with the obligations for reporting adverse events.

_____ _____

Name Date
Title
Institution

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Version 1.0	25 June 2021
Version 2.0 (Amendment 1)	27 August 2021
Version 3.0 (Amendement 2)	30 September 2021
Version 3.1 (Amendement 2.1)	19 November 2021
Version 4.0 (Amendement 3)	15 April 2022
Version 4.1 (Amendement 3.1)	7 July 2023
Version 5.0 (Amendement 4)	6 February 2024

AMENDMENT 1 (27 August 2021)		
Overall Description for the Amendment		**Brief Rationale**
Section Number and Name	**Description of Change**	
Front page, synopsis, section 4	University of Rochester Medical Center added as Principal Investigator	University of Rochester Medical Center responsible of the UBDRS rating
Section 1.3	Safety labs added at Week 52, Week 78 and Week 104 as per protocol	Safety labs are to be checked every 3 months during maintenance as per protocol
Synopsis, sections 3. and 8.8	Additional PK parameters to analyze at Week 10 and 18 in Scheme A for miglustat, and at Week 10 and 18 in Scheme B for trehalose	PK parameters analysis to be also provided from the same subject for trehalose, miglustat administered alone and in combination
Section 5.3.2	Additional statement re. re-assessment of the benefit/risk ratio of therapy and consideration of treatment discontinuation in case of symptoms such as numbness and tingling	Alignment with Zavesca prescriber information
Section 7.3.1	Addition of total volume of blood drawn	Specification needed of the total volume of blood collected during the whole study
Section 8.8	Correction of typos in Statistical section regarding time of PK assessment	Ensure consistency between the different PK Sections (synopsis, Sections 7.2.1, 7.2.2, 8.8)

AMENDMENT 2 (30 September 2021)		
Overall Description for the Amendment		**Brief Rationale**
Section Number and Name	**Description of Change**	
Cover page, Section Study Design, Section 4	Removal of Rochester University Medical Center as Principal Invetigator site	UBDRS Rating performed remotely, no involvement of the site in recruitment and patient visits
Synopsis and Section 6.2	Integration of Direct to Patient Investigational Product Shipment	To introduce Direct-To-Patient shipment option in case of operational need
Synopsis and Section 3	Addition of clearance in PK parameters	PK assessment exhaustiveness
Section 1.3 Schedule of activities	Clarification of wording	Clarification of wording
Section 5.3 and Section 7.1.8	Inclusion of a “Screen Failure” section and a “Unanticipated Problems” section	Integration from NIH Addendum
Section 11.5	Introduction of DSMB rules for escalation	Rules validated by DSMB

AMENDMENT 2.1 (19 November 2021)		
Overall Description for the Amendment		**Brief Rationale**
Section Number and Name	**Description of Change**	
Synopsis, Section 6.2 and Appendix 8	Addition of the procedure for home administration of investigational product	Related procedure for home administration following introduction of Direct-To-Patient shipment option

AMENDMENT 3.1 (7 July 2023)		
Overall Description for the Amendment		**Brief Rationale**
Section Number and Name	**Description of Change**	
Section 1.3 page 17: Schedule of activities	Add collection of blood biomarkers at Week 78	To add an exploratory endpoint at Week 78 to increase the knowledge of biomarkers evolution in blood under long-term miglustat treatment
Section 1.3 page 23: Schedule of activities	Dates expressed in weeks instead of days	Simplification of schedule presentation
Section 7.1.3 Laboratory parameters	Change in volume of blood drawn in the study	Change in volume following additional blood biomarker dosing

AMENDMENT 4.0 (6 February 2024)		
Overall Description for the Amendment		**Brief Rationale**
Section Number and Name	**Description of Change**	
Synopsis, schedule of activities, Sections 4.1, 6.9.2, 7.2 and 8.8.	Early termination of the study with removal of the Week 104 efficacy visit at NIH and early termination visit placed at TCH	Collection of safety and efficacy data considered sufficient after 18 months of treatment in a population of young adults. Patients will be switched to an early access program after study termination to ensure treatment continuity.
Section 8.8	Through PK and miglustat dosage in CSF removed	Protocol simplification's sake ; data redundancy

TABLE OF CONTENTS

Tables in Text

Figures in Text

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Rationale:

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

Juvenile Batten (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.

Miglustat (Batten-1), an iminosugar, has been shown to inhibit the accumulation of gangliosides implicated in disease pathogenesis of related lysosomal storage diseases Type 1 Gaucher Disease and Niemann-Pick disease, type C. In addition, anti-inflammatory effects have also been reported. Miglustat is approved in the United States (US) and in the European Union (EU) for adult Type I Gaucher Disease at doses of 300mg/d. Miglustat is also approved in the EU for treatment of adult and pediatric patients with Niemann-Pick Type C Disease at doses up to 600mg/d. Over 18 years of safe use is available for miglustat, whose most common adverse effect is gastro-intestinal which can be mitigated with changes in diet and appears to lessen over time.

CLN3 disease pathology also includes accumulation of gangliosides and chronic neuroinflammation and therefore, patients may benefit from daily miglustat therapy. These assertions are supported by studies in CLN3 animal models and in vitro cerebellar cells from those models demonstrating significant increases in GM3 ganglioside levels over wild type, which are significantly reduced by treatment with miglustat as well as a reduction of globoside Gb3, Gb4, and ganglioside GM1 accumulation in vitro.

In a model of Batten disease, in *Cln3*$^{-/-}$ mice, microglial and astrocyte activation was analyzed along with apoptosis (BBDF-04042022 internal report). In this model, *Cln3*$^{-/-}$ mice display astrocytosis and microglial activation in brain regions where neuronal loss is subsequently most pronounced. Previous work had established that astrocyte and microglial activation may be causally related to neuronal loss (Parviainen et al, 2017).. Thus, quantification of glial activation is an appropriate proxy for disease state. Finally, brain atrophy is among the hallmarks of Batten disease and is the result of progressive neurodegeneration. *Cln3*$^{-/-}$ mice recapitulate this feature, which can be observed as a global loss of brain weight with age, or decreased neuronal number in various regions including the thalamus, cerebellum, and the somatosensory regions of the cortex (BBDF-04042022).

Miglustat alone and the combination of trehalose and miglustat similarly exerted their beneficial effects on the pathological hallmarks of Batten disease. Trehalose treatment given alone also significantly reduced microglial and astrocytic activation as well as apoptosis, but in a limited number of brain regions. Miglustat has a clear modifying action on *Cln3*$^{-/-}$ mouse neuropathology that is stronger than that of trehalose alone. Miglustat is currently approved for the treatment of Gaucher disease and Niemann-Pick type C in various countries, based on its potent effects as an inhibitor of the synthesis of glycosphingolipids, molecules that accumulate in these and other lysosomal storage diseases.

The potent neuroprotective effects exerted by miglustat suggest that certain biochemical products of the glycosphingolipid pathway may also accumulate in Batten disease and contribute to its pathogenesis. However, it seems that the combination of trehalose and miglustat did not demonstrate any difference versus the use of miglustat alone. Indeed, treatment with miglustat alone presented the same impact on *Cln3*$^{-/-}$ mice phenotype as the combination of miglustat and trehalose.

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 (AUC0-∞), elimination half-life (T1/2) • Week 9 - Repeated dose (steady state): Cmin, Cmax, Tmax, AUC 0-8hr
• To assess the effect of the Batten-102 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.

Study Design:

This is an open label study in approximately 6 subjects in 2 centers to assess the safety, 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. Patients will have their last efficacy visit at NIH at week 78 and their last on-treatment visit at TCH, and will continue to be treated until they can be switched to an early access program..

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 subject 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.

This 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.

Table 1-1 Miglustat Dose Escalation

Dose Escalation Step	Morning (8 AM)	Afternoon (2 PM)	Evening (8 PM)
Step 1	X	X	100 mg
Step 2	100 mg	X	100 mg
Step 3	100 mg	100 mg	100 mg
Step 4	100 mg	100 mg	200 mg
Step 5	200 mg	100 mg	200 mg
Step 6	200 mg	200 mg	200 mg

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 TEAEs and at the discretion of the TCH 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.

Study Population:

Inclusion Criteria:

1.	Have provided informed consents (TCH and NIH) by subject or parent/legal guardian/legally authorized representative (as appropriate).
2.	Are males or females ≥ 17 years of age at the time of screening
3.	Have genetically confirmed diagnosis of syndromic CLN3 disease with EITHER: A. Two pathogenic mutations in the CLN3 gene, OR B. One confirmed pathogenic AND one variant of unknown significance, OR 2 variants of unknown significance, PLUS secondary confirmation with evidence of characteristic inclusions on electron microscopy AND characteristic clinical course. There is no restriction on the specific CLN3 mutations for eligibility to enroll in the study. The mutations will be recorded in the electronic case report form (eCRF) for potential use in determining if CLN3 genotype is associated with tolerability or effectiveness of Batten-102 therapy.
4.	Male and female participants must use a highly effective method of contraception and must continue for the duration of the trial (and for 30 days after the end of treatment). Appropriate methods of contraception are described in appendix 6.
5.	Are able to complete study assessments (subject and/or caregiver) and return to the clinic as scheduled

Exclusion Criteria:

1.	Have a medical condition that in the opinion of the PI would interfere with the safety assessments or increase the subject's risk of AEs
2.	Use of any therapy (approved, off-label, or unapproved) intended to modify the course of any neuronal ceroid lipofuscinosis disease, including but not limited to flupirtine or flupirtine derivatives, cerliponase alfa (Brineura)
3.	Have, in the opinion of the PI, a clinically significant abnormality in their clinical laboratory values (hematology, chemistry, or urinalysis) at screening that would preclude their participation in the study
4.	Have a known allergy or hypersensitivity to miglustat, or any component of the study drug
5.	Have a severe renal disease (creatinine clearance < 30 ml/min/1.73 m2)
6.	Have a history of substance abuse or alcohol abuse within 2 years before screening
7.	Have a medical history of HIV, hepatitis B, hepatitis C, or positive results at screening
8.	Have any active malignancy of any type except non-melanoma skin cancer
9.	Have a medical history of major mental illness that, in the opinion of the PI may affect the ability of the subject to participate in the study. Institutionalized subjects are not eligible for participation.
10.	Have received gene therapy intended to modify the course of CLN3 disease
11.	Have been exposed to any miglustat or investigational agent, including but not limited to, flupirtine or flupirtine derivatives, within 30 days or 5 half-lives (whichever is longer) prior to check-in for the Week 1 visit, or is scheduled to receive an investigational device or drug (other than test product) during the course of the study
12.	Participation in another interventional study during the last three months before screening.

Number of Participants and Duration of Participation:

Approximately 6 subjects are expected to enroll in the study. Subject participation will be up to 120 weeks (Screening to first dosing approximately 4 weeks, treatment duration up to 116 weeks for the longest treatment duration). Subjects who withdraw or are withdrawn from the study during the titration period may be replaced. The total study duration will be determined based on the early access program actual start for the last patient that will take place within 116 weeks of treatment.

Safety Assessments:

Safety will be assessed by the incidence of treatment emergent adverse events and serious adverse events, safety labs, ECG, slit lamp evaluation, vital signs and physical and neurological examination.

PK Assessments:

Pharmacokinetic data will be assessed at first miglustat dosing, and at the maximum tolerated dose (MTD) during the titration period.

Efficacy Assessments:

Efficacy assessments include Unified Batten Disease Rating Scale (UBDRS); seizure frequency (diary), Vineland-3; ophthalmic assessments including visual acuity, visual field, and retinal thickness using optical coherence tomography (OCT); and volumetric assessments using magnetic resonance imaging (MRI); they will be assessed at baseline and during the maintenance period. Cerebrospinal fluid (CSF), blood and urine biomarkers will also be assessed as exploratory endpoints of treatment activity.

Statistical Methods:

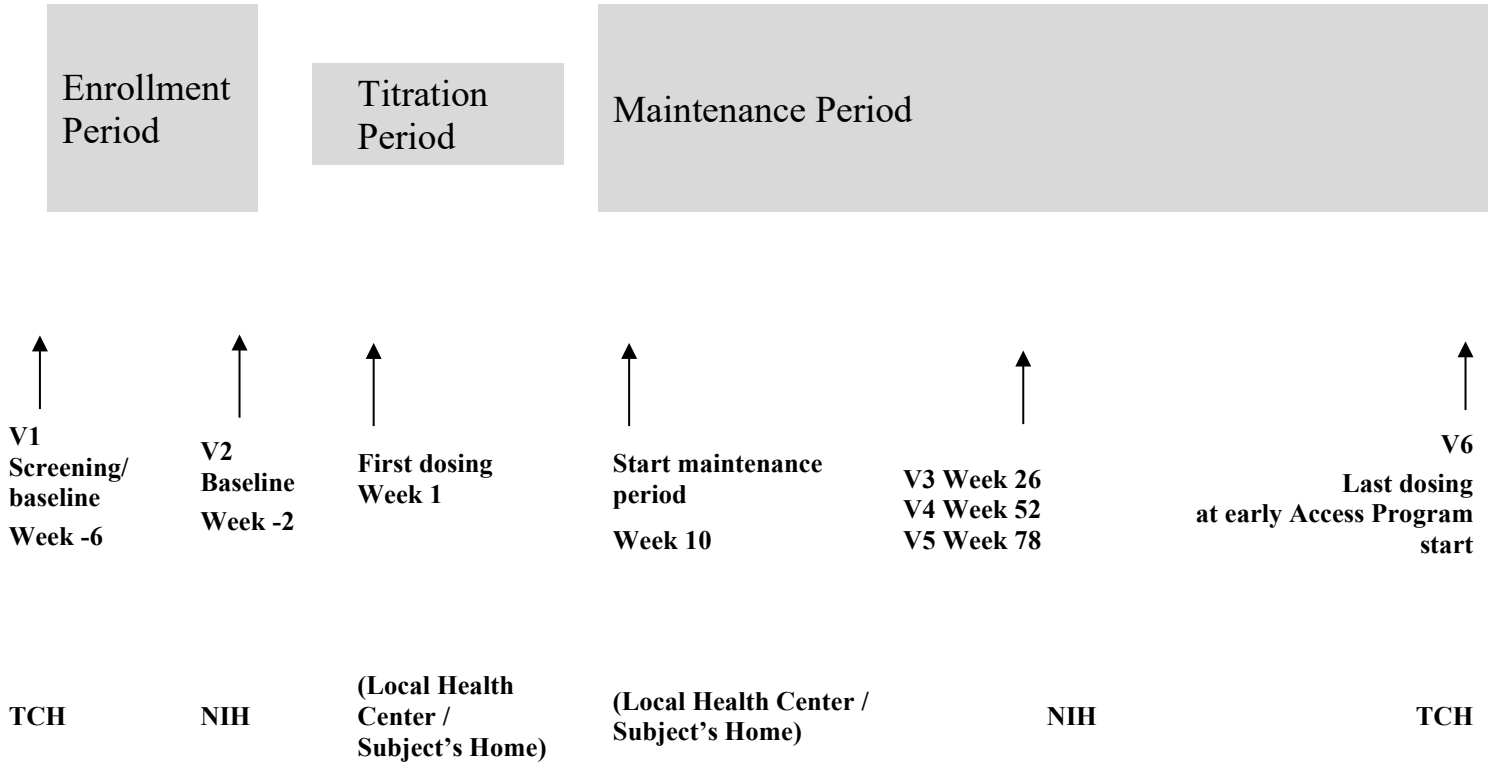
Safety Analysis: Safety data will be summarized using descriptive statistics by visit or time point, as appropriate. Treatment-emergent AEs and SAEs will be tabulated and summarized by system organ class, preferred term, severity, and relationship to study drug.

PK Analysis: Single-dose and steady-state descriptive statistical analyses will be performed for miglustat plasma concentration data. A specific pharmacokinetic SAP will be prepared.

Efficacy Analysis: Efficacy will be assessed as a secondary outcome using descriptive statistics.

1.2 Schema

Figure 1-1 Schema of the Study Design



EOT=end of treatment; ET= Early Termination; NIH=National Institutes of Health; TCH=Texas Children's Hospital; V=visit

1.3 Schedules of Activities

Table 1-2 Activities at TCH and NIH CC (Screening, Enrollment, Baseline, Weeks 26, 52, 78, EOT/ET, and End of Study Visit

	Visit 1 **Assessments at TCH (Screening and Baseline Safety)**	**Screening confirmation by TCH[A] (Phone Visit)**	**Visit 2** **Assessments at NIH CC [B] and final enrollment (Baseline Efficacy Assessments)**	**Treatment start Local Health Center/ Subject's Home**	**Visit 3 NIH CC [B]**	**Visit 4 NIH CC [B]**	**Visit 5 NIH CC [B]**	**Visit 6** **Early termination TCH [B]**
	Days -42 to -1			**Day 1 Week 1 Up to 14 days between V2 and first dose**	**Week 26 (± 1 month)**	**Week 52 (± 1 month)**	**Week 78 (± 1 month)**	**Early Access Program start**
General Assessments								
Informed consent	X		X					
Inclusion/exclusion	X	X						
Enrollment	X		X					
Medical history	X							
Demographics	X							
Medications/procedures (history)	X							
Physical examination	X		X		X	X	X	X
Vital signs [C]	X		X		X	X	X	X
Weight	X		X		X	X	X	X
Height	X							

	Visit 1 **Assessments at TCH (Screening and Baseline Safety)**	**Screening confirmation by TCH[A] (Phone Visit)**	**Visit 2** **Assessments at NIH CC [B] and final enrollment (Baseline Efficacy Assessments)**	**Treatment start Local Health Center/ Subject's Home**	**Visit 3 NIH CC [B]**	**Visit 4 NIH CC [B]**	**Visit 5 NIH CC [B]**	**Visit 6** **Early termination TCH [B]**
	Days -42 to -1			**Day 1 Week 1 Up to 14 days between V2 and first dose**	**Week 26 (± 1 month)**	**Week 52 (± 1 month)**	**Week 78 (± 1 month)**	**Early Access Program start**
Neurological examination[D]			X		X	X	X	X
12-lead ECG [E]			X		X	X	X	X
Slit-lamp evaluation			X		X	X	X	X
Concomitant medications	X		X		X	X	X	X
Adverse events [F]	X		X		X	X	X	X
Contraception (if applicable)	←							→
Laboratory Assessments								
Pregnancy test (females)	X		X		X	X	X	X
Chemistry, hematology, urinalysis [G]	X		X[B]		X	X	X	X
HIV and hepatitis B and C testing [H]	X							
Efficacy Assessments								
UBDRS[I]			X		X	X	X	
Vineland 3[J]			X			X		
Ophthalmic exams including, OCT[K]			X		X	X	X	

	Visit 1 **Assessments at TCH (Screening and Baseline Safety)**	**Screening confirmation by TCH[A] (Phone Visit)**	**Visit 2** **Assessments at NIH CC [B] and final enrollment (Baseline Efficacy Assessments)**	**Treatment start Local Health Center/ Subject's Home**	**Visit 3 NIH CC [B]**	**Visit 4 NIH CC [B]**	**Visit 5 NIH CC [B]**	**Visit 6** **Early termination TCH [B]**
	Days -42 to -1			**Day 1 Week 1 Up to 14 days between V2 and first dose**	**Week 26 (± 1 month)**	**Week 52 (± 1 month)**	**Week 78 (± 1 month)**	**Early Access Program start**
MRI[K]			X			X		
Seizure diary dispentiation[L]	X							
Blood for biomarkers			X			X	X	
Spot urine for biomarkers			X			X		
Lumbar puncture for CSF collection (biomarkers)[K]			X			X		

A After TCH PI determination of subject eligibility, study staff will inform the subject and will schedule NIH CC baseline visit.

B In cases of any event precluding safe travel by participants to NIH (i) for inclusion visit: beyond 1.5 months, the safety labs will be repeated at NIH. However, the total duration between the 2 inclusion visits should not exceed 3 months. Time between NIH visit and first drug administration should be also maintained within a reasonable timeframe (1 month). (ii) during the course of the study: evaluations will be performed (1) at the Local Health Center / Subject's Home for: labs, ECG (if feasible), physical exam, vital signs, weight, adverse events, or (2) via remote methods for : history, UBDRS, Vineland-3, adverse events, concomitant meds, seizure diary or (3) could be deferred (+/- 1 month) for: neurological exam, ophthalmology exam, MRI, lumbar puncture.

C Vital signs include systolic and diastolic blood pressure [sitting for 5 minutes] and pulse rate.

D A standardized neurological exam will be performed by a pediatric neurologist or qualified individual. The neurological exam will take into account potential visual impairment. The evaluation will include, but is not limited to mental status, cranial nerves, motor function, and sensory and cerebellar functions.

E The subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. Electrocardiograms should be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

F Since last Local Health Center/ Subject's Home visit.

G Chemistry laboratory parameters include HbA1c, creatinine, total bilirubin (direct and indirect if values were above normal ranges), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, creatine kinase, sodium, potassium, cholesterol, and triglycerides. Hematology laboratory parameters include hemoglobin, hematocrit, erythrocytes, thrombocytes, and white blood cell count with differential (for an absolute neutrophil count, lymphocyte count and monocyte count). Dipstick urinalysis includes glucose, nitrate, hemoglobin, leukocytes, protein, pH, ketones, and specific gravity.

H All subjects will be assayed for anti-hepatitis C antibody, hepatitis B surface antigen, and human immunodeficiency virus.

I Assessment will be done either before or > 24 hours after sedation. All domains are administered at baseline. If video interview is not possible for technical reasons, patients will be assessed at the NIH by a UBDRS trained rater. In cases of any event precluding safe travel by participants to NIH, the assessment will be performed remotely according to instructions delivered by URMC

J Assessment will be done either before or > 24 hours after sedation. The Communication, Daily Living Skills, Socialization and Motor Skills domains are assessed.

K Subjects who cannot cooperate with the MRI study, ophthalmology exam, or lumbar puncture procedure may be sedated. Baseline OCT will be obtained in all study participants. In those participants with no light perception vision, dense cataracts, or other ophthalmologic findings that produce significant artifacts in the OCT images, OCT imaging will not be repeated.

L A seizure diary will be completed on a daily basis, beginning at screening. The baseline seizure frequency will be calculated based on data collected from screening to first dose of study drug.

Table 1-3 Miglustat Dose-titration and Pharmacokinetic Sampling Period – Local Health Center or Subject's Home (Weeks 1 Through 9)

	Day 1 – Week 1 (Within 42 days of screening)	Dose-titration Period							
		Day 8±2 Week 2	Day 15±2 Week 3	Day 22±2 Week 4	Day 29±2 Week 5	Day 36±2 Week 6	Day 43±2 Week 7	Day 50±2 Week 8	Day 57±2 Week 9
General Assessments									
Abbreviated physical examination [A]	X				X				X
Vital signs [B]	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Telephone follow-up by TCH PI [C]					X				X
Laboratory Assessments									
Pregnancy test (females)[D]	(X)					X			
Chemistry [E]	(X)					X			
Hematology [F]	(X)					X			
Urinalysis [G]	(X)					X			
Study Drug Administration									
Miglustat dose[H]	X	X	X	X	X	X	X	X	X
Miglustat supplied [I]	X	X	X	X	X	X	X	X	X
PK									
Draw blood	X [J]								X [K]
Efficacy Assessments									
Seizure diary collection [L]					X				X
Seizure diary dispentiation					X				X

A An abbreviated physical examination will assess only the general appearance of the patient and is only required when a complete exam is not indicated.

B Vital signs include systolic and diastolic blood pressure [sitting for 5 minutes] and pulse rate.

C The TCH PI will conduct monthly telephone safety check-ins during the dose-titration period and every 2 to 4.5 months thereafter to discuss AEs and concomitant medications. If the subject cannot be reached. TCH will contact the Local Health Center to organize the call.

D Urine test is acceptable. If first dosing visit is scheduled > 28 days after the NIH visit, pregnancy test should be repeated within 7 days prior to the first dosing visit

E Chemistry laboratory parameters include HbA1c, creatinine, total bilirubin (direct and indirect if values were above normal ranges), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, creatine kinase, sodium, potassium, cholesterol, and triglycerides. Those tests are to be repeated prior to the first dosing visit only if first dosing visit is scheduled >42 days after the TCH visit.

F Hematology laboratory parameters include hemoglobin, hematocrit, erythrocytes, thrombocytes, and white blood cell count with differential (for an absolute neutrophil count, lymphocyte count and monocyte count). Those tests are to be repeated prior to the first dosing visit only if first dosing visit is scheduled > 42 days after the TCH visit.

G Dipstick urinalysis includes glucose, nitrate, hemoglobin, leukocytes, protein, pH, ketones, and specific gravity. If first dosing visit is scheduled > 42 days after the TCH visit, safety labs should be repeated prior to the first dosing visit.

H Miglustat dose initiated at 100 mg QD; dose assess weekly according to titration scheme and subject tolerance. Week 8 is the last permitted time point for miglustat dose titration. On PK sample collection days for miglustat measurement at Weeks 1 and 9, the first miglustat dose is administered at the Local Health Center / Subject's Home if there is no Health Center near subject's home. All other miglustat doses may be administered at home.

I Miglustat will be supplied according to the subject's MTD. Miglustat accountability will be performed weekly during this time.

J Blood will be obtained at the following nominal time points: pre-miglustat dose (0), 1, 2, 2.5, 3, 4, 6, 8, and 24 hours. Confinement between the 8-hour and 24-hour time points is not required. Blood drawn for the 24-hour time point should be done prior to the Day 2 miglustat morning dose.

K Blood will be obtained at the following nominal time points: pre-miglustat dose (0), 1, 2, 2.5, 3, 4, 6, and 8 hours. Subsequent daily miglustat doses, if applicable will be administered after PK sampling is completed and may be taken at home.

L A seizure diary will be completed all along the study and will be shared as collected with TCH.

Table 1-4 Maintenance Period – Local Health Center/Subject's Home Visit and Phone Calls (Week 10 Through End of Treatment) 1/2

	Maintenance Period									
	Week 10 ±2 days	**Week 12 ±2 days**	**Week 14 ±4 days**	**Week 18 ±1 Week**	**Week 22 ±1 Week**	**Week 30 ±1 Week**	**Week 34 ±1 Week**	**Week 38 ±1 Week**	**Week 42 ±1 Week**	**Week 46 ±1 Week**
	Visit	**Phone**	**Visit**	**Phone**	**Visit**	**Phone**	**Visit**	**Phone**	**Visit**	**Phone**
General assessments										
Vital signs [A]	X		X		X		X		X	
Weight	X		X		X		X		X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Telephone follow-up by PI[B]			X		X		X		X	
Abbreviated physical exam[C]	X		X		X		X		X	
Laboratory Assessments										
Pregnancy test[D]	X		X		X		X		X	
Study Drug Administration										
Miglustat dose[E]	←	—	—	—	—	—	—	—	—	→
Miglustat supplied[F, E]	X		X		X		X		X	
Efficacy assessments										
Seizure diary issued[G]	X		X		X		X		X	
Seizure diary collected[G]	X		X		X		X		X	

A Vital signs include systolic and diastolic blood pressure [sitting for 5 minutes] and pulse rate.

B The PI will conduct telephone safety check-ins between site visits to discuss concomitant medications, AEs and in case of premature discontinuation

C An abbreviated physical examination will assess only the general appearance of the patient and is only required when a complete exam is not indicated.

D Female with childbearing potential only. Urine test is acceptable.

E Miglustat dose may be administered at home. Subjects should take their daily miglustat dose as usual.

F Miglustat will be supplied according to the subject's MTD. Miglustat accountability will be performed at each in-person visit

G Seizure diaries will be completed and will be collected by the Local Health Center where the new seizure diary will be issued.

Table 1-5 Maintenance Period – Local Health Center/Subject's Home Visit and Phone Calls (Week 10 Through End of Treatment) 2/2

	Maintenance Period								
	W58 ±1 week Visit	**W64 ±1 week Phone**	**W70 ±1 week Visit**	**W76 ±1 week Phone**	**W82 ±1 week Visit[A]**	**W88 ±1 week Phone[A]**	**W94 ±1 week Visit[A]**	**W100 ±1 week Phone[A]**	**Premature discontinuation (before early access program start)**
General Assessments									
Complete Physical exam									X
Vital signs[B]	X		X		X		X		X
Weight	X		X		X		X		X
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Telephone follow-up by PI [C]	X		X		X		X		X
Abbreviated physical exam[D]	X		X		X		X		
Laboratory Assessments									
Pregnancy test [E]	X		X		X		X		X
Chemistry, hematology, urinalysis [F]									X
Study Drug administration									
Miglustat dose	←								→
Miglustat supplied [G]	X		X		X		X		
Efficacy Assessments									
Seizure diary issued [H]	X		X		X		X		
Seizure diary collected	X		X		X		X		X

Note: Weeks 26, 52, and 78have site visits as outlined in Table 1-3.

A Additional phone calls and visits may be performed according to the duration of treatment after Week 78 Visit and up to the switch to the early access program

B Vital signs include systolic and diastolic blood pressure [sitting for 5 minutes] and heart rate.

C The PI will conduct telephone safety check-ins every three months between site visits to discuss concomitant medications, AEs and in case of premature discontinuation.

D An abbreviated physical examination will assess only the general appearance of the patient and is only required when a complete exam is not indicated

E Female only. Urine test is acceptable.

F Chemistry laboratory parameters include HbA1c, creatinine, total bilirubin (direct and indirect if values were above normal ranges), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, creatine kinase, sodium, potassium, cholesterol, and triglycerides. Hematology laboratory parameters include hemoglobin, hematocrit, erythrocytes, thrombocytes, and white blood cell count with differential (for an absolute neutrophil count, lymphocyte count and monocyte count). Dipstick urinalysis includes glucose, nitrate, hemoglobin, leukocytes, protein, pH, ketones, and specific gravity.

G Miglustat will be supplied according to the subject's MTD. Miglustat accountability will be performed during each in-person visit.

H Seizure diaries will be completed and will be collected by the Local Center where the new seizure diary will be issued.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AUC0-8hr	Area under the concentration-time curve from time 0 to 8 hours
AUC0-∞	Area under the concentration-time curve extrapolated to infinity
AUC0-t	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC0-tau	Area under the concentration-time curve calculated for the dosing interval
BBDF	Beyond Batten Disease Foundation
BMI	Body mass index
CFR	Code of Federal Regulations
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CSF	Cerebral spinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
EAP	Early Access Program
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End Of Treatment
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonization
IRB	Institutional Review Board
ISF	Investigator site file
IV	Intravenous
LDL	Low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCL	Neuronal ceroid lipofuscinoses
NIH CC	National Institutes of Health Clinical Center
OCT	Optical coherence tomography
PI	Principal investigator
PK	Pharmacokinetic(s)
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SPECT	Single-photon emission computed tomography
T1/2	Elimination half life
TCH	Texas Children's Hospital
TEAE	Treatment-emergent adverse event
TID	Three times daily
Tmax	Time to maximum plasma concentration
UBDRS	Unified Batten Disease Rating Scale
URMC	University of Rochester Medical Center
US	United States
WHO	World Health Organization

2 INTRODUCTION

2.1 Rationale

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

Miglustat, an iminosugar, has been shown to inhibit the harmful accumulation of gangliosides implicated in disease pathogenesis of related lysosomal storage diseases Type 1 Gaucher Disease and Niemann-Pick Type C disease. Lesser-known anti-inflammatory effects have also been reported (Dechecchi et al., 2008). Miglustat is approved in the United States (US) and in the European Union (EU) for adult Type I Gaucher Disease at doses of 300mg/d. Miglustat is also approved in the EU for treatment of adult and pediatric patients with Niemann-Pick Type C Disease at doses up to 600mg/d. Over 18 years of safe use is available for miglustat, whose most common adverse effect is gastro-intestinal which can be mitigated with changes in diet and appears to lessen over time (Pineda et al., 2009).

Patients with CLN3 disease also have increased systemic accumulation of gangliosides and chronic neuroinflammation (Bosch & Kielian.2015) and therefore, may benefit from daily miglustat therapy. These assertions are supported by studies in CLN3 animal models and in vitro cerebellar cells from those models demonstrating significant increases in GM3 ganglioside levels over wild-type, which are significantly reduced by treatment with miglustat as well as a reduction of globoside Gb3, Gb4, and ganglioside GM1 accumulation in vitro (Somogy et al., 2018 and Lloyd-Evans & Waller-Evans, 2020). This accumulation of Gb3 appears to be key in the pathophysiology of the disease with this element being recently confirmed by Soldati et al. (2021).

In the previous versions of the protocol (Version 1 to Version 3.1), the combination of miglustat and trehalose was considered as the Investigation Products. Recent additional preclinical data strongly indicate that the therapeutic effect in CLN3 can be obtained with miglustat alone, as presented below.

In a model of Batten disease, in *Cln3*$^{-/-}$ mice, microglial and astrocyte activation were analyzed along with apoptosis (BBDF-04042022 internal report). In this model, *Cln3*$^{-/-}$ mice display astrocytosis and microglial activation in brain regions where neuronal loss is subsequently most pronounced. These regions include thalamic nuclei that relay somatosensory information to the primary somatosensory cortex (ventral posterior medial and lateral nuclei, VPM/VPL), the somatosensory barrelfield cortex (S1BF), the primary visual (V1) cortex, and the dorsolateral geniculate (dLG).

Previous work had established that astrocyte and microglial activation may be causally related to neuronal loss ((Parviainen et al, 2017). Thus, quantification of glial activation is an appropriate proxy for disease state. Finally, brain atrophy is among the hallmarks of Batten disease and is the result of progressive neurodegeneration. *Cln3*$^{-/-}$ mice recapitulate this feature, which can be observed as a global loss of brain weight with age, or decreased neuronal number in various regions including the thalamus, cerebellum, and the somatosensory regions of the cortex (BBDF-04042022).

Miglustat alone and the combination of trehalose and miglustat similarly exerted their beneficial effects on the pathological hallmarks of Batten disease. Trehalose treatment given alone also

significantly reduced microglial and astrocytic activation as well as apoptosis but only in a limited number of brain regions (BBDF-04042022).

Miglustat alone has a clear modifying action on *Cln3*$^{-/-}$ mouse neuropathology similar to the combination of miglustat and trehalose, and that is significantly stronger than that of trehalose alone. Miglustat is currently approved for the treatment of Gaucher disease and Niemann-Pick type C in various countries, based on its potent effects as an inhibitor of the synthesis of glycosphingolipids, molecules that accumulate in these and other lysosomal storage diseases.

Table 2-1 - Activity of miglustat, trehalose and their combination on *Cln3*$^{-/-}$ mouse neuropathology

	Microglial activation				Astrocyte activation				Apoptosis			
	VPM/ VPL	dLG	S1BF	V1	VPM/ VPL	dLG	S1BF	V1	VPM/ VPL	dLG	S1BF	V1
Trehalose	-	-	↓	-	-	↓	-	-	-	↓	-	↓
Miglustat	↓	↓	↓	-	↓	↓	-	-	↓	↓	-	↓
Combination trehalose/ miglustat	↓	↓	↓	-	↓	↓	-	-	↓	↓	-	↓

- : no effect, ↓ : significant decrease.

The potent neuroprotective effects exerted by miglustat suggest that certain biochemical products of the glycosphingolipid pathway may also accumulate in Batten disease and contribute to its pathogenesis. Treatment with miglustat alone presented the same impact on *Cln3*$^{-/-}$ mice phenotype as the combination of miglustat and trehalose. These results are summarized in the table above.

2.2 Background

First described in 1826, juvenile Batten (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 4-7 years, when progressive vision loss becomes noticeable (Bozorg et al., 2009 and Aberg et al., 2011). 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 or dementia can appear anytime during the disease. Eventually, children become wheelchair-bound, then bed-ridden, and die in their late teens or early twenties (Bozorg et al., 2009, Aberg 2001, and Ostergaard 2016).

CLN3 disease is not preventable, and although a cure is desperately needed for these patients, no treatment that can slow, halt or reverse the symptoms of CLN3 disease has been identified to date. Therefore, there is a significant unmet medical need for meaningful treatment options for these patients.

On a molecular level, CLN3 disease is the result of loss-of-function mutations in the *CLN3* gene and the absence or dysfunction of its gene product, CLN3 protein. This disease is characterized by lysosomal accumulation of fatty, granular autofluorescent material (ceroid, lipofuscin) within cells of the brain and all other tissues of the body. The normal function of CLN3 protein is unknown;

however, CLN3 deficiency has been linked to defects in microtubule-dependent antero- and retrograde trafficking, autophagy, and endocytosis (Cotman & Staropoli, 2012 and Tecedor et al., 2013).

Most cases of CLN3 disease are the result of a 966 bp deletion removing exons 7 and 8 from the transcript. Approximately 74% of patients are either homozygous for this deletion or heterozygous for the deletion with a less common mutation in their other *CLN3* allele. Carriers of *CLN3* mutations have no known CLN3-type disease or susceptibility to other diseases. It is possible there may be common disease pathophysiology between neuronal ceroid lipofuscinoses (NCLs) and late-onset conditions. The symptoms of Parkinson disease and parkinsonism, such as bradykinesia and rigidity, are known to occur in CLN3 disease (Jarvela et al., 1997). Functional evidence for nigrostriatal pathology in these patients has been demonstrated via single-photon emission computed tomography (SPECT) imaging using the labelled cocaine analogue [^{131}I]β-CIT (Ruottinen et al., 1997 and Aberg et al., 2000). Extrapyramidal symptoms of juvenile NCL have been shown, in some cases, to respond to antiparkinsonian therapy (Aberg et al., 2001).

CLN3 protein has been shown in vitro to exhibit anti-apoptotic properties in response to serum starvation, and proapoptotic agents vincristine, etoposide and staurosporine (Puranam et al., 1999). In cancer tissues, CLN3 mRNA and protein are overexpressed in glioblastoma, neuroblastoma, prostate, ovarian, breast, and colon cancer cell lines. Indeed, CLN3 expression is 22%–330% higher in 8 of 10 solid colon tumors when compared to the corresponding normal colon tissue control (Rylova et al., 2002, An Haack et al., 2011, and Zhu et al., 2014). Together, these results suggest that the protective function of CLN3 is lost in CLN3 disease.

The pathological hallmark of CLN3 disease is the accumulation of cellular waste in lysosomes, resulting in a block in autophagic flux (Fossale et al., 2004 and Cotman & Staropoli, 2012) which is amplified by chronic neuroinflammation (Nixon & Yang 2012). Recent preclinical evidence suggests that these defects in autophagy may underlie the enhanced levels of α-synuclein oligomers and gangliosides GM1, GM2, and GM3 (Lloyd-Evans & Waller-Evans 2020), as well as reduced levels of sphingomyelin and autophagy observed in cellular models of CLN3 disease (Kang et al., 2014).

Further details can be found in the Investigator's Brochure (Batten-1 Edition 3.0) which contains comprehensive information on the investigational product.

2.3 Risk-Benefit Assessment

2.3.1 Anticipated Risks

This protocol involves the use of an investigational drug with limited data in animal models and in humans with the disease thus, there may be risks that cannot be identified. There is no available data on its reproductive toxicity and its effect on pregnant/lactating women. Thus, all participants will use effective contraceptive measures and all women of childbearing potential will undergo a pregnancy test to exclude those identified as being pregnant from enrolling in the study.

2.3.1.1 Miglustat

Miglustat has been shown, in both clinical trials and real-world use, to cause gastrointestinal adverse events (diarrhea, abdominal pain/discomfort, flatulence) due to inhibition of intestinal disaccharide enzymes (see Section 2.2). Transient weight loss is often observed and has been

attributed to carbohydrate malabsorption and a corresponding decrease in effective caloric intake. These side effects typically are seen during the initiation of miglustat dosing and resolve over time with continued use. A low-carbohydrate diet, initiated at the time or just prior to initiation of miglustat dosing, has been shown to improve gastrointestinal tolerability of miglustat and lessen the magnitude of weight loss. Taking miglustat on an empty stomach (between meals) and an initial dose escalation of miglustat are also recommended by some physicians as another factor in reducing the severity of side effects, although the efficacy of these measures has not been tested in clinical trials (Belmatoug at al., 2011).

If a low carbohydrate diet (Section 13.1) does not sufficiently prevent diarrhea during miglustat dose escalation, miglustat dose adjustments or antidiarrheal treatment (e.g., loperamide) may be considered.

In clinical trials of people with Gaucher disease, cases of peripheral neuropathy have been reported in 3% of patients treated with miglustat. All subjects receiving miglustat treatment should undergo baseline and repeat neurological evaluations at approximately 6-month intervals. Subjects who develop symptoms of peripheral neuropathy such as pain, weakness, numbness and tingling should have a careful re-assessment of the risk/benefit of miglustat therapy, and cessation of treatment may be considered (Actelion Pharmaceuticals 2017).

Approximately 30% of people with Gaucher disease have reported tremor or exacerbation of existing tremor on miglustat treatment. These tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month of therapy and in many cases resolved between 1 to 3 months during treatment. Reduce dose to ameliorate tremor or discontinue treatment if tremor does not resolve within days of dose reduction (Actelion Pharmaceuticals 2017).

2.3.1.2 Study Procedures

Blood draws

Blood draws are associated with discomfort, bruising, vasovagal syncope, and, rarely, bleeding and infection.

ECG

The adhesive used to conduct electrocardiograms may result in local irritation, as well as discomfort when the contacts are removed.

MRI

MRI may cause anxiety, due to the noise of the machine and the enclosed space. If sedation is used, there are additional risks associated with the use of the specific sedative agent. Imaging procedures carry the possibility of incidental findings. In the event of incidental findings on the MRI, results will be shared with the patient's primary care physician for appropriate follow-up.

Ophthalmic Evaluation

Iris dilatation can make patients transiently sensitive to light. If done while awake, patients will be asked to remain still for approximately 15 minutes, which may be uncomfortable. If done under sedation, patients may experience drying of the eyes. This will be minimized by application of eye drops lubrication.

Lumbar puncture

The risks associated with lumbar puncture include headache, backache, infection, bleeding, and medullary herniation. Up to one third of adults experience headache after a lumbar puncture. In NIH CC experience, post-lumbar puncture headaches occur in ~5% of pediatric cases. Most are very transient. This is thought to be due to CSF leakage at the site of the procedure. To minimize this, small bore needles will be used, and the bevel of the needle will be kept parallel to the fibers of the ligamentum flavum if using a cutting needle. Atraumatic needles may also be used. If possible, the patient will be asked to lie flat for 1–2 hours after the procedure. Analgesics, such as Tylenol, will also be used if clinically indicated. Rarely, headaches can persist for a prolonged period of time. In these cases, the CSF leakage is treated by a "blood patch".

The lumbar puncture will be performed as a sterile technique to minimize the possibility of infection. Medullary herniation is a complication that is encountered when raised intracranial pressure is present. This is unlikely in individuals with CLN3 disease; if clinically indicated, neuroimaging will be done to exclude the rare possibility of an intracranial mass. The lumbar puncture will not be done in a child with marked spinal deformity or evidence of an overlying skin infection.

Sedation

Young and impaired patients who cannot cooperate with the MRI study, ophthalmology exam, or lumbar puncture procedure may be sedated. If possible, procedures for blood drawing will be coordinated or the IV catheter placed for sedation will be used for blood drawing. The major risk associated with sedation is respiratory compromise.

In order to minimize risk, sedation will be performed by an NIH CC anesthesiologist. An anesthesiologist experienced with pediatric patients will perform the sedation if indicated due to patient's size, age, or medical condition. Facilities for maintenance of a patent airway, artificial ventilation, and circulatory resuscitation will be immediately available and ready for use. Depending upon the clinical situation, as judged by the anesthesiologist, patients may receive oxygen via nasal cannula or have their airway protected using either a laryngeal airway or by intubation. The anesthesiologist will also select the anesthetic agent used based on their clinical judgment. Criteria used in making this judgment include patient age, size, history of reflux, history of difficult airway management, and overall medical status. Another risk of sedation is aspiration. If clinically indicated, intubation will be used to protect against aspiration.

As fasting is required prior to sedation, study participants may develop symptoms relating to this (including but not limited to hypoglycemia and hypovolemia) if oral intake is inadequate following recovery from sedation. Death is a rare complication of sedation when performed by a licensed anesthesiologist under controlled conditions.

The effects on fetuses of repeated or prolonged anesthesia are unclear. Thus, a urine or serum pregnancy test will be done in female patients 10 years of age or older prior to sedated procedures.

General

Study visits involve an associated inconvenience and are time-consuming. Participation in any drug study may create anxiety, as the effects of the drugs in the study population are unknown.

There is a risk to privacy, due to the use of personal health information for study purposes.

2.3.2 Anticipated Benefits

If miglustat is effective in reducing the aggregation of compounds that lead to the pathology and symptoms of CLN3 disease, potential benefits include slowing or halting the progression of disease symptoms, which may significantly improve the quality of life for individuals with CLN3 disease.

2.3.3 Summary

Given the progressive and ultimately fatal nature of CLN3 disease and the lack of available treatments for the condition, the potential for Batten-1 to ameliorate the cellular accumulation of compounds that are believed to cause the progressive symptoms of the disease outweighs the risks associated with the known risks of the study drugs. While the study involves greater than minimal risk to potential subjects, it also provides the prospect of direct benefit to study subjects.

3 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 in baseline in clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiogram (ECG) findings, slit lamp evaluation, vital signs (heart rate and systolic and diastolic 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 (AUC0-∞), 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 signs or 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 applicable), 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.

4 OVERALL DESIGN AND PLAN OF THE STUDY

4.1 Overall Design

This is an open label study in approximately 6 subjects in 2 centers to assess the safety, 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, enrollment, and end-of-treatment visits for follow-up safety assessments will be conducted by TCH. Eligibility will be confirmed by TCH after all inclusion/exclusion criteria are assessed; enrollment decision will be communicated to subject via telephone call by TCH. If the subject is eligible, the study staff will schedule NIH CC baseline visit. TCH will also review all subject safety data throughout the duration of the study.
- Baseline, every 6 months 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.

This study includes a dose-titration period of 9 weeks.

Once the dose titration and PK sampling period is completed, subjects will continue their MTDs during the maintenance period. Temporary or permanent dose reductions for tolerability are permitted at any time during the remainder of the study in the dose increments shown in Section 6.2. As not all subjects will have the same duration of treatment, additional safety phone calls and visits will be organized as need at regular timepoints for patients with longer duration of treatment.

Safety will be assessed at all study visits, and safety labs will be collected at baseline, during titration at Week 6 and every 6 months during maintenance phase. The TCH Principal Investigator (PI) will also conduct monthly telephone safety checks during the dose-titration period and every 2 to 4.5 months calls thereafter to discuss adverse events (AEs).

Efficacy assessments include UBDRS; seizure frequency (diary); Vineland-3; ophthalmic assessments including visual acuity, visual field (if feasible), and retinal thickness using OCT; and volumetric assessments using MRI. They will be assessed at baseline and during the maintenance period. Baseline OCT will be obtained in all study participants. In those participants with no light perception vision, dense cataracts, or other ophthalmologic findings that produce significant artifacts in the OCT images, OCT imaging will not be repeated.

Blood, urine and cerebrospinal fluid biomarkers of neurodegeneration will also be assessed as exploratory endpoints of treatment activity.

In case of any event precluding safe travel by participants to NIH after the baseline visit, evaluations could be done at the Local Health Center/ Patient's Home (labs, ECG (if feasible), physical exam, vital signs, weight) or via remote methods (history, UBDRS, Vineland-3, adverse events, concomitant meds, seizure diary) or be deferred (+/- 1 month: neurological exam, ophthalmology exam, MRI, lumbar puncture).

After the Week 78 efficacy assessment, patients will continue to be treated with miglustat until they can be included, if they wish to continue to receive the treatment, in the early access program.

4.2 Rationale for Study Design

The current study is designed to evaluate the safety and pharmacokinetics of the Batten-1 regimen for the treatment of CLN3 disease using up-titration to MTDinvestigational drug. Given the rarity of the disease an open-label design in a small subject sample was chosen for feasibility reasons.

4.3 Justification for Dose

Miglustat is approved by the EMA for treatment of a related lysosomal storage disorder, Niemann-Pick type C disease, in adult and pediatric subjects. The dose and dosing regimen for adults and pediatric subjects 12 years of age and older is 200 mg TID (Janssen Cilag 2020). Accordingly, Batten-1 will use the same dose/dosing regimen as for Niemann-Pick type C disease.

4.4 End of Study Definition

End of Study is defined as the last subject's last visit in the study.

5 STUDY POPULATION

5.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible to participate in the study.

1.	Have provided informed consent by subject or parent/legal guardian/legally authorized representative (as appropriate).
2.	Are males or females ≥ 17 years of age at the time of screening
3.	Have genetically confirmed diagnosis of syndromic CLN3 disease with EITHER: A. Two pathogenic mutations in the CLN3 gene, OR B. One confirmed pathogenic AND one variant of unknown significance, OR 2 variants of unknown significance, PLUS secondary confirmation with evidence of characteristic inclusions on electron microscopy AND characteristic clinical course. There is no restriction on the specific CLN3 mutations for eligibility to enroll in the study. The mutations will be recorded in the electronic case report form (eCRF) for potential use in determining if CLN3 genotype is associated with tolerability and/or effectiveness of Batten-1 therapy.
4.	Male and female participants must use a highly effective method of contraception and must continue for the duration of the trial (and for 30 days after the end of treatment). Appropriate methods of contraception are in appendix 6.
5.	Are able to complete study assessments (subject or caregiver) and return to the clinic as scheduled

5.2 Exclusion Criteria

Individuals who meet any of the following criteria are not eligible to participate in the study.

1.	Have a medical condition that in the opinion of the PI would interfere with the safety assessments or increase the subject's risk of AEs
2.	Use of any therapy (approved, off-label, or unapproved) intended to modify the course of any neuronal ceroid lipofuscinosis disease, including but not limited to flupirtine or flupirtine derivatives, cerliponase alfa (Brineura)
3.	Have, in the opinion of the PI, a clinically significant abnormality in their clinical laboratory values (hematology, chemistry, or urinalysis) at screening that would preclude their participation in the study
4.	Have a known allergy or hypersensitivity to miglustat, or any component of the study drug
5.	Have a severe renal disease (creatinine clearance < 30 ml/min/1.73 m^2)
6.	Have a history of substance abuse or alcohol abuse within 2 years before screening

7.	Have a medical history of HIV, hepatitis B, hepatitis C, or positive results at screening
8.	Have any active malignancy of any type except for non-melanoma skin cancer
9.	Have a medical history of major mental illness that, in the opinion of the PI may affect the ability of the subject to participate in the study. Institutionalized subjects are not eligible for participation
10.	Have received gene therapy intended to modify the course of CLN3 disease
11.	Have been exposed to any miglustat or investigational agent, including but not limited to, flupirtine or flupirtine derivatives, within 30 days or 5 half-lives (whichever is longer) prior to check-in for the Week 1 visit, or is scheduled to receive an investigational device or drug (other than test product) during the course of the study
12.	Participation in another interventional study during the last three months before screening

5.3 Screen failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).
Individuals who do not meet the criteria for participation in this trial (screen failure) because of an acute or reversible medical finding may be rescreened.. Rescreened participants will be assigned with a different participant number.

5.4 Discontinuation of Study Intervention and Participant Discontinuation / Withdrawal

5.4.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation).

If study intervention is definitively discontinued, the participant will perform an early termination visit at the NIH CC for efficacy assessments as soon as this visit can be organized, and an end of study visit at TCH 30 days after the last dosing.

If not possible, a remote visit could be organized via telemedicine for applicable evaluations or at least a phone contact will be established with the participant or the caregiver to collect safety information (AEs). See the schedule of activities for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed. In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, and/or future collection of additional

information. Participants can continue their participation in the NIH cohort study and will continue to be assessed.

5.4.2 Participant Discontinuation

The participation of an individual subject may be discontinued prematurely for reasons such as:

- Any condition which in the opinion of the investigator no longer permits safe participation in the study, in particular, if a participant develops a CTCAE Grade 3 or higher (See section 7.1.1.1). Participants who develop symptoms such as numbness and tingling should have a careful re-assessment of the risk/benefit of therapy and cessation of treatment may be considered.
- Subject becomes pregnant
- Lack of study compliance

A subject may discontinue participation in the clinical study at his/her own request at any time without stating a reason.

At the time of discontinuing from the study, if possible, an early termination visit and a 30-day end of study visit should be conducted, as shown in the schedule of activities. If not possible, a remote visit could be organized via telemedicine for applicable evaluations or at least a phone contact will be established with the participant or the caregiver to collect safety information (AEs). See schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The reason for withdrawal of the subject must be documented by the investigator together with all data collected until the day of premature study discontinuation including laboratory results and assessment of AEs.

Subjects who withdraw or are withdrawn from the study before exposure to the study drugs or during the titration period may be replaced.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly. If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

5.4.3 Lost to follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the site for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and advise the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- In cases in which the subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.5 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

5.6 Lifestyle Considerations

If the low carbohydrate diet (section 13.1) does not sufficiently prevent diarrhea during miglustat dose escalation, miglustat dose adjustments and/or antidiarrheal treatment (e.g., loperamide) may be considered.

6 STUDY INTERVENTION

6.1 Identity

Batten-1 is an oral miglustat capsule (100 mg). Information about the investigational product is presented in Table 6-1.

Table 6-1 Identity of Investigational Product

Intervention Name	Miglustat
Type	Drug
Dose Formulation	Dry
Unit Dose Strength(s)	100 mg
Dosage Level(s)	From 100 mg QD to 200 TID
Route of Administration	Oral
Excipients	Magnesium stearate Gelatine Titanium dioxide (E171) Black iron oxide (E172) Potassium Hydroxide Shellac Propylene glycol (E1520)
Manufacturer	Delpharm

6.2 Administration

The proposed dosing regimen is a daily oral miglustat (MTD, up to 200 mg TID).

- Subjects will be dispensed miglustat at Week 1 and dosing will be escalated as presented in Table 62. If a subject has not reached the maximum dose (600 mg/d) by Week 8, the Week 8 dose will be subject's MTD.

The appropriate miglustat doses will be distributed either by the Local Health Centers at these visits or directly shipped at patient's home. Appendix 8 provides the details of the procedure for the IPs home administration.

Once the dose titration and PK sampling period is 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 in the dose increments shown in Table 6-2 (miglustat dose escalation).

6.2.1 Miglustat

A supply of miglustat capsules will be provided to subjects/caregivers to administer orally. If subjects cannot swallow miglustat capsules whole, the capsules may be opened, and the contents mixed with unsweetened fruit juice and consumed immediately. The contents of the capsule should not be crushed.

Table 62 Miglustat Dose Escalation

Dose Escalation Step	Morning (8 AM)	Afternoon (2 PM)	Evening (8 PM)
Step 1	X	X	100 mg

Dose Escalation Step	Morning (8 AM)	Afternoon (2 PM)	Evening (8 PM)
Step 2	100 mg	X	100 mg
Step 3	100 mg	100 mg	100 mg
Step 4	100 mg	100 mg	200 mg
Step 5	200 mg	100 mg	200 mg
Step 6	200 mg	200 mg	200 mg

Treatment with miglustat will begin at a dose of 100 mg QD. If the initial dose of miglustat is 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 TEAEs and at the discretion of the TCH 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.

6.3 Packaging, Labelling and Storage

Miglustat will be supplied by the sponsor according to all local legal requirements. Study drug will be labelled in accordance with applicable regulatory requirements.

Miglustat will be provided as commercial product in boxes containing several blisters.

All study drug supplies must be stored in accordance with the manufacturer's instructions (< 30°C). Until dispensed to the subjects, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

Packaging and labelling of study drug will comply with Good Manufacturing Practice (GMP), GCP rules, Annex 13, and country specific regulatory requirements; this information will be available in the local language.

6.4 Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm study. All subjects will receive miglustat. Drug Accountability

The Local HealthCenter is responsible for maintaining accurate study drug accountability records throughout the study.

Each dispensing of study drug will be documented in the eCRF.

The Local HealthCenter is responsible for returning all unused or partially used study drug to the Sponsor and must verify that all unused or partially used drug supplies have been returned by the subject and that there is no remaining supplies at the Local Center / Subject's Home.

6.5 Compliance

6.5.1 Miglustat

During the dose-titration period, subjects will be instructed either to bring their miglustat to the Local Health Center or to keep it at home in case of visit at Subject's home. The subject's parent/caregiver will be asked about any missed doses or other deviations from the planned dosing schedule, and an assessment (count) or any unused capsules will be performed.

Information regarding missed doses/dosing deviations and the result of the unused drug assessment will be recorded.

During the Maintenance Period, subjects will be instructed to bring their miglustat at the time of the visit to the Local Health Center and an assessment (count) of any unused capsules will be performed. Alternatively, this accountability can be performed at home in case of visits at Subject's Home.

At each visit to the Local Health Center / Subject's Home, the subject's parent/caregiver will be asked about any missed doses or other deviations from the planned dosing schedule.

6.6 Concomitant Therapy

Any medication the subject takes other than the study drug is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. If possible, subjects should try to remain on the pre-study dose(s) of concomitant medication(s) throughout the study. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At screening, subjects will be asked what medications they have taken during the last 3 months. At each subsequent study visit, subjects will be asked what concomitant medications they are currently taking.

6.6.1 Permitted Concomitant Therapy

Any treatments (including alternative treatments) that the subject is taking to manage symptoms at the time of study entry may be continued and must be documented at the time of screening and upon any changes to the doses.

Initiation of new treatments should be avoided if possible. Subjects or caregivers should check with the PI before starting any new treatments; any new treatments should be documented at the next study visit.

Antidiarrheal treatments may be allowed in case of a TEAE (e.g., loperamide).

Participants must use a highly effective method of contraception during the study treatment period and until 30 days after end of treatment.

6.6.2 Prohibited Concomitant Therapy

The use of any of the following is prohibited at inclusion and during the study:

- therapy (approved, off-label, or unapproved) intended to modify the course of any neuronal ceroid lipofuscinosis disease, including but not limited to flupirtine or flupirtine derivatives,cerliponase alfa (Brineura)

6.7 Rescue Medication

Not applicable.

6.8 Dose Modification

Please see Section 6.2.1 for dose escalation instructions for miglustat.

6.9 Treatment of Overdose

6.9.1 Miglustat

No information regarding miglustat overdosage is provided in the current FDA-approved labeling for Zavesca. However, the EU labeling for Zavesca states the following (Janssen Cilag 2020):

Symptoms

No acute symptoms of overdose have been identified. Zavesca has been administered at doses up to 3000 mg/d for up to 6 months in HIV-positive subjects during clinical trials. Adverse events observed included granulocytopenia, dizziness, and paresthesia. Leukopenia and neutropenia have also been observed in a similar group of subjects receiving 800 mg/d or higher dose.

Management

In case of symptomatic overdose, general medical care is recommended.

For this study miglustat overdose is defined as >800 mg/d for SAE reporting.

6.9.2 Intervention After the End of the Study

An early access program will be proposed to subjects who wish to continue treatment. This early access program will be described in a separate protocol.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Safety Assessments

Safety will be assessed at all study visits. Safety labs will be collected at Week 6 during miglustat titration and every 6 months during maintenance phase. An ECG will be performed at baseline and every 6 months. The TCH PI or designated sub-investigator(s) will also conduct monthly telephone safety checks during the dose-titration period and every 2 to 4.5 month calls thereafter to discuss AEs.

7.1.1 Adverse Events

7.1.1.1 Definitions

Adverse events and laboratory parameters will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5, sample of which is provided in Appendix 7 (US Department of Health and Human Services, 2017).

Per ICH, an AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The AE may be any of the following:

- A new illness
- An exacerbation of a sign or symptom or the underlying condition or of a concomitant illness under treatment
- Unrelated to participation in the clinical study or an effect of the study medication or comparator drug
- A combination of one or more of the above factors

No causal relationship with the study medication is implied by the use of the term adverse event.

Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.

When an AE occurs after written consent has been obtained but before the first dose of study drug, the AE will be considered a non-treatment emergent AE. An AE that occurs from the time the subject receives his/her first dose of study drug until his/her last study visit will be considered a treatment-emergent AE regardless of the assessed relationship to the administration of the study drug.

For the recording of pregnancy and relevant laboratory data see Section 7.1.1.2.

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is another medically important condition

An important medical event that is not immediately life threatening or will result in death or hospitalization, but which may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above, should be reported as “serious” as well.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

“Occurring at any dose” does not imply that the subject is receiving study drug at the time of the event.

Severity of Adverse Event:

Severity will be categorized using criteria based on CTCAE v.5:

Grade 1 Mild	asymptomatic or mild symptom; clinical or diagnostic observation only; intervention not indicated
Grade 2 Moderate	minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3 Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated, disabling; limiting self-care ADL
Grade 4 Life-threatening consequences	Urgent intervention indicated
Grade 5 death	Death related to AE

The term "severity" is used to describe the intensity of an event. This is not the same as "serious". Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

Causality of Adverse Event:

Refers to the relationship of the AE to study drug. Causality will be categorized according to the following criteria:

Unrelated:	A clinical event with no evidence of any causal relationship.
Unlikely:	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possible:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.
Definite:	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

Outcome of the Event:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Fatal

Action Taken with Regard to the Event

- None
- Study drug dose decreased
- Study drug withdrawn
- Subject Temporarily/permanently discontinued from study

7.1.1.2 Recording Adverse Events

Period: Subject Screening to the First Administration of Study Drug: Non-treatment emergent AEs will be recorded from the time when the subject is screened into the study (date of signature of the informed consent) until first administration of study drug.

Period: First Administration of Study Drug to Subject's Last Study Visit: Thereafter all AEs are TEAEs (see Definitions, Section 7.1.1.1) and will be recorded until the end of study visit has been performed.

Period After Last Study Visit: Any SAE occurring after the subject's last study visit that the investigator becomes aware of but considered to be related to the study drug will be reported to the sponsor.

If an AE (serious or not) started during the study but did not end before the final follow-up visit, the investigator should make a reasonable effort to establish the outcome and the end date. If this is not possible, the outcome recorded at the final follow-up visit will be assumed to be the final outcome.

If an event stops and later restarts, all the occurrences must be reported. Adverse events assessed as related to study medication by the investigator and all SAEs must be followed up until resolution.

Signs/symptoms should be documented if a definite diagnosis cannot be established. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the symptoms have to be reported separately.

7.1.1.3 Responsibilities of the Investigator

Adverse event data should be obtained through observation of the subject, from any information volunteered by the subject or caregiver, or through subject or caregiver questioning. The general type of question asked could be similar to: “Do you have any health problems?” or “Have you had any health problems since your last clinic visit?”

Adverse events are to be documented/recorded accurately and completely on the AE pages of the respective eCRF and in the subject's source data.

All non-treatment and treatment-emergent AEs will be recorded.

This is true even if the study drug was not administered according to the study protocol.

For conditions leading to unplanned surgical procedures the underlying condition, should be documented as an AE, but not the procedure.

Reporting SAEs:

For AEs that are "serious" (SAEs) additional separate documentation is required using the electronic SAE Forms.

The following variables will be recorded on the electronic SAE Form and on the eCRFs provided in accordance to the eCRF completion guidelines:

- Description of the event, including its duration (date of onset and resolution),
- Whether the event constitutes a SAE or not (if yes, see event seriousness criteria in Section 7.1.1.1)
- Any action taken (e.g., changes to study treatment, other treatment given and follow up tests)
- Outcome of the event
- Investigator’s assessment of causality (the relationship to the study treatment[s] and study procedures)
- Severity

For all SAEs where important or relevant information is missing, active follow-up should be undertaken.

The assumption of a causal relationship between the study drug/study conduct and the AE is irrelevant to the obligation to record AEs and notifying AEs to the Sponsor.

For withdrawals due to AEs the eCRF page "Study completion / Study termination Form" and a copy of the eCRF AE page needs to be completed and forwarded to [redacted]'s Drug Safety Department.

Overdose needs to be reported to [redacted]'s Drug Safety Department following the criteria for SAE reporting. For this study miglustat overdose is defined as > 800 mg/d.

If additional information is required by the [redacted]'s Drug Safety Department, then as a representative of the Sponsor/Pharm-Olam must be granted access to the medical records.

7.1.1.4 Notifying of Serious Adverse Events

In the event of an SAE, the investigator must inform the [redacted]'s Drug Safety department via e-mail or fax using the SAE report/ eCRF page within 24 hours of the study site being informed of the event. At a later date, the [redacted] Safety Contact will report to the Sponsor, the Clinical Study Manager, and the Principal Investigator.

Adverse Event Reporting Contact:

Pharm-Olam Drug Safety

E-mail: [redacted]

For questions regarding SAEs, or to provide information that cannot be provided electronically, or to notify the Sponsor of an SAE in the event of technical failure, the investigator should contact Pharm Olam's Drug Safety Department. Contact information will be provided in a separate document.

Investigators or other site personnel should inform [redacted]'s Drug Safety department of any follow-up information that becomes available for a previously reported SAE immediately but no later than 24 hours of becoming aware of the information. Follow-up reports (as many as required) should be completed and faxed or e-mailed following the same procedure above. Any requested supporting documentation (e.g., ECG, laboratory results, autopsy report) should be sent to the [redacted]'s Drug Safety department.

Prior to forwarding any personal data for safety reporting, the documents need to be coded in a way that keeps the subject's identity confidential (e.g., by using the subject's identification code, randomization number, etc.).

For fatal and life-threatening SAEs, [redacted]'s Drug Safety department will work with the investigator to ensure that any additional information is provided by the investigator within 1 business day. The investigator will ensure that all the necessary information for all other SAEs will be provided within the timelines stipulated by the Sponsor when the request for information is made.

If required, the investigator is responsible for informing local Institutional Review Boards (IRBs) of safety reports in compliance with applicable regulatory requirements. Copies of all correspondence relating to reporting of any safety reports to the IRB should be maintained in the Investigator Site File (ISF) / Regulatory Binder.

The Sponsor's representative is responsible for fulfilling all obligations regarding notification of Regulatory Authorities and IRBs according to applicable regulatory requirements (expedited and periodic reporting, e.g., serious unexpected suspected adverse reactions, Development Safety

Update Report). In addition, the Sponsor will provide safety information to investigators according to the current regulations.

7.1.1.5 Laboratory Values

Laboratory values are also defined as AEs if they are outside the normal and if, in the opinion of the investigator, they represent a clinically relevant change versus pre-treatment values.

If abnormal laboratory values are signs of an AE (e.g., an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE.

Wherever reasonable the reporting investigator will use the clinical term rather than the laboratory term (e.g., anemia versus low hemoglobin value).

7.1.2 Pregnancy

Occurrence of pregnancy in a subject during a clinical study must be recorded.

Each pregnancy that starts during the study must be reported by the investigator to [redacted]'s Drug Safety department within 24 hours of the investigator's knowledge of the pregnancy by using the Pregnancy Reporting Form. Study treatment should be stopped immediately after being aware of the event. Any adverse outcome of the pregnancy must be recorded and notified on the "Drug Exposure via Parent Report Form" or SAE Form if this meets SAE reporting criteria. The investigator should make any reasonable effort to follow any pregnancy until birth of the child.

Blood test at baseline then urine test is acceptable.

7.1.3 Laboratory Parameters

Laboratory assessments will be performed by a central laboratory. The tests listed in Table 7-1 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points designated on the Schedules of Activities (Section 1.3). Tests that are not done must be reported as such on the eCRFs. The total volume of blood drawn per patient for the entire duration of the study is planned to be approximately 440 ml.

Table 7-1 Laboratory Parameters

Hematology		
Hemoglobin Hematocrit Erythrocytes	Leukocytes Differential white blood cell count Thrombocytes	
Biochemistry		
Creatinine Total bilirubin (direct and indirect if values were above normal ranges) HbA1C	Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transpeptidase Creatine kinase	Sodium Potassium Cholesterol (total, HDL, LDL) Triglycerides

Urine		
Glucose Nitrate pH	Hemoglobin Leukocytes Specific gravity	Protein Ketones
Other Tests		
HIV [A]	Hepatitis B [A]	Hepatitis C [A]
Pregnancy test in women of childbearing potential		

HbA1c=hemoglobin A1c; HDL=high-density lipoprotein; LDL=low-density lipoprotein

A Only if there is no medical history of these diseases or no previous testing.

7.1.4 Vital Signs

Vital signs will be measured before any IP intake and recorded at the time points designated on the Schedules of Activities (Section 1.3). The following measurements must be performed: systolic/diastolic blood pressure and heart rate. Vital signs will be measured after the subject has been in the sitting position for at least 5 minutes. All measurements will be recorded on the vital signs eCRF. Abnormal test results may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF. When vital signs, ECGs, and/or blood sample collection occur at the same time, vital signs should be performed before ECGs and/or blood sample collection.

7.1.5 Electrocardiograms

During the study, 12-lead ECGs will be performed at the time points designated on the Schedules of Activities (Section 1.3).

The subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. All ECGs should be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, corrected QT, RR, and PR intervals.

A designated cardiologist will review and sign all ECGs. Results must be summarized in writing and classified as normal; abnormal; abnormal, clinically relevant; or abnormal, not clinically relevant. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the Sponsor, a copy of the original ECG will be made available.

7.1.6 Physical Examination

The investigator or qualified designee will perform a physical examination (genitourinary examination not required) at screening and baseline and at the time points designated on the Schedules of Activities (Section 1.3). Pre-dose abnormal findings will be reported on the medical history eCRF. Any adverse change from the baseline physical examination will be documented on the AE eCRF.

A physical examination will include inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, musculoskeletal system, and nervous system.

An abbreviated physical examination will assess only the general appearance of the patient and is only required when a complete exam is not indicated.

A standardized neurological exam will be performed by a pediatric neurologist or qualified individual. The neurological exam will take into account potential visual impairment. The evaluation will include, but is not limited to mental status, cranial nerves, motor function, and sensory and cerebellar functions.

7.1.7 Additional Safety Assessments

Slit-lamp evaluation will be performed during ophthalmic efficacy assessment to monitor ocular cataracts and ocular opacity.

7.1.8 Unanticipated problems

Definition

Any incident, experience, or outcome that meets **all** the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; **and**
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **and**
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

Unanticipated problems reporting

See Section 7.1.1.3 Responsibilities of the Investigator

7.2 Other Parameters

Blood samples for analysis of miglustat will be taken at first dose (Week 1) and at end of titration.

The following windows pertain to the PK draw times:

Scheduled PK Draw Time	Allowed Window
Pre-dose (0) to 3 hours	± 5 minutes
4 hours–8 hours	± 30 minutes
24 hours	± 2 hours

Blood draws will occur at the following time points.

- Week 1: pre-miglustat dose (0), 1, 2, 2.5, 3, 4, 6, 8, and 24 hours. Confinement between the 8- and 24-hour time points is not necessary. Subjects may return to the Local Health Center / stay at Subject's Home the following day with a window of 24 ± 2 hours. The 24-hour time point must be done before the Day 2 dose of miglustat is taken.
- Week 9: pre-miglustat dose (0), 1, 2, 2.5, 3, 4, 6, and 8 hours. Subsequent daily miglustat dose(s) (if applicable) will be administered after the 8-hour blood draw has been performed.

7.3 Efficacy Assessments

Efficacy assessments (UBDRS; seizure frequency (diary); Vineland-3; visual acuity, visual field (if feasible) , and retinal thickness using OCT; volumetric assessments using MRI; CSF, blood and urine biomarkers for neurodegeneration) will be conducted at the time points outlined on the Schedules of Assessments (Section 1.3).

7.3.1 Unified Batten Disease Rating Scale

The UBDRS is a scale specifically developed to assess symptoms in CLN3 subjects *(Marshall 2005 et al., Kwon et al., 2011, Cialone et al., 2012., Masten et al., 2020*). The UBDRS consists of 7 different domains: (1) physical, (2) seizure, (3) behavioral, (4) capability normal vision (will not be assessed) (5) capability actual vision, (6) NCL history and (7) clinical summary including 7 global impression scales (Appendix 2). The physical domain consists of 20 different items based on a neurological assessment; higher scores indicate more severe disease. The seizure domain consists of 12 different assessments based on parent/caregiver information: frequency of seizure types (8 items), medical consequences of seizures (4 items), higher scores indicate more severe disease. The behavior domain consists of 10 different assessments based on parent/caregiver information; higher scores indicate more severe disease. The capability domain has 5 different assessments based on parent/caregiver information; lower scores indicate more severe disease, and NCL history including 8 items to document the onset of typical symptoms. The UBDRS assessments via live video -interview will be performed at the time points outlined on the Schedules of Assessments, if video interview is not possible for technical reasons, patients will be assessed at the NIH by a UBDRS trained rater. In cases of any event precluding safe travel by participants to NIH, the assessment will be performed remotely according to instructions delivered by Rochester University (Section 1.3). A copy of the UBDRS is provided in Section 13.2 . In case of sedation for other examinations (e.g. MRI, OCT, lumbar puncture), UBDRS will be performed either before or > 24 hours after sedation.

7.3.2 Seizure Frequency

Subjects will receive a seizure diary to be completed at screening. Diaries will be collected during the Local Health Center / Subject's Home visits and will be shipped to TCH. The baseline seizure frequency will be calculated based on data collected from screening to first dose of study drug. The report template is provided in Section 13.3.

7.3.3 Vineland-3

The Vineland-3 measures the personal and social skills of individuals from birth through age 90 years (Sparrow 2016, FDA Proceedings 2015). It can be administered as a comprehensive interview with the care giver as it will be in this study. The Vineland consists of multiple domains (with subdomains), as follows: Communication (receptive, expressive, written), Daily Living Skills (personal, domestic, community), Socialization (interpersonal relationships, play and leisure, coping skills), Motor Skills (gross, fine), and Maladaptive Behavior (internalizing, externalizing). The Maladaptive Behavioral domain will not be used as part of the trial because it is not specific to this disease process. Vineland interviews will be performed at the time points outlined on the Schedules of Assessments (Section 1.3). A copy of the Vineland-3 interview form is provided in Section 13.4.

7.3.4 Ophthalmic Assessments Including Optical Coherence Tomography

In some cases of CLN3 disease, OCT has enabled unambiguous detection of prominent morphologic abnormalities (degeneration) of the retina that occur over the natural progression of the disease (Hansen et al., 2016). These degenerative retinal changes are known to occur irrespective of different mutations of the CLN3 gene (Bergholz et al., 2015). Thus, OCT can be a valuable tool to evaluate changes in retinal morphology and visual acuity in this population. Dulz et al have evaluated retinal thickness in subjects with CLN3 disease (Dulz et al., 2016) demonstrating both temporal and nasal parafoveal thickness decrease. Retinal thickness will be measured at the time points outlined on the Schedules of Assessments (Section 1.3).

Baseline OCT will be obtained in all study participants. In those participants with no light perception vision, dense cataracts, or other ophthalmologic findings that produce significant artifacts in the OCT images, OCT imaging will not be repeated.

Functional assessments including visual acuity, and visual fields (if feasible) will be performed at the same time points.

7.3.5 Magnetic Resonance Imaging

Grey matter atrophy due to neuronal loss is a striking feature of subjects with CLN3 disease (Hochstein 2017). Subjects will have brain MRI examinations at the time points outlined on the Schedules of Assessments (Section 1.3).

7.3.6 Lumbar Puncture

This procedure is done for the collection of CSF for biomarker analysis. It will be done on an annual basis under sedation in conjunction with other evaluations. The lumbar puncture will be performed by a provider credentialed by the NIH CC for this procedure at the time points outlined on the Schedules of Assessments (Section 1.3). Information about lumbar puncture is provided in Section 13.5

Subjects who cannot cooperate with the MRI study, ophthalmology exam, or lumbar puncture procedure may be sedated. Baseline OCT will be obtained in all study participants. In those participants with no light perception vision, dense cataracts, or other ophthalmologic findings that produce significant artifacts in the OCT images, OCT imaging will not be repeated.

7.3.7 CSF, blood and urine Biomarkers

CSF, blood and urine will be collected for analysis of biomarkers. Applicable technologies include but are not limited to proteomics, lipidomics, expression analysis, gene / exome / genome / transcriptome sequencing, metabolomics, and multi-analytes profiling.

8 STATISTICAL METHODS

Further details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following completion of the protocol and finalized prior to locking the database.

8.1 Disposition of Subjects

A tabulation of subject disposition will be provided for the Safety Population and will include:

- Number of subjects screened
- Number of screen failures
- Number of subjects enrolled
- Number of subjects treated
- Number of subjects who completed the treatment
- Number of subjects who withdrew prior to completing the treatment, and reasons for withdrawal

8.2 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.

All protocol deviations will be presented in a data listing.

8.3 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.

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.

8.4 General Considerations

Tabulations will be produced for appropriate demographic, safety, efficacy, and PK parameters. For categorical variables, summary tabulations of the number and percentage within each category of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented.

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 or higher), unless otherwise noted. Medical History and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA; dictionary Version 21.1). Concomitant

medications will be coded using World Health Organization (WHO) Drug Dictionary Version SEP 2018 B3 GLOBAL.

8.5 Demographics, Baseline Characteristics and Concomitant Medications

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

- Age (years) at screening as continuous summary
- Gender
- Ethnicity
- Race
- Weight [kg]
- Height [cm]
- Body Mass Index (BMI) [kg/m²]: defined as Weight (kg)/(Height (m))^2

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

- UBDRS
- Seizure frequency
- Vineland 3
- Ophthalmic exams including the OCT
- MRI
- Biomarker information based on CSF

8.6 Treatment Compliance

Compliance willbe analyzed. By-subject listings of each study drug administration will be produced.

8.7 Safety Analyses

All subjects who enroll in the study and receive at least 1 dose of study medication will be included in the safety population. Safety will be evaluated by AEs, clinical laboratory tests, vital signs, ECGs, slit lamp evaluation and physical examinations. Safety data will be summarized using descriptive statistics by visit or timepoint, as appropriate. Treatment-emergent AEs and SAEs will be tabulated and summarized by system organ class, preferred term, severity, and relationship to study drug.

8.8 Pharmacokinetic Analyses

Descriptive statistical analyses will be performed for miglustat plasma concentration data. The following PK parameters will be analyzed:

- Week 1 first dosing: Cmax, Tmax, AUC 0-t, AUC0-∞, T1/2
- Week 9 (Repeated dose (steady state), Cmin, Cmax, Tmax, AUC 0-8hr

8.9 Efficacy Analyses

Efficacy will be evaluated as a secondary outcome. Efficacy data will be summarized using descriptive statistics by visit or timepoint, as appropriate as detailed in the SAP.

8.10 Determination of Sample Size

Approximately 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.

8.11 Interim Analysis

An interim analysis will be performed one month after all first three participants have enrolled and completed the titration period for each respective titration scheme, to provide preliminary safety results before the start of the Phase 3 study.

9 DATA MANAGEMENT

9.1 Data Collection

The trained investigator site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture tools as needed) directly into the study database on a central server. All information in the eCRFs must be traceable to these source documents. Clinical Research Associates and a Data Manager will review eCRFs entered by investigational staff for completeness and accuracy. Automatic quality programs check for data discrepancies in the eCRFs and the resulting queries will be notified to the investigational site using an electronic data query process within the Electronic Data Capture (EDC) system. Designated investigator site staff are required to respond to queries and make any necessary changes to the data. Details of the data correction process will be specified in the Data Management Plan.

A validated, electronic database will be employed from the EDC system. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study.

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a data handling plan/ data management plan together with a description of the personnel responsible for data entry.

9.2 Data Correction

Automatic and manual queries will be defined according to the data validation plan. These queries will be generated by the [redacted] Data Management Department and sent through the EDC system for clarification. Corrections will be entered directly into the system. This procedure will be repeated until all queries are resolved. All query forms will be linked to the eCRF in the EDC system.

9.3 Data Handling

The final data will be transferred to the SAS-system for data analyses in accordance with the SAP. The MedDRA dictionary will be used for coding of AEs and concomitant diseases. Concomitant medication will be coded using the World Health Organization Drug Dictionary **A**(natomical) **T**(herapeutical **C**(hemical) code.

9.3.1 Deviations from the Protocol

Deviations from the protocol will be judged during the study and/or when an individual subject's eCRF is completed (monitored).

9.4 Data Quality Assurance

The Sponsor or designee will conduct a site visit to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRFs for this study must be consistent with the subjects' source documentation (i.e., medical records).

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Study Initiation Activities

The investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures at a Pre-Study Visit by the monitor (if necessary), an investigators' meeting, and during the Site Initiation Visit by the monitor.

10.2 Training of Site Staff

The investigator will ensure that everyone assisting with the clinical study is adequately informed about the protocol, the investigational product(s), and their study-related duties and functions. Furthermore, the investigator will maintain a list of qualified persons to whom the investigator has delegated study-related duties.

10.3 Documentation and Filing

10.3.1 eCRF System

All data recorded according to this study protocol must be documented in an eCRF. The investigator and persons authorized by the investigator will be instructed about how to complete the eCRF. Entries in the eCRF must only be made by the investigator or persons authorized by the investigator. A list of all persons who are allowed to make entries in the eCRF must be available in each study site.

The investigator must verify that all data entries in the eCRF are accurate and correct. Entries will be checked against appropriate source documentation by the monitor.

10.3.2 List of Subjects (subject identification log)

The investigator will keep a confidential list of names of all subjects participating in the study, so that the subjects' records can be identified if necessary.

In addition, the investigator will keep a list of all subjects screened on a screening log to document identification of subjects who entered pre-study screening. If someone is not eligible to participate in the study, a reason must be provided.

10.3.3 Source Data

Per ICH, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

10.3.4 Investigator Site File / Regulatory Binder

Before site initiation [redacted] will provide an ISF/ Regulatory Binder to each site. The ISF will include essential documents as defined by the ICH GCP guideline and applicable local requirements.

The investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by the monitor(s). These documents will be reviewed during an audit by the Sponsor or an inspection by the Regulatory Authorities.

All study-related documents are to be archived and stored according to legal requirements.

Prior to destruction of study-related documents, the investigator will contact the Sponsor for approval and confirmation.

10.4 Monitoring

The monitor is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Additionally, the monitor ensures that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

The interval between monitoring visits will depend on the recruitment rate and the complexity of the study.

Source data verification is an essential part of the monitoring process and the investigator must grant direct access to the subject's source data.

The extent and nature of monitoring will be described in detail in the monitoring plan.

10.5 Audits and Inspections

Audits will be performed according to the corresponding audit program. The Sponsor's Quality Assurance Department or designee may visit the investigative site to audit the performance of the study, as well as all study documents. Audits may also be performed by contract auditors who will be instructed about the timing and extent of the audits. In the event of an audit at the investigational site, the monitor will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and IRBs are possible at any time, even after the end of study. The investigator is to notify the Sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IRB and/or Regulatory Authorities and will allow direct access to source data and source documents for monitoring, audits, and inspections.

11 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

11.1 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and investigator abide by the principles of the GCP guidelines of the ICH, and of the Declaration of Helsinki. The study also will be carried out in keeping with local legal requirements.

11.2 Informed Consent

Before each subject is admitted to the study, informed consent will be obtained from the subject (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country (i.e., the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations [CFR] for Protection of Human Subjects (21 CFR 50.25 (a) and (b), CFR 50.27, and CFR Part 56, Subpart A), and other applicable local regulations). This consent form must be dated and retained by the investigator as part of the study records. The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol depending on the requirements of the IRB. If the consent form is revised, it must be reviewed and approved by the appropriate IRB and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

11.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/Regulatory Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC/Regulatory Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

11.4 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

11.5 Data Safety Monitoring Board

Not applicable

11.6 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- For study termination:
    - The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study; in particular if a patient develops a CTCAE-related Grade 4 or higher
    - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
    - A decision on the part of the Sponsor to suspend or discontinue the development of the drug.
- For site termination:
    - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
    - Total number of participants accrued earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

11.7 Confidentiality

All study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on eCRFs and other documents submitted to [redacted] by their subject number, initials and/or birth date, not by name. Documents not to be submitted to [redacted] that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the investigator.

Subject names or any information which would make the participant identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.8 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the investigator, the persons instructed by him and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical product being tested or by medical steps taken in the course of the study.

11.9 Publication Policy

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

An investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. The terms of publication are governed by the agreements executed by the different parties involved in the realization of the study.

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13 APPENDICES

13.1 Appendix 1: Dietary Guidelines for people taking Miglustat (Updated May 2013)

Can miglustat cause gastrointestinal disturbances?
Diarrhea, gas, bloating, abdominal pain or discomfort, nausea and vomiting are symptoms often reported by people taking miglustat. These symptoms are usually mild or moderate and generally decrease over time. Side effects are the worst in the first weeks/months of being on the drug and usually get better after about 3 months.

What is the cause of these symptoms?
Miglustat stops the intestinal enzymes that break down disaccharides (mainly sucrose, maltose, and to a lesser amount lactose) from working. These disaccharides (sugars) are not digested and absorbed properly, and stay in the gut. This can cause diarrhea. These sugars are also "food" for the bacteria in your gut and are fermented, producing gas. This also means your body doesn't absorb these sugars and you aren't getting the calories from them.

What can I do to minimize these symptoms?
• Take miglustat separately from meals (e.g. 2 hours before or after meals)
• Start dietary changes at least 3 days (up to 2 weeks) before you start taking miglustat
• Consider gradually increasing your dose (as recommended by your doctor)
• Eat a diet low in disaccharides (sucrose, maltose, and to a lesser extent lactose)

**Miglustat absorption is not affected if you have diarrhea as it is rapidly absorbed in the gut after it is taken

What is a disaccharide?
Disaccharides are two monosaccharides (single sugars) joined together.
Examples of disaccharides:
-Sucrose (table sugar) is made up of glucose and fructose joined together.
-Maltose is glucose and glucose joined together.
-Lactose (or milk sugar) is a galactose and glucose joined together.

What is a low disaccharide diet?
It is a diet low in sucrose, maltose, and lactose.
Reduce disaccharides to <5g per meal. Look at the sugars on the nutrition label and the ingredient list to get an idea of how much disaccharide is in a food.
Avoid eating foods high in disaccharides (sucrose and maltose)
Desserts: cookies/biscuits, cakes, pies, puddings, custard, ice cream, sweetened yogurt
Certain fruits: bananas, dates, peaches, apricots, pineapples, mangos, tangerines, dried fruits
Additives/condiments: molasses, sugar, chocolate, jam, marmalade, honey, Nutella, sugar-based syrup

Avoid high-carbohydrate drinks such as naturally sweetened soft-drinks, sweetened fruit juices, and alcohol-containing drinks (beer/wine). Fructose containing food and fruit drinks, and artificially sweetened soft drinks may be consumed.

Reduce dairy intake (milk, cream, yogurt, cream cheese)
-Lactose-free and soy based products can be used to replace milk and yogurt
-Unsweetened and/or soy based yogurts allowed
-Ensure you are meeting your calcium and Vitamin D requirements from diet and/or supplements

Reduce intake of starchy foods as the body naturally produces maltose (a disaccharide) as it digests foods such as bread, breakfast cereals, legumes, potatoes, corn, rice, beans, pasta and other grains.
-Avoid large servings starchy foods at one time
-Spread out your intake of starchy foods over the day

If GI symptoms continue, intake of starchy foods may need to be more severely reduced, and then slowly re-introduced one-by-one over several weeks/months.

Will I always have to be this strict with my diet?
As your gut adapts to miglustat therapy and symptoms improve, you may be able to slowly re-introduce foods back into the diet. This would be done slowly and would be based on your tolerance.

What about eating out/special occasions?
For parties or social occasions where it is hard to avoid high disaccharide foods (e.g. birthday cake) consider taking Imodium. Imodium increases the amount of time that food remains in the gut, improving carbohydrate digestion and absorption. This may limit diarrhea and abdominal pain.

Will I lose weight?
Ideally we do not want you to lose weight on miglustat (assuming you are at a healthy weight to start with). It is very important that you maintain an adequate calorie intake while taking miglustat.
If you are getting less calories from carbohydrates, then you will need to get these calories from protein and fats.
Protein Sources: non-breaded meat/fish, eggs, tofu, nuts and seeds
Fat Sources: oils, margarine, and avocado
You may need to snack more often.
Monitor your weight regularly (e.g. at least once a month). Let your doctor, nurse or dietitian know if you are losing weight.

Can probiotics help with my symptoms?
Probiotics (e.g. live cultures in yogurt) may help. There has not been a lot of research done about this. Taking probiotics, which deliver helpful bacteria to the gut, might help with symptoms while on miglustat. Probiotics that break down disaccharides seem to be helpful. One study showed Tilactase and Lactobacillus reuteri improved symptoms related to eating lactose people who were lactose intolerant.

References:
1. Belmatoug, N. et al. Gastrointestinal disturbances and their management in miglustat treated patients. JIMD (2011) 34:991-1001.
2. Helping yourself with healthy choices – Zavesca.

13.2 Appendix 2: Unified Batten Disease Rating Scale

NEURONAL CEROID LIPOFUSCINOSIS (NCL) STUDY GROUP
UNIFIED BATTEN DISEASE RATING SCALE

All items must be completed. Use U if information is Unavailable or Not Applicable.

SUBJECT NO. ☐☐☐ INITIALS (First, Middle, Last) ☐☐☐ SITE NO. ☐☐☐

DATE INFO OBTAINED (mm/dd/yyyy) ☐☐ ☐☐ ☐☐☐☐

I. PHYSICAL ASSESSMENT

1. SPEECH CLARITY 1. ☐

0 = normal
1 = unclear, no need to repeat
2 = must repeat to be understood
3 = mostly incomprehensible
4 = anarthria

1A. ABNORMAL REPETITIVE SPEECH SOUNDS 1A. ☐

0 = none
1 = sometimes
2 = most of the time
3 = constant
4 = anarthric

2. TONGUE PROTRUSION 2. ☐

0 = maintains full protrusion for 10 seconds
1 = maintains full protrusion for more than 5 seconds
2 = maintains full protrusion for less than 5 seconds
3 = cannot fully protrude tongue
4 = cannot protrude tongue beyond lips

3. VISUAL ACUITY 3. ☐

0 = normal
1 = mildly impaired
2 = finger counting only
3 = light/dark perception
4 = blind

4. PASSIVE MOTION-ARMS Right 4a. ☐ Left 4b. ☐

0 = normal tone/full range
1 = mildly increased tone/full range
2 = moderately increased tone/full range
3 = markedly increased tone/incomplete range
4 = minimal or no passive range of motion

5. PASSIVE MOTION-LEGS Right 5a. ☐ Left 5b. ☐

0 = normal tone/full range
1 = mildly increased tone/full range
2 = moderately increased tone/full range
3 = markedly increased tone/incomplete range
4 = minimal or no passive range of motion

6. PASSIVE MOTION-NECK 6. ☐

0 = normal tone/full range
1 = mildly increased tone/full range
2 = moderately increased tone/full range
3 = markedly increased tone/incomplete range
4 = minimal or no passive range of motion

7. POWER-ARMS Right 7a. ☐ Left 7b. ☐

0 = full power
1 = pronator drift/mild weakness
2 = moderate weakness/able to actively resist
3 = severe weakness/able to overcome gravity
4 = paralysis/unable to overcome gravity

SUBJECT NUMBER ☐☐☐ INITIALS (First, Middle, Last) ☐☐☐

All items must be completed. Use U if information is Unavailable or Not Applicable.

8. POWER-LEGS 8a. Right ☐ 8b. Left ☐

0 = full power
1 = mild weakness
2 = moderate weakness/able to actively resist
3 = severe weakness/able to overcome gravity
4 = paralysis/unable to overcome gravity

9. HAND TAPS (table or thigh) 9a. Right ☐ 9b. Left ☐

0 = normal for age
1 = mild slowing and or reduction in amplitude
2 = moderately impaired; definite and early fatiguing; may have occasional arrests in movement
3 = severely impaired; frequent hesitation in initiating movements or arrests in ongoing movements
4 = cannot perform the task

10. MAXIMAL DYSTONIA (UPPER EXTREMITIES) 10a. Right ☐ 10b. Left ☐

0 = absent
1 = slight/intermittent
2 = mild/persistent or moderate/intermittent
3 = moderate/persistent or marked/intermittent
4 = marked/prolonged

11. NORMAL SPONTANEOUS MOVEMENTS 11. ☐

0 = normal
1 = minimally reduced (could be normal)
2 = mildly diminished
3 = moderately diminished
4 = markedly diminished, or absent

12. GAIT 12. ☐

0 = normal gait
1 = small steps and/or slow
2 = walks with difficulty
3 = requires assistance
4 = cannot walk

13. RETROPULSION PULL TEST 13. ☐

0 = normal
1 = recovers spontaneously, may take a step back
2 = would fall if not caught
3 = tends to fall spontaneously
4 = cannot stand

14. HEEL STOMPING 14a. Right ☐ 14b. Left ☐

0 = normal
1 = mild slowing or reduced amplitude
2 = definite and early fatiguing or occasional arrests in movement
3 = frequent hesitation in initiating movement or arrests in ongoing movement
4 = cannot perform task

15. MOTOR TICS OR STEREOTYPIES 15. ☐

0 = absent
1 = rare
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged

16. MYOCLONUS 16. ☐

0 = absent
1 = rare
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged

17. REST TREMOR 17. ☐

0 = absent
1 = mild amplitude and infrequently present
2 = mild amplitude and usually present
3 = moderate amplitude and usually present
4 = marked amplitude and usually present

SUBJECT NUMBER ☐☐☐ INITIALS (First, Middle, Last) ☐☐☐

All items must be completed. Use U if information is Unavailable or Not Applicable.

18. TREMOR WITH MAINTAINED POSTURE OR ACTION 18. ☐

0 = absent
1 = mild amplitude with action
2 = moderate amplitude with action
3 = moderate amplitude with action or sustention
4 = marked amplitude with action or sustention

19. DYSMETRIA (Finger-to-Nose) 19. ☐

0 = normal
1 = mild irregularity
2 = moderate irregularity
3 = marked irregularity
4 = unable to hit target

20. APPENDICULAR CHOREA 20. ☐

0 = absent
1 = slight/intermittent
2 = mild/common or moderate intermittent
3 = moderate/common
4 = marked prolonged

21. WEIGHT(lbs.) 21. ☐☐☐.☐

22. MOTOR EXAMINER 22. ☐☐☐

II. SEIZURE ASSESSMENT

23. GENERALIZED TONIC/CLONIC SEIZURES: AVERAGE FREQUENCY 23. ☐

0 = none
1 = fewer than one per 6 months
2 = more than one per 6 months and up to one per 3 months
3 = more than one per 3 months and up to one per month
4 = more than one per month and up to one per week
5 = more than one per week and up to one per day
6 = more than one per day

24. GENERALIZED TONIC/CLONIC SEIZURES: POST-ICTAL PERIOD 24. ☐

0 = none/not-applicable
1 = less than 1 minute
2 = more than 1 and up to 10 minutes
3 = more than 10 minutes and up to 1 hour
4 = more than 1 hour and up to 3 hours
5 = more than 3 hours

25. ATONIC SEIZURES: AVERAGE FREQUENCY 25. ☐

0 = none
1 = fewer than one per 6 months
2 = more than one per 6 months and up to one per 3 months
3 = more than one per 3 months and up to one per month
4 = more than one per month and up to one per week
5 = more than one per week and up to one per day
6 = more than one per day

26. MYOCLONIC SEIZURES: AVERAGE FREQUENCY 26. ☐

0 = none
1 = fewer than one per 6 months
2 = more than one per 6 months and up to one per 3 months
3 = more than one per 3 months and up to one per month
4 = more than one per month and up to one per week
5 = more than one per week and up to one per day
6 = more than one per day

SUBJECT NUMBER ☐☐☐ INITIALS (First, Middle, Last) ☐☐☐

All items must be completed. Use U if information is Unavailable or Not Applicable.

27. COMPLEX PARTIAL SEIZURES WITHOUT GENERALIZATION AND/OR ABSENCE: AVERAGE FREQUENCY 27. ☐

0 = none
1 = fewer than one per 6 months
2 = more than one per 6 months and up to one per 3 months
3 = more than one per 3 months and up to one per month
4 = more than one per month and up to one per week
5 = more than one per week and up to one per day
6 = more than one per day

28. COMPLEX PARTIAL SEIZURES WITHOUT GENERALIZATION: POST-ICTAL PERIOD 28. ☐

0 = none/not-applicable
1 = less than 1 minute
2 = more than 1 and up to 10 minutes
3 = more than 10 minutes and up to 1 hour
4 = more than 1 hour and up to 3 hours
5 = more than 3 hours

29. SIMPLE PARTIAL SEIZURES: AVERAGE FREQUENCY 29. ☐

0 = none
1 = fewer than one per 6 months
2 = more than one per 6 months and up to one per 3 months
3 = more than one per 3 months and up to one per month
4 = more than one per month and up to one per week
5 = more than one per week and up to one per day
6 = more than one per day

30. SIMPLE PARTIAL SEIZURES: AVERAGE DURATION OF EVENT 30. ☐

0 = none/not-applicable
1 = less than 1 minute
2 = more than 1 minute and up to 10 minutes
3 = more than 10 minutes and up to 1 hour
4 = more than 1 hour and up to 3 hours
5 = more than 3 hours

31. FREQUENCY OF INJURY RELATED TO SEIZURES 31. ☐

0 = never
1 = sometimes
2 = usually
3 = always

32. MAXIMAL LEVEL of CARE FOR SEIZURE COMPLICATIONS (due to any seizure type/past 6 months) 32. ☐

0 = none/no care required
1 = first aid at home
2 = paramedic called
3 = emergency department visit

33. HOSPITALIZATION REQUIRED FOR TREATMENT OF SEIZURES (due to any seizure type/past 6 months) 33. ☐

0 = none/not applicable
1 = once
2 = more than once

34. ANTICONVULSANT ADJUSTMENT REQUIRED TO CONTROL SEIZURES IN PAST MONTH 34. ☐
(0 = No, 1 = Yes)

35. SEIZURE ASSESSOR 35. ☐☐☐

SUBJECT NUMBER ☐☐☐ INITIALS (First, Middle, Last) ☐☐☐

①

All items must be completed. Use U if information is Unavailable or Not Applicable.

III. BEHAVIORAL ASSESSMENT (past month)

36. SAD MOOD
36a. Frequency ☐ 36b. Severity ☐

36a. Frequency	36b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

37. APATHY
37a. Frequency ☐ 37b. Severity ☐

37a. Frequency	37b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

38. ANXIETY
38a. Frequency ☐ 38b. Severity ☐

38a. Frequency	38b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

39. AGGRESSION TOWARD OTHERS
39a. Frequency ☐ 39b. Severity ☐

39a. Frequency	39b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

40. AGGRESSION TOWARD SELF
40a. Frequency ☐ 40b. Severity ☐

40a. Frequency	40b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

41. STEREOTYPED/REPETITIVE BEHAVIOR
41a. Frequency ☐ 41b. Severity ☐

41a. Frequency	41b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

42. COMPULSIONS
42a. Frequency ☐ 42b. Severity ☐

42a. Frequency	42b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

43. AUDITORY HALLUCINATIONS
43a. Frequency ☐ 43b. Severity ☐

43a. Frequency	43b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

44. OBSESSIONS
44a. Frequency ☐ 44b. Severity ☐

44a. Frequency	44b. Severity
0 = never	0 = none
1 = sometimes	1 = mild
2 = frequent	2 = moderate
3 = almost always	3 = severe

45. MEDICATION REQUIRED FOR BEHAVIOR (0 = No, 1 = Yes) 45. ☐

46. BEHAVIORAL ASSESSOR 46. ☐☐☐

SUBJECT NUMBER ☐☐☐ INITIALS (First, Middle, Last) ☐☐☐

All items must be completed. Use U if information is Unavailable or Not Applicable.

IV. CAPABILITY ASSESSMENT ASSUMING NORMAL VISION (answer as if child's vision were normal)

47. SCHOOL 47. ☐

0 = normal ability in mainstream classroom
1 = marginal ability in mainstream classroom
2 = requires special needs classroom
3 = unable to attend special needs classroom

48. CHORES 48. ☐

0 = able to do all age appropriate chores independently
1 = able to do simple chores independently
2 = able to do simple chores with help
3 = unable to do even simple chores

49. PLAY 49. ☐

0 = able to play age appropriate games independently
1 = able to play simple games independently
2 = able to play simple games with help
3 = unable to play even simple games

50. ADL 50. ☐

0 = normal
1 = minimal impairment
2 = gross tasks only
3 = total care

51. CARE LEVEL 51. ☐

0 = home
1 = chronic care at home
2 = full time skilled nursing

V. CAPABILITY ASSESSMENT GIVEN ACTUAL VISION

52. SCHOOL 52. ☐

0 = normal ability in mainstream classroom
1 = marginal ability in mainstream classroom
2 = requires special needs classroom
3 = unable to attend special needs classroom

53. CHORES 53. ☐

0 = able to do all age appropriate chores independently
1 = able to do simple chores independently
2 = able to do simple chores with help
3 = unable to do even simple chores

54. PLAY 54. ☐

0 = able to play age appropriate games independently
1 = able to play simple games independently
2 = able to play simple games with help
3 = unable to play even simple games

55. ADL 55. ☐

0 = normal
1 = minimal impairment
2 = gross tasks only
3 = total care

56. CARE LEVEL 56. ☐

0 = home
1 = chronic care at home
2 = full time skilled nursing

57. CAPABILITY ASSESSOR 57. ☐☐☐

SUBJECT NUMBER ☐☐☐ INITIALS (First, Middle, Last) ☐☐☐

All items must be completed. Use U if information is Unavailable or Not Applicable.

VI. NCL HISTORY (TO BE COMPLETED BY FIRST RATER)

Instructions: For each symptom, ask if child has experienced the symptom and if so, obtain approximate age of onset in years and months (e.g., age 4 1 / 2 should be coded as 04 for years and 06 for months). For each symptom reported as experienced, the rater should rank in order of onset beginning with 1. If child has not experienced symptom, code as U for not applicable.

	Symptom	Experienced Symptom 0 = No, 1 = Yes	Onset Age Years	Onset Age Months	Rater Ranking Order of Onset (1 = first, 8 = last)
58a.	Loss of vision	58a. ☐	58a1. ☐☐	58a2. ☐☐	58a3. ☐
58b.	Motor difficulties	58b. ☐	58b1. ☐☐	58b2. ☐☐	58b3. ☐
58c.	Cognitive difficulties	58c. ☐	58c1. ☐☐	58c2. ☐☐	58c3. ☐
58d.	Behavioral difficulties	58d. ☐	58d1. ☐☐	58d2. ☐☐	58d3. ☐
58e.	Seizures	58e. ☐	58e1. ☐☐	58e2. ☐☐	58e3. ☐
58f.	Weight loss/feeding difficulties	58f. ☐	58f1. ☐☐	58f2. ☐☐	58f3. ☐
58g.	Sleep disturbance	58g. ☐	58g1. ☐☐	58g2. ☐☐	58g3. ☐
58h.	Other (Specify)_____	58h. ☐	58h1. ☐☐	58h2. ☐☐	58h3. ☐

59. COMMENTS_____

60. NCL HISTORY RATER 60. ☐☐☐

VII. CLINICAL SUMMARY

61. ASSESSOR'S GLOBAL IMPRESSION OF CHANGE SINCE LAST ASSESSMENT 61. ☐

1 = much better
2 = somewhat better
3 = about the same
4 = somewhat worse
5 = much worse
N = not applicable (never seen before)

SUBJECT NUMBER ☐☐☐ INITIALS (First, Middle, Last) ☐☐☐
①

All items must be completed. Use U if information is Unavailable or Not Applicable.

62. CLINICAL GLOBAL IMPRESSION – SEVERITY OF SEIZURES 62. ☐
1 = none
2 = minimal
3 = mild
4 = moderate
5 = severe

63. CLINICAL GLOBAL IMPRESSION – COGNITIVE FUNCTION 63. ☐
1 = no impairment
2 = minimally impaired
3 = mildly impaired
4 = moderately impaired
5 = severely impaired

64. CLINICAL GLOBAL IMPRESSION – BEHAVIOR 64. ☐
1 = no impairment
2 = minimally impaired
3 = mildly impaired
4 = moderately impaired
5 = severely impaired

65. CLINICAL GLOBAL IMPRESSION – MOOD 65. ☐
1 = no impairment
2 = minimal distress
3 = mild distress
4 = moderate distress
5 = severe distress

66. CLINICAL GLOBAL IMPRESSION – MOTOR 66. ☐
1 = no impairment
2 = minimally impaired
3 = mildly impaired
4 = moderately impaired
5 = severely impaired

67. CLINICAL GLOBAL IMPRESSION – OVERALL 67. ☐
1 = no impairment
2 = minimally impaired
3 = mildly impaired
4 = moderately impaired
5 = severely impaired

68. CLINICAL SUMMARY RATER 68. ☐☐☐

13.3 Appendix 3: Seizure Diary

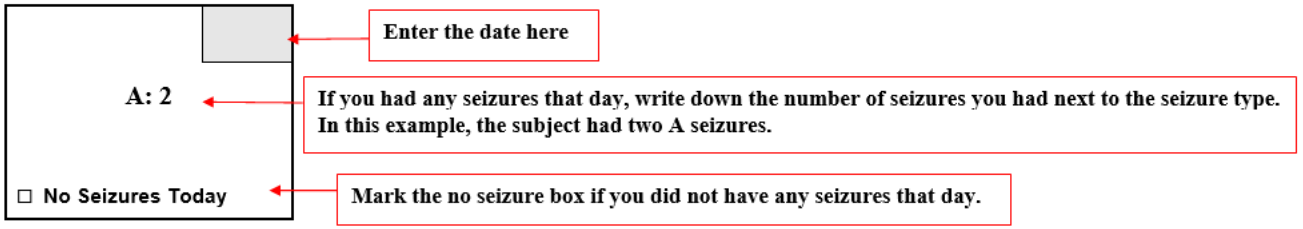
Protocol # _____

Subject ID: _____ Page 1 of 3

1. Take this diary home and use it every day to keep track of your seizures.
2. The staff will review your seizures with you and each seizure type will be assigned a special code.
3. If you have a seizure, record the number of seizures and the type of seizure (using the assigned code below) on the diary.
4. If you do not have any seizures on that day, mark the 'no seizure' box.
5. Bring the seizure diary with you to your next appointment.

Seizure Code	Description given by patient/caregiver

Example:



Protocol # _______________

Subject ID: ____________

Month: _________ Year: _________

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures

Who is completing the seizure diary? (check all that apply) ☐ Patient ☐ Caregiver

Comments: ____

____

Protocol # _______________

Subject ID: ____________ Page 3 of 3

Month: _________ Year: _________

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures

Who is completing the seizure diary? (check all that apply) ☐ Patient ☐ Caregiver

Comments: ____

____

13.4 Appendix 4: Vineland Adaptive Behavior Scales Scoring Sheet, Third Edition

Appendix A: Item Content

Comprehensive Interview Form Items

Communication Domain

Receptive Subdomain

1. Looks toward parent or caregiver when hearing parent's or caregiver's voice.
2. Looks toward parent or caregiver who is gesturing to get his/her attention.
3. Responds upon hearing his/her name called (for example, turns toward speaker, smiles).
4. When parent or caregiver looks or points at something, looks in that direction.
5. Understands at least 10 words.
   Scoring Tip: Score 2 for Yes or 0 for No.
6. Responds appropriately to at least three basic gestures (for example, head nod for *yes*, head shake for *no*, hand out for *give me*, reaching, waving, clapping).
7. Understands the meaning of *no*.
8. Responds appropriately to at least three facial expressions being made by others (for example, frown, smile, surprised look, angry face).
9. Understands the meaning of *yes*.
10. Follows instructions requiring only one action (for example, "Sit down"; "Come here").
11. Identifies at least three *actual* objects when asked (for example, points to a dog, car, cup, key, etc.).
12. Understands at least 50 words.
    Scoring Tip: Score 2 for Yes or 0 for No.
13. Responds to the tone of spoken words (for example, approaches eagerly when "Come here" is spoken lovingly, but hesitantly when "Come here" is spoken sharply).
14. Identifies at least three body parts on self when asked (for example, points to own nose, mouth, hands, feet, etc.).
15. Follows instructions with one action and one object (for example, "Bring me the book"; "Close the door").
16. Responds appropriately to at least three more advanced gestures (for example, motioning *come here*, finger over lips meaning be quiet, hands apart to show *this big*).
17. Identifies at least three objects pictured in a book, magazine, or electronic screen when asked (for example, points to a dog, car, cup, key, etc.).
18. Identifies at least three body parts pictured in a book, magazine, or electronic screen when asked (for example, points to a nose, a mouth, hands, feet, etc.).

19. Responds to questions that use *what* (for example, when asked "What is this?" replies "A ball").
20. Responds to questions that use *who* (for example, when asked "Who is that?" replies "Auntie Kesha").
21. Identifies at least three basic actions pictured in a book, magazine, or electronic screen when asked (for example, points to someone eating, sitting, jumping, etc.).
22. Responds to questions that use *where* (for example, when asked "Where did Felipe go?" points where Felipe went).
23. Follows instructions with two related actions (for example, "Pick up those toys and put them away"; "Get your coat and put it on").
24. Follows instructions with one action and two objects (for example, "Bring me the crayons and the ball"; "Put on your shirt and your shoes").
25. Follows instructions in "if–then" form (for example, "If you're thirsty, then get a drink"; "If you are cold, then get a sweatshirt").
26. Pays attention to a story for at least 15 minutes.
    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown listening to stories.
27. Responds to questions that use *why* (for example, when asked "Why are you crying?" replies "My toy broke").
28. Follows instructions with two unrelated actions (for example, "Turn off the TV and get my keys").
29. Responds to questions that use *when* (for example, when asked "When do you eat breakfast?" replies "In the morning").
30. Pays attention to a show for at least 30 minutes and understands what is happening.
31. Identifies left and right on own body (for example, hands, feet, arms).
32. Follows instructions requiring three actions (for example, "Get dressed, eat breakfast, and brush your teeth").
33. Pays attention to a show for at least 60 minutes and understands what is happening.
34. Understands sarcasm (for example, understands when a comment such as "That's just great!" really means "That's awful!").
35. Pays attention to a 15-minute informational presentation and understands what is being said.
36. Follows instructions involving left and right (for example, "Go to the left"; "Look to the right").
37. When instructed to do something up to an hour later, remembers to do it (for example, "When your show is over, put your dishes in the sink").
38. When instructed to do something several hours later, remembers to do it (for example, "When you get home from school, let the dog out").
39. Pays attention to a 30-minute informational presentation and understands what is being said.

Expressive Subdomain

1. Makes sounds of pleasure (for example, coos, laughs).
2. Cries or fusses when uncomfortable (thirsty, hungry, wet, etc.).
   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
3. Vocalizes or gestures (for example, cries or waves arms) to get parent's or caregiver's attention.
   Scoring Tip: Score 2 if the individual did this when younger, but now says words.
4. Makes at least three one-syllable speech sounds (for example, "Mah," "Bah," "Ee," "Oh").
   Scoring Tip: Score 2 if the individual did this when younger, but now says words.
5. Babbles in strings of sounds (for example, "Ba-ba-ba-ba," "Ma-ma-ma-ma," "Da-da-da-da").
   Scoring Tip: Score 2 if the individual did this when younger, but now says words.

6. Vocalizes or gestures if he/she wants an activity to keep going or stop (for example, says "Again," shakes head *no*).
7. Says "Dada," "Mama," or another name for parent or caregiver (including parent's or caregiver's first name or nickname).
8. Uses at least three basic gestures (for example, head nod for yes, head shake for *no*, reaching or pointing toward something desired, waving, clapping).
9. Repeats or tries to repeat common words immediately upon hearing them (for example, *ball*, *car*, *more*).
   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
10. Says "No"; must actually mean no, not just repeat the word.
11. Names at least three objects (for example, ball, dog, favorite toy).
12. Says one-word requests (for example, "Want," "More," "Open").
13. Names at least 10 objects.
    Scoring Tip: Score 2 for Yes or 0 for No.
14. Says "Yes"; must actually mean yes, not just repeat the word.
    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
15. Names at least three actions (for example, drink/drinking, eat/eating, play/playing).
16. Calls brothers, sisters, or friends by their name or nickname.
17. Says at least 50 words.
    Scoring Tip: Score 2 for Yes or 0 for No.
18. Uses phrases with a noun and a verb (for example, "Mommy stay," "Give ball").
19. Says own first name or nickname.
20. Uses pronouns to refer to self; grammar need not be correct (for example, "Give me," "Me want," "Mine toy").
21. Uses simple adjectives to describe things (for example, *dirty*, *pretty*, *big*, *loud*).
22. Says what he/she is doing using simple sentences; grammar need not be correct (for example, "Ginger and me play," "Dan read me a book").
23. Uses at least three more advanced gestures (for example, motioning *come here*, finger over lips meaning *be quiet*, hands apart to show *this big*).
24. Uses negatives in sentences; grammar need not be correct (for example, "I won't drink it," "Me no go").
25. Says correct age when asked; holding up correct number of fingers counts.
26. Uses possessives in phrases or sentences; grammar need not be correct (for example, "This is mine," "Your book," "This is Carol's desk").
27. Uses *and* in phrases or sentences (for example, "Mom and Dad," "I want ice cream and cake").
28. Asks questions beginning with *who* (for example, "Who's that?," "Who went to the store?"); just asking "Who?" (one word) doesn't count.
29. Uses plural nouns (for example, "Two cats," "More crackers," "Those flowers").
30. Uses pronouns to refer to others; pronoun gender and grammar need not be correct (for example, "You want?," "Her happy," "Him ball").
31. Uses *in*, *on*, and *under* correctly in phrases or sentences (for example, "In the box," "Ball go under table").
32. Asks questions beginning with why (for example, "Why do I have to go?," "Why did you put my stuff away?"); just asking "Why?" (one word) doesn't count.
33. Says first and last name when asked; saying first name only doesn't count.

34. Uses pronouns correctly; pronoun gender and grammar must be correct (for example, "I want," "Their ball," "Call her").
35. Asks questions beginning with when (for example, "When is dinner?," "When can we go home?"); just asking "When?" (one word) doesn't count.
36. Uses *because* in phrases or sentences (for example, "Because I want to," "Kathy went home because she was sick").
37. Says his/her age at next birthday correctly when asked; holding up correct number of fingers counts.
38. Uses past tense verbs (for example, *walked*, *baked*).
39. Tells the basic parts of a familiar story or book or movie plot (the characters, what happens, how it ends, etc.).
40. Uses *behind*, *in front of*, and *between* correctly in phrases or sentences (for example, "Terrell is behind you," "I walked in front of her," "The ball went between the cars").
41. Gives simple directions involving one or two steps (for example, how to make, find, or do something).
42. Uses compound sentences joined by *and* or *but* (for example, "She asked me, and I told her no"; "Jerome wanted to go, but I didn't").
43. Uses own knowledge or opinions to comment on things, situations, and emotions (for example, "I think he's mad at her because she said mean things about him").
44. Tells about everyday (i.e., routine) experiences in detail (for example, when asked what he/she did with a friend today, tells who was involved, where the activity took place, etc.).
45. Tells about one-time (i.e., non-routine) experiences in detail (for example, when asked to describe a trip, tells who was involved, where the activity took place, etc.).
46. Says both the month and day of his/her birthday when asked.
47. Clarifies by restating with different words when he/she is not fully understood at first.
48. Says complete home address correctly when asked (that is, street or rural route, apartment number, city, and state, with or without zip code).
49. Gives complex directions involving three or more steps in logical order (for example, to a distant location, for a recipe requiring many steps).

Written Subdomain

1. Holds a book correctly for reading and turns the pages from front to back.
2. Recognizes one or more simple signs and icons/symbols (for example, STOP signs, bathroom door signs, arrows, smiley face).
3. Identifies one or more alphabet letters.
4. Recognizes own name in printed form.
5. Identifies at least 10 alphabet letters.

   Scoring Tip: Score 2 for Yes or 0 for No.
6. Understands what direction his/her language is written in (for example, from left to right in English; in other languages from right to left or top to bottom).
7. Writes in the correct direction (for example, from left to right in English; in other languages from right to left or top to bottom).
8. Copies own first name without mistakes.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

9. Copies simple words from an example without mistakes (for example, cat, see, go); copying name doesn't count.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

10. Identifies all alphabet letters, both uppercase and lowercase.

    Scoring Tip: Score 2 for Yes or 0 for No.

11. Writes alphabet letters using the correct orientation (that is, not reversed or upside down).
12. Reads at least 10 words.

    Scoring Tip: Score 2 for Yes or 0 for No.

13. Writes own first and last name from memory; writing first name only doesn't count.
14. Reads simple sentences of three or more words out loud.
15. Copies phrases or sentences of four or more words without mistakes.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

16. Writes at least 10 simple words from memory (for example, *hat*, *ball*, *the*); may make small spelling errors.

    Scoring Tip: Score 2 for Yes or 0 for No.

17. Reads simple stories out loud.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

18. Writes simple sentences of three or more words; may make small errors in spelling or grammar.
19. Writes at least 20 words from memory; may make small spelling errors.

    Scoring Tip: Score 2 for Yes or 0 for No.

20. Reads and understands material of a second-grade level or higher.

    Scoring Tip: Score 2 for Yes or 0 for No.

21. Writes simple notes, letters, emails, or texts that include at least three sentences (for example, thank you notes, postcards, invitations); may use abbreviated words and make small errors in spelling or grammar.
22. Finds or sorts things in alphabetical order (for example, finds a name in an alphabetized address book or list of phone numbers, finds a word in a dictionary, alphabetizes a list of words or movie titles).
23. Accurately interprets information presented in simple tables, graphs, or charts.
24. Writes short reports or summaries (for example, a summary of something read) at least three sentences long; must use own words rather than simply borrowing or copying from other sources.

    Scoring Tip: Score 2 if the individual did this when younger, but now no longer needs to write reports or summaries.

25. Accurately interprets visual instructions (for example, assembly instructions, directions shown on a map).
26. Uses a table of contents or index to find information within a book or electronic resource.
27. Reads and understands material of a fourth-grade level or higher.

    Scoring Tip: Score 2 for Yes or 0 for No.

28. Writes emails, stories, letters, journal entries, etc. at least 10 sentences long; may use abbreviated words and make small errors in spelling or grammar.

    Scoring Tip: Score 2 for Yes or 0 for No.

29. Uses the Internet or a library to find information for writing a paper or completing a job assignment.

30. Writes reports, papers, or essays at least one page long; must use own words rather than simply borrowing or copying from other sources.

    Scoring Tip: Score 2 if the individual did this when younger, but now no longer needs to write reports, papers, or essays.

31. Writes or draws instructions for others (for example, how to do something, how to get somewhere).
32. Edits or corrects own written work before handing it in (for example, checks punctuation, spelling, grammar, etc.); use of computer spell-checker is okay.
33. Accurately completes paper or electronic forms of one page or less (for example, forms for school or work).
34. Reads and understands material of a sixth-grade level or higher.

    Scoring Tip: Score 2 for Yes or 0 for No.

35. Writes reports or compositions at least three pages long; must use own words rather than simply borrowing or copying from other sources.

    Scoring Tip: Score 2 if the individual did this when younger, but now no longer needs to write reports or compositions.

36. Reads and understands material of a ninth-grade level or higher.

    Scoring Tip: Score 2 for Yes or 0 for No.

37. Accurately completes paper or electronic forms of two pages or more (for example, a job, college, or credit application).
38. Writes business or application letters (for example, requests information, makes a complaint, applies for a job or to a school).

Daily Living Skills Domain

Personal Subdomain

1. Opens mouth when food is offered.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown being fed.

2. Drinks from a bottle or spill-proof drinking cup (often called a "sippy cup"); must hold the bottle or cup himself/herself.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

3. Sucks or chews on finger foods (for example, crackers, cookies, toast).
4. Eats solid foods (for example, cooked vegetables, chopped meats).
5. Cooperates actively in undressing and dressing (raises arms for removing top, holds out feet for putting on pants or shoes, etc.).

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

6. Cooperates actively in washing of hands and face (holds out hands, turns face toward parent or caregiver, etc.).

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

7. Feeds self with a spoon; may spill.
8. Removes shoes and socks.
9. Drinks from a regular cup or glass (sippy cups don't count); some spilling may occur.
10. Feeds self with a fork; may spill.
11. Removes clothing that opens in the front (for example, a coat or jacket); does not have to unbutton or unzip the clothing.

12. Lets someone know when he/she has a wet or soiled diaper or pants (for example, points, vocalizes, pulls at diaper).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

13. Pulls up clothing with elastic waistbands (for example, underwear, sweatpants).
14. Drinks from a regular cup or glass without spilling (sippy cups don't count).
15. Urinates in a toilet or potty chair; parent or caregiver may initiate.
16. Washes hands using soap and water and dries them; does not need to turn the water on and off or adjust the temperature.
17. Feeds self with a spoon without spilling.
18. Removes pullover garments (for example, T-shirt, sweatshirt, dress).
19. Puts on shoes; may be on the wrong feet and does not need to tie or fasten.
20. Puts on clothing that opens in the front (for example, a coat or jacket); does not need to zip or button.
21. Defecates in a toilet or potty chair; parent or caregiver may initiate.
22. Is toilet-trained during the day; may require help with undressing, flushing, wiping, or washing hands, *but must initiate using the toilet*.
23. Puts on pullover garments (for example, T-shirt, sweatshirt, dress).
24. Wipes or blows nose using tissue, napkin, toilet paper, or other appropriate material.
25. Washes and dries face; does not need to turn the water on and off or adjust the temperature.
26. Wipes or cleans face and hands as needed during or after meals.
27. Puts clothing on with the right side forward and correct side out.
28. Is toilet-trained during the night; may require help with undressing, flushing, wiping, or washing hands, *but must initiate using the toilet*.
29. Covers mouth and nose when coughing or sneezing.
30. Uses the toilet during the day and at night without help; must wipe, flush, and wash hands by himself/herself.
31. Fastens snaps.
32. Buttons large buttons, in the correct buttonholes (for example, coat buttons).
33. Brushes teeth; must put toothpaste on toothbrush, brush adequately, and rinse.
34. Changes clothing that has become dirty, wet, muddy, or smelly.
35. Connects and zips zippers that are not already fastened at the bottom (for example, on a coat or jacket).
36. Bathes or showers and dries self; does not need to turn the water on and off or adjust the temperature.
37. Puts shoes on the correct feet and securely ties or fastens them.
38. Spreads food with a table knife (for example, butter, jam, mustard).
39. Buttons small buttons, in the correct buttonholes (for example, shirt buttons).
40. Shows awareness that some foods are healthier than others (for example, states that fruits and vegetables are healthier than foods high in sugar or fat).
41. Finds and uses an appropriate restroom when away from home.
42. Turns faucets on and adjusts the water temperature.
43. Selects appropriate clothing during wet or cold weather (for example, raincoat, boots, sweater).
44. Cuts easy-to-cut food with a table knife (for example, fish, pancakes, butter).

45. Shows awareness that physical exercise is good for people (for example, states that exercise is healthy, that people should exercise, etc.).
46. Washes and rinses hair; does not need to turn the water on and off or adjust the temperature.
47. Chooses to exercise for health and/or enjoyment.
48. Uses the toilet before going out if uncertain about the availability of a restroom.
49. Makes healthy eating choices (eats a balanced diet, eats unhealthy foods in moderation, etc.).
50. Cuts harder-to-cut food with a sharp knife (for example, meat, raw vegetables).
51. Plans for changes in weather by taking along an umbrella, a sweater, etc.
52. Takes own temperature when needed.
53. Takes medicine as directed on his/her own.
54. Goes to the doctor when needed (that is, when illness or injury requires professional care).
55. Monitors supply of medications (nonprescription and prescription) and replaces them as needed.

Scoring Tip: If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box.

Domestic Subdomain

1. Is careful around hot objects (for example, the stove or oven, an open fire).
2. Is careful when using sharp objects (for example, scissors, knives).
3. Wipes up own spills; must get wiping material and clean the spill adequately.
4. Puts dirty clothes in the proper place to be washed (for example, a laundry basket or chute).
5. Removes dirty shoes or wipes them on a doormat before entering a residence.
6. Puts away his/her books, toys, etc. when done using them.
7. Washes hands before preparing food.
8. Fully clears own dishes, utensils, napkins, cups, etc. after eating.
9. Does at least two simple household chores (for example, dusts, empties trash cans, feeds pet).
10. Prepares a simple snack or meal (for example, a sandwich, cheese and crackers, microwave foods).
11. Understands what to do in dangerous situations (for example, when to get help, when to call 911, how to distance self from danger).
12. Hangs wet towel on a towel rack or hook, or puts in the proper place to be washed.
13. Puts clean clothes away where they belong (for example, in drawers or closet, on hooks).
14. Uses at least two simple kitchen appliances (for example, toaster, microwave, electric can opener).
15. Washes fruits and vegetables before eating or cooking them.
16. Secures home against intruders when home (keeps doors locked, finds out who is at the door before opening it, etc.).
17. Uses at least three kitchen utensils to prepare food (for example, knives, tongs, spatula, vegetable peeler).
18. Is careful when operating household appliances or equipment (for example, vacuum cleaner, lawnmower, iron, power tools).
19. Prepares and eats leftovers.
20. Uses household products correctly (for example, laundry detergent, furniture polish, glass cleaner).
21. Puts dishes away when clean and dry.

22. Secures home against intruders when leaving home (locks doors, closes windows, turns on alarm, etc.).
23. Washes dishes (either by hand, or by loading and running the dishwasher when needed).
24. Cleans floors thoroughly (sweeps, vacuums, mops, etc.).
25. Puts leftover food away (for example, in plastic bags or wrap, in containers).
26. Uses the stove or oven for cooking or baking (turns burners on and off, sets oven temperature, etc.).
27. Recognizes when simple maintenance tasks need to be done and does them (for example, replaces light bulbs, batteries, filters, or vacuum cleaner bag).
28. Cleans bathroom (toilet, sink, tub or shower, etc.).
29. Does laundry; must wash, dry, and fold/hang.
30. Prepares a full meal consisting of three or more food items.

Community Subdomain

1. Talks to a familiar person using a phone, computer, or other electronic device; does not need to place the call.
2. Understands that money is used to buy things.
3. Counts at least 10 objects, one by one.
4. Remains within safe distance of caregiver when in public places; being carried, pushed in a stroller, etc. doesn't count.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
5. Understands and follows safety precautions while riding in a car (for example, keeps seat belt on, refrains from unnecessarily distracting the driver).
6. Understands that a clock is used to tell time.
7. Operates at least two technology devices for entertainment (for example, a television, DVD player, music player, handheld game, computer used for entertainment).
8. Uses appropriate manners when eating in public, (for example, uses utensils, sits properly, doesn't disrupt others).
9. Says all seven days of the week in order when asked.
10. Looks both ways when crossing streets or roads.
11. Respects the right to personal privacy for self and others (for example, while using the restroom or changing clothes; not opening others' mail).
12. Names a penny, nickel, dime, and quarter when asked; does not need to know the value of the coins.
13. Says the current day of the week when asked.
14. Understands that some items cost more than others (for example, might say "I have enough money to buy stickers but not a book" or "Which pens cost less?").
15. Knows what phone number to call in an emergency and how to make the call (for example, knows how to call 911 or an emergency contact).
16. Obeys traffic lights and *Walk/Don't Walk* signs when crossing streets or roads.
17. Tells time using a digital clock or watch.
18. Understands and follows community rules and laws (for example, rules and laws regarding littering, pet control, respecting others' property, etc.).
19. Makes calls to others using a phone, computer, or other electronic device.
20. Knows the difference between bills of different values ($1, $5, $10 bills, etc.).

21. Understands signs or symbols used to indicate danger (for example, skull and crossbones for poison, circle with slash for "don't do").
22. Identifies a specific date (either the current date or another) on a calendar when asked.
23. Says the value of a penny (1 cent), nickel (5 cents), dime (10 cents), and quarter (25 cents) when asked.
24. Chooses to avoid dangerous or risky activities or situations (for example, walking in an unsafe area, jumping off high places, picking up a hitchhiker).
25. Makes small purchases at a store (for example, candy, stickers).
26. Combines coins to equal a specific amount (for example, 87 cents).
27. Follows safety precautions in work and/or leisure activities (for example, wears safety equipment, uses caution when operating tools and machinery).
28. Watches or listens to TV or radio or uses the Internet to obtain current information (for example, news, weather report, traffic conditions).
29. Uses a clock to keep track of when to do something (for example, watch a TV show, meet a friend).
30. Sets a short-term goal and achieves it (for example, completes all homework by Thursday night in order to have the weekend free).
31. Finds a needed phone number (for example, uses a contact list, the Internet, a phone book, 411).
32. Keeps personal belongings secure (wallet, purse, phone, etc.) when away from home (for example, when shopping, eating out, or traveling).
33. Gets up on time when needed (for example, sets alarm, arranges to be awakened).
34. Carries or stores money/debit card/credit cards safely, without losing (for example, in a wallet, purse, or money belt).
35. Operates technology to accomplish at least two kinds of tasks (for example, writing documents, school-related email, organizing information, finding information on the Internet).
36. Understands the right to vote.
37. Uses at least two social interaction technologies (for example, personal email, texting, social media, Skype™; telephone calls don't count).
38. Checks change to make sure it is correct after buying something.
39. Evaluates quality and price when deciding what to buy.
40. Understands the right to begin or discontinue services (for example, telephone or Internet service).
41. Understands the right to report legitimate problems with products, services, living situation, etc.
42. Notifies an appropriate person when he/she will be late or absent for school, work, an appointment, etc.
43. Sets a goal that can be done in six months or more and achieves it (for example, works and saves money to buy something expensive, gets in better physical shape).
44. Travels at least one mile to a familiar destination when needed (using public transportation, walking, biking, driving, etc.).
45. Has worked to earn money outside the home (for example, babysitting or yard work for a neighbor, having a job).

    Scoring Tip: Score 2 for Yes or 0 for No.
46. At a restaurant, gets seating, chooses what to order, places order, and pays for meal.
47. Understands the right to access records and information (for example, school or medical records, credit history).

48. Travels at least one mile to an unfamiliar destination when needed (using public transportation, walking, biking, driving, etc.).
49. Sets a long-range goal requiring two years or more and achieves it (for example, makes a sports or academic team, gets into college).
50. Uses a city, highway, bus, or electronic map (or GPS) to figure out how to reach a destination when needed.
51. Buys groceries and household supplies when needed.
52. Manages daily expenses responsibly (for example, meals, bus fare).
53. Uses a bank account responsibly (keeps money in the account, keeps tracks of the balance, doesn't overdraw, etc.).
54. Has held a job (10 hours or more a week) for at least one month.

    Scoring Tip: Score 2 for Yes or 0 for No.
55. Uses a credit or debit card in his/her name responsibly (for example, does not exceed credit limit, pays on time).
56. Manages monthly expenses responsibly (for example, rent, utilities).
57. Pays bills on time.
58. Has held the same job (10 hours or more a week) for at least one year.

    Scoring Tip: Score 2 for Yes or 0 for No.

Socialization Domain

Interpersonal Relationships Subdomain

1. Looks at the face of parent or caregiver.
2. Smiles in response to a smile or a friendly voice.
3. Recognizes family members or other significant people.
4. Smiles or makes sounds when approached by a familiar person.
5. Shows at least three different emotions (for example, happiness, sadness, surprise, fear).
6. Tries to interact with others (for examples, smiles or makes noises at someone, reaches for someone).
7. Reaches for familiar person when that person holds out arms to him/her.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
8. Shows affection to familiar people (for example, touches, hugs, kisses, cuddles).
9. Shows interest in children the same age, other than brothers or sisters (for example, watches them, smiles at them).
10. Looks around from time to time to check that parent, caregiver, or other familiar person is nearby.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
11. Identifies self while looking at own image in mirror or photo.
12. Smiles in response to praise or compliments (for example, "Good job," "That's a nice shirt").
13. Imitates or tries to imitate parent's or caregiver's facial expressions (for example, when parent or caregiver makes a happy, sad, or surprised face).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
14. Recognizes emotions in others (for example, might say "You look sad" or "Rachel is happy").

15. Imitates relatively complex actions as they are being performed by another person (for example, shaving, putting on makeup, vacuuming, hammering nails).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

16. Uses actions or words to show happiness, sympathy, or concern for others on own initiative (for example, hugs, holds hands, asks "Are you okay?").
17. Tries to make friends with others his/her age (that is, shows particular interest in interacting with certain other children).
18. Says the relationship of family members to self (for example, "That's my mom," "He's my brother"); simply calling parents Mom, Dad, or equivalent doesn't count.
19. Uses words to express own emotions (for example, "I'm happy," "I'm scared," "I don't like him").
20. Maintains culturally appropriate eye contact during social interactions.
21. Answers politely when familiar adults make small talk (for example, if asked "How are you?" says "I'm fine"; if told "You look nice," says "Thank you").
22. Imitates relatively complex actions several hours after watching someone else perform them (for example, shaving, putting on makeup, vacuuming, hammering nails).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

23. Speaks using a loudness, speed, and level of excitement that is appropriate for the conversation.
24. Does things to try to please others on own initiative (for example, makes someone a card or gift, helps without being asked).
25. Has a best friend or a few good friends.

    Scoring Tip: Score 2 for Yes or 0 for No.

26. Maintains an acceptable distance between self and others in social situations (for example, does not get too close to another person when talking).
27. Is a good friend: Treats his/her friends fairly and with respect, is supportive, etc.
28. Talks with others about shared interests (for example, sports, TV shows, summer plans).
29. Maintains friendships over time (for example, has had the same good friend for over a year).
30. Recognizes that the likes and dislikes of others can differ from his/her own (for example, might say "Kelly likes pizza, but I don't"; "I liked that movie, but Gretchen hated it").
31. Starts small talk when he/she meets people he/she knows (for example, says "How are you?," "What's up?").
32. Chooses friends with good qualities: Friends who treat him/her with respect, are supportive, stay out of trouble, etc.
33. Moves easily from one topic to another in conversation when needed; does not "get stuck" on one topic.
34. Talks with others without interrupting or being rude.
35. Tells others what he/she is thinking and feeling instead of assuming that they know.
36. Stays on topic in conversations when needed; does not digress.
37. Responds positively to the good fortune of others on own initiative (for example, congratulates a friend who receives an award).
38. Gives cards and/or gifts to immediate family members on "special days" on own initiative.
39. Will engage in activities suggested by friends, even if not preferred.

    Scoring Tip: If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box.

40. Starts conversations with others by talking about things that interest them (for example, "Tyrone tells me you like cars").
41. Participates in conversations on a topic not of interest to him/her.
42. Responds to hints or indirect cues in conversation (for example, knows that a yawn may mean "I'm bored," an abrupt change of subject may mean "I don't want to talk about that," looking at the time may mean "I need to end this conversation").
43. Provides additional explanation when needed in order for someone to follow what he/she is saying (for example, "In case you missed what I said…," "What we were talking about was…").

Play and Leisure Subdomain

1. Responds when parent or caregiver is playful (for example, smiles, laughs, claps hands).
2. Shows interest in surroundings (for example, looks or moves around, touches objects or people).
3. Plays simple interaction games with others (for example, peek-a-boo, patty-cake).

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
4. Plays near another child, each doing different things.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
5. Copies the play of a child playing nearby with little or no interaction between the two.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
6. Plays interactively with one or more children for at least 5 minutes with someone older supervising.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
7. Chooses to join other children who are playing rather than watching them or playing alone.
8. Uses common household objects or other objects for make-believe activities (for example, pretends a block is a car or a box is a house).

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
9. Shares toys or possessions when told to do so.
10. Joins in with a group when verbal cues indicate that he/she is welcome.
11. Plays interactively with one or more children for at least 30 minutes with someone older supervising.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
12. Protects self by moving away from those who try to hurt others or destroy things (those who bite, hit, throw things, smash things, etc.).
13. Plays simple make-believe activities with other children (for example, plays "dress-up," pretends to be superheroes).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
14. Plays with others at simple outdoor group games with no score (for example, tag, jump rope, catch).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
15. Seeks out others for play or companionship (for example, asks others to play or spend time together).
16. Plays with other children with minimal supervision.
17. Takes turns when asked while playing games or sports.
18. Engages with other children in elaborate make-believe activities involving more than one role (for example, plays "school" or "restaurant," enacts a TV show or movie).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

19. Shares toys or possessions without having to be told to do so.
20. Joins in with a group when nonverbal cues indicate that he/she is welcome.
21. Takes turns without having to be asked while playing games or sports.
22. Plays with others at simple indoor or outdoor games where the players keep score (for example, tic-tac-toe, kickball, card games).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
23. Follows rules in games or sports without being told to do so.
24. Plays with others at simple card or board games based only on chance (for example, Candyland®, the card game "war").
25. Refrains from entering a group when verbal cues indicate that he/she is not welcome.
26. Asks permission before using things that belong to or are being used by another.
27. Shows good sportsmanship in games or sports: Plays fair, is not overly aggressive, congratulates winning players, does not act mean when he/she loses, etc.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
28. Gets together with two or more peers at someone's home.
29. Refrains from entering a group when nonverbal cues indicate that he/she is not welcome.

    Scoring Tip: If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box.
30. Goes places with peers during the day or evening with someone supervising (for example, shopping, a movie, a sports event).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown needing to be supervised.
31. Plays with others at two or more board, card, or electronic games requiring skill and decision making (for example, Monopoly™, poker, Scrabble®, interactive video games).
32. Plans ahead to do things with peers on his/her own.
33. Obtains schedule information for movies, sports events, concerts, etc. (for example, looks at a newspaper or on the Internet, phones a movie theater).
34. Goes places with peers during the day without someone supervising (for example, a shopping mall, park, community center).
35. Plans fun activities with more than two things to be arranged (for example, birthday party, group outing).
36. Goes places with peers in the evening without someone supervising (for example, a concert, lecture, sports event, movie).

Coping Skills Subdomain

1. Seeks comfort from parent, caregiver, or other when hurt or upset.
2. Looks or moves toward parent or caregiver when approached by an unfamiliar person.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
3. Separates easily from parent or caregiver when left with another person (that is, does not have a temper tantrum, sulk, etc. when parent or caregiver leaves or attempts to leave).
4. Transitions easily from one activity to another.
5. Responds politely when given something (that is, expresses thanks either verbally or nonverbally).
6. Is polite when asking for something (that is, uses please or an appropriate nonverbal gesture).
7. Handles changes in routine without becoming overly distressed.

8. Recovers quickly from a minor setback or disappointment (for example, doesn't pout for long after losing a game or not getting something that he/she wants).
9. Uses words or gestures to express distress rather than screaming, hitting, throwing something, etc.
10. Apologizes for small, unintentional mistakes (for example, burping, bumping into someone).
11. Acts appropriately when introduced to new people (for example, smiles, shakes hands, says "Happy to meet you").
12. Requests help when encountering a problem beyond own capability to solve (for example, a computer problem, fixing something).
13. Changes behavior intentionally depending on how well he/she knows another person (for example, acts more formally with someone new than with a friend or family member).
14. Accepts helpful suggestions or solutions from others.
15. Apologizes with sincerity after hurting another's feelings.
16. Copies appropriate behavior of others when in a new situation and unsure how to act.
17. Is willing to compromise in order to get along with peers.
18. Controls anger or hurt feelings when plans change for reasons that can't be helped (for example, an event cancelled due to bad weather, a trip postponed due to car trouble).
19. Follows time limits imposed by parent or caregiver (for example, amount of time allowed to watch TV, play a game, use the Internet, or play outside).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
20. Understands that when someone does or says something that hurts, it may be accidental rather than intentional.
21. Adjusts behavior to keep from disrupting others nearby (for example, is quiet near others who are working, listening to a show, etc.).
22. Controls anger or hurt feelings when he/she does not get his/her way (for example, when not allowed to watch television or attend a party, when a suggestion is rejected by a friend or supervisor).
23. Keeps promises.
24. Controls anger or hurt feelings when given constructive criticism (for example, correction of misbehavior, discussion of a test score or grade, a performance review).
25. Understands that a friendly appearing person may actually intend harm.
26. Respects others' time (for example, doesn't keep others waiting or interrupt others who are busy).
27. When possible, avoids or leaves harmful relationships or situations (for example, being bullied, coerced into breaking the law, taken advantage of sexually or financially).

    Scoring Tip: If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box.
28. Avoids being manipulated, dominated, or taken advantage of by others.
29. Thinks through the consequences of his/her actions before acting (for example, refrains from acting impulsively, considers relevant information).
30. Obeys curfews (that is, comes home when he/she is told to, during the day or at night).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.
31. Is aware of and uses caution when encountering risky social situations (for example, Internet solicitations, a stranger's offer of a ride or money, "binge" drinking parties, social media, personal ads).

    Scoring Tip: If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box.

32. Informs parent or caregiver about his/her plans when he/she goes out (for example, what time he/she is leaving and returning, where he/she is going).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

33. Recognizes that advertising messages may not be accurate.

Motor Skills Domain

Gross Motor Subdomain

1. Sits supported (for example, in a chair, with pillows, etc.) for at least 1 minute.
2. Rolls over from back onto stomach.
3. Sits unsupported for at least 1 minute.
4. Moves, scoots, or crawls across the floor.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

5. Sits unsupported for at least 10 minutes.
6. Stands holding on to a stable object for at least 5 seconds.

   Scoring Tip: Score 2 if the individual did this when younger, but now stands without holding on to anything.

7. Pulls self up to standing position.
8. Stands supported with one hand and reaches for an object with the other hand without falling.

   Scoring Tip: Score 2 if the individual did this when younger, but now stands without holding on to anything.

9. Takes steps while supporting self using furniture or another stable object.

   Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

10. Crawls up stairs.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

11. Stands unsupported for at least 1 minute.
12. Takes at least two steps without support.
13. Stands unsupported and reaches for an object without falling.
14. Walks to get around; does not need to hold on to anything.
15. Safely climbs on and off low objects (for example, child's chair, step stool, low bench).

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

16. Goes down stairs by crawling backwards or scooting on bottom.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

17. Squats or bends down to pick up objects without falling.
18. Throws a ball with one hand; accuracy not important.
19. Safely gets on and off an adult-sized chair.
20. Runs without falling; may be awkward and uncoordinated.
21. Walks up stairs, putting both feet on each step; may use railing.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

22. Kicks a ball while standing; accuracy not important.
23. Walks two or more blocks without having to rest or needing physical support.

24. Walks down stairs, facing forward, putting both feet on each step; may use railing.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

25. Jumps off the ground with both feet without falling.
26. Runs smoothly without falling.
27. Safely climbs up and down high objects (for example, jungle gym, ladder, tree).
28. Walks carefully on a sidewalk or road that is slippery or uneven.
29. Jumps forward at least three times with both feet without falling.
30. Runs smoothly, changing speed and direction (for example, when playing tag or sports, or chasing a pet).
31. Catches a beach ball-sized ball from a distance of 2 or 3 feet.
32. Walks up stairs, alternating feet; may use railing.
33. Walks down stairs, alternating feet; may use railing.
34. Climbs a flight of eight or more stairs at a normal pace; may use railing.
35. Pedals a tricycle or other three-wheeled vehicle for at least 6 feet.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

36. Hops on one foot at least once without falling; may hold on to something for balance.
37. Pedals a tricycle or other three-wheeled vehicle around corners.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

38. Catches a beach ball-sized ball from at least 6 feet away.
39. Hops forward on one foot with ease without holding on (for example, during hopscotch).
40. Catches a tennis- or baseball-sized ball from a distance of 2 or 3 feet, using one or both hands extended away from body.
41. Rides a balance bike or bicycle with training wheels for at least 10 feet.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

42. Catches a tennis- or baseball-sized ball from a distance of at least 10 feet, moving to catch it if necessary.
43. Rides a regular bicycle without training wheels without falling.

Fine Motor Subdomain

1. Reaches for a toy or object.
2. Picks up objects; may use both hands.
3. Moves an object from one hand to the other.
4. Removes an object (for example, a block or small toy) from a box or other container with no lid.
5. Picks up small objects (no larger than 2 inches on any side) with thumb and fingers (for example, raisins, beads, small blocks).
6. Picks up a small toy or object with one hand and hands it to someone without dropping it.
7. Puts an object (for example, a block or small toy) into a box or other container with no lid.
8. Marks on paper with a crayon, pen, or pencil; method of grasping the crayon, pen, or pencil is not important.
9. Opens doors that require only pushing or pulling (for example, cabinet, refrigerator, sliding, or swinging doors).

10. Stacks at least four small blocks or other small objects; alignment need not be perfect, but the stack must remain upright.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown it.

11. Turns book or magazine pages one by one; books with cardboard pages don't count.
12. Unwraps small objects (for example, gum or candy).
13. Opens doors by turning a doorknob or handle.
14. Uses a twisting hand–wrist motion (for example, winds up a toy or music box, screws/unscrews the lid of a jar).
15. Holds a crayon, pen, or pencil in proper position (that is, using a tripod grasp, not with fist) for writing or drawing.
16. Presses buttons accurately on a small keyboard or touch screen (for example, on a calculator, cell phone, or other handheld device).
17. Opens and closes scissors with one hand; does not have to cut with them.
18. Draws a circle freehand while looking at an example.
19. Colors simple shapes or animals; more coloring is inside the lines than outside.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown coloring.

20. Draws more than one recognizable form (for example, a person, house, tree).
21. Pours liquid from one container to another with little or no spilling (for example, pouring milk or juice into a glass).
22. Draws a square freehand while looking at an example.
23. Uses scissors to cut along a straight line across a standard sheet of paper.
24. Draws a triangle freehand while looking at an example.
25. Uses an eraser without tearing the paper.
26. Cuts out simple shapes (circles, squares, rectangles, etc.).
27. Colors simple pictures with all coloring inside the lines.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown coloring.

28. Colors a full-page drawing or scene using two or more colors; all coloring is inside the lines.

    Scoring Tip: Score 2 if the individual did this when younger, but has now outgrown coloring.

29. Draws a straight line using a ruler or straightedge.
30. Ties a knot.
31. Cuts out complex shapes (for example, stars, animals, alphabet letters).
32. Ties a secure bow (for example, shoe laces, gift wrapping).
33. Manipulates very small objects (for example, sets hands on a watch, threads a sewing needle, glues miniature model parts).
34. Assembles, builds, or creates complex building toy structures, model sets, homemade jewelry, arts and crafts, etc.

13.5 Appendix 5: Lumbar Puncture/CSF Collection

This procedure is done for the collection of CSF for biomarker and miglustat concentration analysis. It will be done on an annual basis under sedation in conjunction with other evaluations. The lumbar puncture will be performed by a provider credentialed by the NIH CC for this procedure.

The participant will be taken to a procedure room and placed in the left lateral position on a stretcher, bed or examination table. A member of the Anesthesia team will monitor sedated patients constantly throughout the procedure. A local anesthetic (lidocaine dose as appropriate) will be administered in the skin and underlying tissue above the chosen interspace. A small spinal needle will be inserted under sterile conditions into the lumbar spinal sac. Approximately 10 mL of CSF will be collected, and the volume will be reduced proportionally for children under 4 years of age.

For participants who can cooperate, the lumbar puncture may be done awake, with anxiolytics if needed. Local anesthesia will be used.

CSF Biomarkers

CSF will be collected for analysis of biomarkers. Applicable technologies include but are not limited to proteomics, lipidomics, expression analysis, gene/exome/genome/transcriptome sequencing, metabolomics, and multi-analytes profiling.

13.6 Appendix 6: Contraception Guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 13-1when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration

Refrain from donating sperm for the duration of the study and for 30 days after the last dose of study treatment.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 13-1.

Table 13-1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 30 days, after the last dose of study treatment

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive Batten-1.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within [24 hours] of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant:

Continuation of study intervention may only be allowed if either of the following criteria is met:
The study intervention has an approved label that indicates it can be used safely in pregnant females
OR
All of the following apply:
The participant has a high mortality disease
The Investigator determines the participant is benefitting from study participation and there is no other reasonable treatment for her.
The Sponsor and the relevant IRB/IEC give written approval
The participant gives signed informed consent.
The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.
The protocol is amended to allow such participation on a case-by-case basis, if such participation is not already addressed in the protocol.
Under exceptional circumstances (see related instructional text), the continuation of study intervention can be considered.

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.

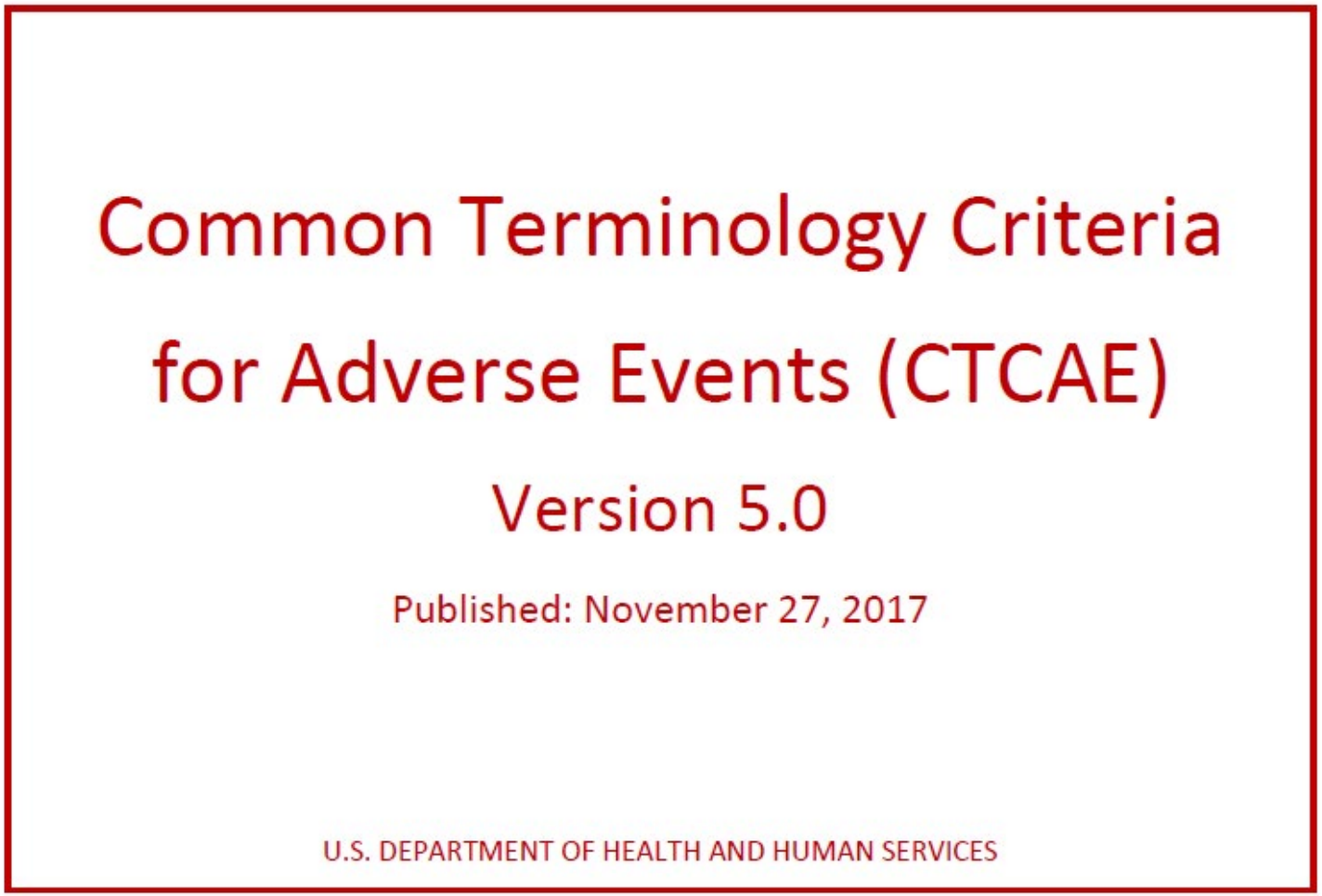
The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 7.1.1.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

13.7 Appendix 7: Extract of Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0



Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Publish Date: November 27, 2017

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

13.8 Appendix 8: Plan for miglustat administration

Enrolled participants will be contacted by the study team and will have their visit scheduled according to the schedule of events listed in the protocol to occur either at home or at the local health center. Once the visit is scheduled at home, adequate quantities of the miglustat IP will be dispensed from the central pharmacy and shipped directly to the patient's home to arrive on the day of the scheduled visit.

All IP shipments will be temperature controlled and monitored to prevent any temperature excursions while IP is in transit. The assigned home nurse will meet with the participant at the proposed home setting and will complete all assessments per the study protocol. Completed assessments will be relayed to the PI and study team. The PI will then determine the appropriate dosage based on the completed assessments and will communicate that order to the pharmacist and home health nurse.

- Regarding the miglustat oral dosing, the PI will verify the dosage prior to administration and relay that order back to the study team, to provide guidance to the pharmacist and home health nurse on how much IP should be administered.
- The nurse will provide IP accountability for the miglustat by counting how much miglustat is left following the completion of each visit.