CLINICAL STUDY PROTOCOL

Open-label Evaluation of Adrabetadex in Patients with Neurologic Manifestations of Niemann-Pick Type C Disease (NPC)

Protocol Number: VTS-270-001

Date of Original Protocol: 01 December 2017

Date of Protocol Amendment 3: 23 June 2021

Vtesse LLC, a Mallinckrodt Pharmaceuticals Company

90 Washington Valley Road

Bedminster, NJ 07921

PROTOCOL AMENDMENT 3 CHANGES

SUMMARY OF CHANGES

The objective of this amendment is reinforce the need for the investigator to assess whether subjects treated with intrathecal adrabetadex for Niemann-Pick type C1 disease (NPC1) are benefiting from treatment, to review and discuss the risk-benefit assessment of the treatment with those subjects who are benefiting from treatment, and to document this discussion in the subject's medical record.

For subjects continuing in this study after 21 June 2021, the investigator must assess whether the subject is benefiting from treatment with adrabetadex. For those subjects who appear to benefit from treatment, the investigator must review with them the risks associated with intrathecal adrabetadex, including hearing loss, and the data from the randomized, controlled trial that demonstrated no significant differences between subjects treated with adrabetadex and sham-treated subjects on any efficacy measures. Subjects must be discontinued from the study if the investigator does not consider them to be benefiting from treatment and/or they do not understand the risks associated with adrabetadex, including hearing loss. A summary of changes for Amendment 3.0 is provided below.

SUMMARY OF CHANGES FOR AMENDMENT 3.0

1. For subjects continuing in the study after 21 June 2021, the investigator must assess whether the subject is benefiting from treatment with intrathecal adrabetadex.
2. For those subjects who appear to benefit from treatment, the investigator must review with them the risks associated with adrabetadex, including hearing loss, and the data from the randomized, controlled trial that demonstrated no significant differences between subjects treated with adrabetadex and sham-treated subjects on any efficacy measures.
3. After 21 2021, subjects must be discontinued from the study if the investigator either does not consider them to be benefiting from treatment and/or they do not understand the risks associated with adrabetadex, including hearing loss.

   This discussion with the subject should be documented in the subject's medical record and only those subjects (or legally authorized representative) who have demonstrated an understanding of the risk/benefit of adrabetadex treatment should be permitted to continue in the study. The relevant sections of protocol amendment 3.0 where the above changes may apply, either in whole or in part, are provided in the Study Synopsis, Duration of Patient Participation; Section 7.3, Benefit-Risk Assessment; Section 13, Evaluation by Visit; and Section 15.1, Early Discontinuation.

In addition, text changes were made throughout the document to correct residual minor errors of grammar, style or abbreviation(s). These minor text changes were not considered substantive.

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1. SPONSOR SIGNATURE PAGE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States (US) Code of Federal Regulations (CFR) (where applicable), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Refer to the e-signature page

Approved: _____ **Date:** _____

[redacted]
[redacted]
Mallinckrodt Pharmaceuticals

[redacted]

2. INVESTIGATOR AGREEMENT

My signature confirms that I have read the VTS-270-001 clinical study protocol amendment and pledge that this study will be conducted in accordance with the protocol. In addition, by completing and signing the Statement of Investigator (FDA-Form 1572), I agree to abide, for the duration of this clinical trial, by all applicable laws and regulations including, but not limited to, the International Council for Harmonisation (ICH E6[R2)] Guideline for Good Clinical Practice (GCP), which has its ethical foundation in the Declaration of Helsinki, the US Code of Federal Regulations (CFR) (where appropriate), all applicable national and local regulations, protections for privacy, and provisions of my local Institutional Review Board.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Investigator's Signature	Date of Signature (DD Month YYYY)
Investigator's Name and Title (print)	

3. LIST OF ABBREVIATIONS

Abbreviations	Description of Abbreviations
ABR	Auditory brainstem response
ADL	Activities of daily living
AE	Adverse event
ALCOA	Attributable, legible, contemporaneous, original, accurate
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CNS	Central nervous system
CRF	Case report form
CSF	Cerebrospinal fluid
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	Electrocardiogram
EQ-5D-3L	EuroQol five-dimensional three-level version (health status instrument)
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HP-β-CD	2-hydroxypropyl-β-cyclodextrin
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug application

IRB	Institutional Review Board
IT	Intrathecal(ly)
LP	Lumbar puncture
NPC	Niemann-Pick type C disease
NPC1	Niemann-Pick type C1 disease (also gene and phenotype in humans)
NPC1	Niemann-Pick type C1 cat phenotype
Npc1	Niemann-Pick type C1 mouse phenotype
NPC-SS	NPC Severity Scale
PT	Prothrombin time
PTA	Pure tone audiometry
SAE	Serious adverse event
SUSAR	Serious and unexpected suspected adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
Vtesse	Vtesse LLC, a Mallinckrodt Pharmaceuticals company

4. SYNOPSIS

<table>
<tr><td>Title</td><td>Open-label Evaluation of Adrabetadex in Patients with Neurologic Manifestations of Niemann-Pick Type C Disease (NPC)</td></tr>
<tr><td>Sponsor</td><td>Vtesse LLC, a Mallinckrodt Pharmaceuticals Company</td></tr>
<tr><td>Number of Patients and Sites</td><td>Approximately 60 subjects at 30 sites in the United States (US)</td></tr>
<tr><td>Study Design</td><td>No new subjects can be enrolled in the study effective 20 January 2021.
This is a prospective, open-label study to evaluate the safety of adrabetadex in subjects with neurologic symptoms of Niemann-Pick type C disease (NPC). Eligible subjects will receive adrabetadex intrathecally (IT) via lumbar puncture (LP) every 2 weeks, and assessments of safety measures will be performed at prescribed intervals. Patients who had not previously been treated with adrabetadex will start at a dose of 400 mg, and subjects who had been previously receiving adrabetadex will receive their current stable dose of adrabetadex. Following a determination of a negative benefit/risk balance by the Sponsor, treatment will be allowed to continue up to 20 October 2021. Continuation of treatment is contingent upon re-consent by the subject/legally acceptable representative as well as approval by the Institutional Review Board (IRB)/Ethics Committee (EC) and Food and Drug Administration (FDA).</td></tr>
<tr><td>Dose Adjustment</td><td>Effective as of the date of Amendment 2 (21 April 2021), subjects will remain at their current dose or their dose may be decreased for tolerability reasons. A subject’s dose may not be increased.</td></tr>
<tr><td>Objectives</td><td>Primary and secondary objectives and endpoints are presented in the table below.
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<tr><th>Primary Objectives</th><th>Primary Endpoints</th></tr>
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• Laboratory changes from baseline (hematology, chemistry, coagulation, urinalysis.)
• Vital sign measurements.
• Physical and neurological examination.</td></tr>
</table>
IT=intrathecal(ly); LP=lumbar puncture; SAE=serious adverse event; TEAE=treatment-emergent adverse event</td></tr>
<tr><td>Outcome Measures</td><td>None. Efficacy assessments (NPC-severity scale [NPC-SS], Clinician Clinical Global Impression of Change [CGIC]) and self-reported outcomes (EuroQol five-dimensional three-level version [EQ-5D-3L]) will not be collected or analyzed.</td></tr>
</table>

Patient Selection Criteria	**No new subjects can be enrolled in the study effective 20 January 2021.** **Inclusion Criteria** To be included in the study, subjects must meet the following criteria: 1. Male or female and at least 4 years of age at time of screening. 2. Has a confirmed diagnosis of NPC and exhibits neurologic symptoms. 3. Patient or parent/guardian must provide written informed consent to participate in the study. In addition to parental consent, assent to participate must also be sought from minor children. 4. Has the ability to undergo LP and IT drug administration. 5. If taking miglustat (Zavesca®), must have been on a stable dose for the past 6 weeks and be willing to remain on a stable dose for the duration of participation in the study. Alternatively, subjects may elect to discontinue miglustat use and be eligible for entry into the study after undergoing a minimum 6-week washout period prior to study Day 1. 6. If there is a history of seizures, the condition must be adequately controlled, ie, the pattern of seizure activity must be stable and the subject must be on a stable dose and regimen of antiepileptic medication during the 1 month prior to Screening, with no change in dose or regimen up to and including the day of the first dose of adrabetadex (Day 1). 7. If not currently receiving adrabetadex, agrees to discontinue any other investigational treatments for at least 1 month prior to first dose of adrabetadex (Day 1); subjects who are currently receiving intrathecal adrabetadex are eligible to participate. 8. Sexually active females and males must use a medically acceptable method of contraception and must agree to continue use of this method for the duration of the study and for 30 days after participation in the study. Acceptable methods of contraception include barrier method with spermicide, intrauterine device, steroidal contraceptive in conjunction with a barrier method, abstinence, or same-sex partner. 9. Patient or parent/guardian must possess the ability, in the clinician's opinion, to understand and comply with study requirements, including clinical outcome measurements and instructions, for the entire duration of the study. 10. Caregiver, parent, guardian, or responsible adult must be able and willing to accompany the subject to study visits. **Exclusion Criteria** Patients will be excluded from the study if they meet any of the following criteria: 1. Weighs less than 15 kg. 2. Has uncontrolled psychosis. 3. Has a history of hypersensitivity reactions to any product containing 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) or has a history of hypersensitivity reactions or allergy to anesthesia/sedation. 4. Has received treatment with any other investigational product (other than adrabetadex) within 1 month prior to Day 1 of treatment. 5. Is a female who is pregnant or nursing. 6. Has a suspected infection of the central nervous system (CNS) or any systemic infection.

	7. Has a spinal deformity that, in the opinion of the clinician, is likely to impact the ability to perform repeated LPs. 8. In the opinion of the clinician, has a serious skin infection in the lumbar region within 2 months of entry into the study. 9. Has neutropenia, defined as an absolute neutrophil count of less than 1.0×10^9/L. 10. Has thrombocytopenia (platelet count less than 75×10^9/L). 11. Has an activated partial thromboplastin time (aPTT) or prothrombin time (PT) prolonged by greater than 1.5 times the upper limit of normal (ULN) or a known history of a bleeding disorder. 12. Has evidence of obstructive hydrocephalus or normal pressure hydrocephalus. 13. Has recently used anticoagulants (in the 2 weeks prior to first dose of adrabetadex [Day 1]). 14. In the opinion of the clinician, is unable to comply with the protocol or has a medical condition (eg, cardiovascular, respiratory, hematologic, neurologic, renal) that would potentially increase the risk of participation.
Test and Control Product, Dose, and Route of Administration	Adrabetadex will be provided in appropriately labeled vials, formulated as a 200 mg/mL injectable solution. A pharmacist/designee at each site will be responsible for dispensing or preparing the assigned dosage: 400 mg in 2 mL of solution, 600 mg in 3 mL of solution, or 900 mg in 4.5 mL of solution. The total infusion volume should be 10 mL; to achieve a final total volume of 10 mL, 0.9% sterile sodium chloride for injection, USP should be added to the adrabetadex solution. Doses other than 400 mg, 600 mg or 900 mg will be prepared in the same manner. Adrabetadex administration via LP will be conducted every 2 weeks. Sedation or anesthesia may be used as indicated by the clinical condition of the subject. Sedation and anesthesia will follow institutional guidelines and procedures. Ultrasound or other imaging techniques may be used to guide IT administration of adrabetadex. Adrabetadex will be administered as an IT slow bolus (1 to 2 minutes, depending on the volume administered) LP injection (maximum rate of administration = 4.5 mL/minute). Prior to the adrabetadex injection, a volume of cerebrospinal fluid approximately equal to the infusion volume (approximately 10 mL) will be removed. Patients will be required, if possible, to lie flat with feet elevated for 30 to 45 minutes following dosing. For the 3 days following each procedure, subjects should avoid acoustic overstimulation and minimize exposure to loud noises, eg, headphones for music or video games.
Duration of Patient Participation	Effective 20 January 2021, Mallinckrodt is recommending that treatment with adrabetadex be discontinued as soon as possible with appropriate clinician oversight. In recognition of the complexity of patient care, Mallinckrodt will make adrabetadex available for up to 9 months to allow time for the physician and subject/family to develop a transition plan. Continued treatment with adrabetadex is contingent upon a discussion between the treating physician and subject/family and re-consent. Likewise, continuation of treatment is also contingent upon approval by the respective IRB/Ethics Committee (EC) and health authority. After 21 June 2021 subjects may not continue to receive intrathecal adrabetadex, except for those subjects (and legally authorized representatives, as appropriate): • who appear to be benefiting from intrathecal adrabetadex based on the investigator's assessment, AND • who are aware of the risks associated with adrabetadex, including hearing loss, and understand that no significant differences were seen between subjects treated with

	adrabetadex and sham-treated subjects on any efficacy measures in this randomized, controlled trial.
Primary Safety Evaluations	• Summary of TEAEs, SAEs, discontinuation due to TEAEs, and deaths
Secondary Safety Evaluations	• Changes in audiologic testing • Laboratory changes from baseline (hematology, chemistry, coagulation, urinalysis) • Vital sign measurements • Physical and neurological examination.
Statistics	Data from the study will be summarized using descriptive statistics. No hypothesis testing will be conducted.
Date	23 June 2021

5. INTRODUCTION

Niemann-Pick disease type C (NPC) is a lethal, neurodegenerative, autosomal recessive disease caused by a mutation in the NPC gene. Mutations result in defective NPC protein, which affects the intracellular trafficking of lipids and cholesterol. The defective NPC protein leads to a progressive accumulation of unesterified cholesterol and other lipids in the central nervous system (CNS) and certain visceral organs (Vanier 2010; Ory 2000). Niemann-Pick type C1 (NPC1) disease has an estimated incidence of approximately 1 in 120,000 to 150,000 live births (Vanier 2003). The disease becomes apparent in patients at varying ages and with varying neurological manifestations; affected individuals typically exhibit ataxia, swallowing problems, and progressive impairment of motor and intellectual function in early childhood, and usually die in adolescence (Vanier 2010; Sévin 2007).

Vtesse LLC, a Mallinckrodt Pharmaceuticals Company (hereafter referred to as Mallinckrodt), is developing adrabetadex (USAN for VTS-270), a specific and well-characterized mixture of 2-hydroxypropyl-beta-cyclodextrin (HP-β-CD), a cyclic oligosaccharide, for the treatment of patients with NPC1. New treatments for NPC are urgently needed (Ottinger 2014). Currently there is no approved treatment for NPC1 in the United States (US). Miglustat (Zavesca®), approved in the European Union [EU] and used off label in the US, is a small iminosugar that partially inhibits glucosylceramide synthase and the synthesis of relevant glycosphingolipids. Miglustat use delays the onset of clinical signs in animal models of NPC1, but shows limited effect in humans (Patterson 2015; Patterson 2007; Lyseng-Williamson 2014; Pineda 2018).

HP-β-CD has shown improvements in a mouse model of NPC1, and in a cat model of NPC1 where it also showed the potential to preserve neurons and neurologic function, and impact cholesterol homeostasis, inflammation, and lifespan (Vite 2015; Ory 2017). Adrabetadex is believed to work in lysosomes (Rosenbaum 2010) by facilitating the release of abnormally accumulated cholesterol so that it can be metabolized normally (Liu 2012).

Although there are case reports from a few expert treating physicians indicating a potential benefit of adrabetadex in NPC patients treated over a period of time, a comprehensive evaluation of all available clinical data shows no clear evidence of benefit of adrabetadex in the treatment of neurologic symptoms of NPC. In view of established risks of treatment with adrabetadex, Mallinckrodt concludes that the benefit/risk balance is negative.

Effective 20 January 2021, Mallinckrodt is recommending that treatment with adrabetadex be discontinued as soon as possible with appropriate clinician oversight.

In recognition of the complexity of patient care, Mallinckrodt will make adrabetadex available for up to 9 months to allow time for the physician and subject/family to develop a transition plan. Continued treatment with adrabetadex is contingent upon a discussion between the treating physician and subject/family and re-consent. Likewise, continuation of treatment is also contingent upon approval by the respective Institutional Review Board (IRB)/Ethics Committee (EC) and health authority.

Hearing impairment has been associated with the use of adrabetadex in nonclinical and clinical studies. Disease progression in NPC1 (King 2014) is also associated with impacts on hearing. In

Study 13-CH-0001, mid- to high-frequency hearing impairment was documented in all 14 participants (Ory 2017). The hearing impairment associated with adrabetadex is complex. The mechanism of hearing impairment associated with adrabetadex is not fully understood; however, based on nonclinical data and clinical experience, the dose and/or duration of dosing of adrabetadex may possibly be related to hearing changes.

Information on nonclinical and clinical studies with adrabetadex can be found in the Investigator's Brochure.

6. STUDY OBJECTIVES, ENDPOINTS AND OUTCOME MEASURES

Primary and secondary objectives and endpoints are presented in the table below.

Primary Objectives	Primary Endpoints
To evaluate the longer-term safety and tolerability of adrabetadex administered IT via LP every 2 weeks	• Summary of TEAEs, SAEs, discontinuation due to TEAEs, and deaths.
Secondary Objectives	**Secondary Endpoints**
To summarize longer-term additional safety and tolerability of adrabetadex administered IT via LP every 2 weeks	• Changes in audiologic testing. • Laboratory changes from baseline (hematology, chemistry, coagulation, urinalysis). • Vital sign measurements. • Physical and neurological examination.

IT=intrathecal(ly); LP=lumbar puncture; SAE=serious adverse event; TEAE=treatment-emergent adverse event

7. TREATMENT AND ASSESSMENT PLAN

7.1. Study Design

This is a prospective, open-label study to evaluate the longer-term safety of adrabetadex in subjects with neurological symptoms of NPC type C disease. The study is anticipated to enroll approximately 60 subjects from 30 sites in the US. Eligible subjects will receive adrabetadex intrathecally (IT) via lumbar puncture (LP) every 2 weeks, and assessments of safety measures will be performed at prescribed intervals. Patients who have not previously been treated with adrabetadex will start at a dose of 400 mg, and subjects who have been previously receiving adrabetadex will receive their current stable dose of adrabetadex.

7.2. Dose Adjustment

Patients who, in the opinion of the clinician, experience a drug-related adverse event (AE) after any IT treatment that is considered clinically relevant and impactful to the subject's function may have their dose reduced back to the previously tolerated dose. The lowest dose is 400 mg; subjects unable to tolerate 400 mg will be discontinued from the study.

The medical monitor can be consulted when there are questions regarding dose adjustment.

7.3 Risk/Benefit Assessment

Niemann-Pick type C1 () is a fatal disorder with both systemic and CNS signs and symptoms. Currently, no treatment has been shown to alter the course of the disease in a clinically meaningful manner in subjects with NPC1 disease. Although age of onset varies, subjects typically develop progressive cerebellar dysfunction, hearing loss, and motor and cognitive deterioration with death typically occurring during adolescence.

2-hydroxypropyl-β-cyclodextrin (HP-β-CD) administered IT into the cerebrospinal fluid (CSF) has shown effectiveness in the naturally occurring mouse and cat models of NPC1. Importantly, it decreased cerebellar neuronal loss, delaying or preventing the development of the neurologic signs and symptoms of the disease. In the cat, there was an 8-fold prolongation of survival. Efficacy was associated with dose-related and irreversible ototoxicity at the highest and maximally efficacious dose tested.

There are several ongoing independent investigations in which subjects with NPC1 are receiving VTS-270 (under Investigational New Drug application [IND]).

In the Phase 1/2a study (Study 13-CH-0001), an effect of adrabetadex above that seen with miglustat cannot be demonstrated in a post-hoc comparison of the NPC-SS sub-setted by baseline miglustat use.

Analysis of data from Part A/B of Study VTS301, a prospective, randomized, double-blind, sham-controlled trial of adrabetadex in subjects with neurologic manifestations of NPC1 shows no benefit of adrabetadex on the pre-specified co-primary endpoints, which were the sum of 4 components of the Neimann Pick Type C Severity Scale (NPC-SS): ambulation, fine motor, cognition, and swallowing and the blinded Clinician-Global Impression of Change (CGIC). A post-hoc analysis evaluating the effect of miglustat use showed that subjects receiving miglustat (with or without adrabetadex) showed evidence of disease stabilization but subjects receiving

adrabetadex without miglustat showed disease worsening comparable to sham subjects not on miglustat.

Vtesse has been provided data from 3 subjects being treated under an iIND at Rush University Medical Center who have been receiving IT VTS-270 every 2 weeks, the dosing regimen used in the *NPC1* mutant cat model that was shown to improve neurologic symptoms and improve survival. It is important to note that this regimen is different from that employed in the National Institutes of Health phase 1/2a study, where subjects are dosed once a month.

In the proposed study, it is expected that subjects may experience some degree of nonreversible hearing loss; how much of this hearing loss may be attributable to NPC1 disease progression, which occurs in approximately 64% of subjects, versus study drug toxicity is not ascertainable at the present time. At this stage of clinical development, apart from animal model data and uncontrolled clinical reports, there is at present only a theoretical benefit and a known risk of ototoxicity in those subjects randomized to study drug. However, given the fatal and irreversible nature of NPC1, the continued clinical evaluation of efficacy, despite potential drug-related ototoxicity and in the absence of other known dose-limiting AEs or SAEs, is supported, only in those subjects (or legally authorized representative):

- who appear to be benefiting from intrathecal adrabetadex based on the investigator's assessment, AND
- who are aware of the risks associated with adrabetadex, including hearing loss, and understand that no significant differences were seen between subjects treated with adrabetadex and sham-treated subjects on any efficacy measures in this randomized, controlled trial.

8. CRITERIA FOR EVALUATION

8.1. Primary Safety Evaluations

- Adverse events.

8.2. Secondary Safety Evaluations

- Audiologic testing.
- Clinical laboratory tests (hematology, chemistry, coagulation, and urinalysis).
- Vital signs.
- Physical and neurological examinations.

9. PATIENT SELECTION

Effective 20 January 2021, no new subjects can be enrolled in the study.

9.1. Inclusion Criteria

To be included in the study, subjects must meet the following criteria:

1. Male or female and at least 4 years of age at time of screening.
2. Has a confirmed diagnosis of NPC and exhibits neurologic symptoms.
3. Patient or parent/guardian must provide written informed consent to participate in the study. In addition to parental consent, assent to participate must also be sought from minor children.
4. Has the ability to undergo LP and IT drug administration.
5. If taking miglustat (Zavesca®), must have been on a stable dose for the past 6 weeks and be willing to remain on a stable dose for the duration of participation in the study. Alternatively, subjects may elect to discontinue miglustat use and be eligible for entry into the study after undergoing a minimum 6-week washout period prior to study Day 1.
6. If there is a history of seizures, the condition must be adequately controlled, ie, the pattern of seizure activity must be stable and the subject must be on a stable dose and regimen of antiepileptic medication during the 1 month prior to Screening, with no change in dose or regimen up to and including the day of the first dose of adrabetadex (Day 1).
7. If not currently receiving adrabetadex, agrees to discontinue any other investigational treatments for at least 1 month prior to first dose of adrabetadex (Day 1); subjects who are currently receiving intrathecal adrabetadex are eligible to participate.
8. Sexually active females and males must use a medically acceptable method of contraception and must agree to continue use of this method for the duration of the study and for 30 days after participation in the study. Acceptable methods of contraception include barrier method with spermicide, intrauterine device, steroidal contraceptive in conjunction with a barrier method, abstinence, or same-sex partner.
9. Patient or parent/guardian must possess the ability, in the clinician's opinion, to understand and comply with study requirements, including clinical outcome measurements and instructions, for the entire duration of the study.
10. Caregiver, parent, guardian, or responsible adult must be able and willing to accompany the subject to study visits.

9.2. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

1. Weighs less than 15 kg.
2. Has uncontrolled psychosis.

3. Has a history of hypersensitivity reactions to any product containing HP-β-CD or has a history of hypersensitivity reactions or allergy to anesthesia/sedation.
4. Has received treatment with any investigational product (other than adrabetadex) within 1 month prior to Day 1 of treatment.
5. Is a female who is pregnant or nursing.
6. Has suspected infection of the CNS or any systemic infection.
7. Has a spinal deformity that, in the opinion of the clinician, could impact the ability to perform repeated LPs.
8. In the opinion of the clinician, has a serious skin infection in the lumbar region within 2 months of entry into the study.
9. Has neutropenia, defined as an absolute neutrophil count of less than 1.0×10^9/L.
10. Has thrombocytopenia (platelet count of less than 75×10^9/L).
11. Has an activated partial thromboplastin time (aPTT) or prothrombin time (PT) prolonged by greater than 1.5 times the upper limit of normal (ULN) or a known history of a bleeding disorder.
12. Has evidence of obstructive hydrocephalus or normal pressure hydrocephalus.
13. Has recently used anticoagulants (in past 2 weeks prior to first dose of adrabetadex [Day 1]).
14. In the opinion of the clinician, is unable to comply with the study or has a medical condition (eg, cardiovascular, respiratory, hematologic, neurologic, renal) that would potentially increase the risk of participation.

10. CONCOMITANT MEDICATIONS

Any changes to medications should be noted in the subject's medical record/source documents. Concomitant medications must be added to the appropriate case report form (CRF).

Use of anticoagulants is prohibited during the study. The use of other investigational medications and treatments is also prohibited. (If a clinician has any questions about whether a medication is allowed or prohibited, he/she should contact the medical monitor).

11. TREATMENTS

11.1. Method of Assigning Patients to Treatment Groups

Effective 20 January 2021, no new subjects can be enrolled in the study.

11.2. Blinding

This is an open-label study.

11.3. Test and Control Product

Adrabetadex will be provided in appropriately labeled vials, formulated as a 200 mg/mL injectable solution. A pharmacist/designee at each study site will be responsible for dispensing or preparing the assigned dosage. The 400 mg dose will be administered in 2 mL of solution; a 600 mg dose will be administered in 3 mL of solution, and a 900 mg dose will be administered in 4.5 mL of solution. The total infusion volume should be 10 mL; to achieve a final total volume of 10 mL, 0.9% sterile sodium chloride for injection, USP should be added to the adrabetadex solution. Doses other than those provided in the examples above will be prepared in the same manner.

No control product will be used in the study.

11.3.1. Formulation of Test Product

The formulation and filling of adrabetadex involves dissolving the Active Pharmaceutical Ingredient in water for injection, adding sodium chloride to 0.9% weight/volume (w/v) and adjusting the pH if necessary with sodium hydroxide or hydrochloric acid, and bringing to the final volume with water for injection. The product is then filled into vials (4.5 mL fill with sufficient overfill to allow product withdrawal) and autoclaved. The product is a clear, colorless solution that is free from visible foreign matter.

11.3.2. Packaging and Labeling

Preparation, packaging, and labeling of all study drugs will be in accordance with standard operating procedures, Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations. All investigational drug used in this study will be prepared, packaged, and labeled under the responsibility of the sponsor and its designees. Refer to the Pharmacy Manual for information on packaging and labeling.

11.3.3. Supply of Investigational Drug at the Site

The sponsor (or designee) will ship adrabetadex to the study sites. The initial adrabetadex shipment will occur after site activation (ie, all required regulatory documentation has been received by the sponsor or designee, and a contract has been executed). Subsequent adrabetadex shipments will be made after site request for resupply. Instructions for ordering, preparing, and handling study drug are provided in the Pharmacy Manual.

11.3.4. Dispensing

A pharmacist/designee at each study site will be responsible for preparing the assigned dosage in a sterile environment (eg, under a laminar airflow hood or other clean room environment). Alternatively, the pharmacist/designee may dispense the assigned dosage for subsequent preparation by the IT administrator within the sterile field of the LP procedure room.

11.3.5. Storage

Investigational product should be stored between 15 and 25°C (59-77°F), inclusive. The pharmacy/designee is responsible for the secure and temperature-controlled storage of adrabetadex. This includes daily documentation of the storage and temperature conditions of adrabetadex as described in the Pharmacy Manual.

11.3.6. Investigational Drug Accountability

Drug supply will be managed by a designee at the site and the pharmacy/designee will maintain an accountability log for adrabetadex. The clinician is responsible for the accountability of the investigational product. This will include documentation of receipt, storage, and dispensing of adrabetadex. The clinician will return or destroy (per instruction of sponsor or designee) unused investigational drug at the conclusion of the study.

11.4. Dosage/Dosing Regimen

Adrabetadex will be provided in labeled 10 mL Type I glass vials, formulated as a 200 mg/mL injectable solution (4.5 mL fill with overfill). Examples of how the assigned dosage will be administered are provided in Table 1.

The total infusion volume should be 10 mL; to achieve a final total volume of 10 mL, 0.9% sterile sodium chloride for injection, USP should be added to the adrabetadex solution (eg, add 8 mL of 0.9% sodium chloride to 400 mg dose).

Adrabetadex administration via LP will be conducted every 2 weeks. Sedation or anesthesia may be used as indicated by the clinical condition of the subject. Sedation and anesthesia will follow institutional guidelines and procedures. Ultrasound or other imaging techniques may be used to guide IT administration of adrabetadex.

Treatment with adrabetadex will continue until the clinician considers adrabetadex to be no longer beneficial to the subject, the subject withdraws from the study, adrabetadex receives marketing authorization in the US, or the development program is discontinued. There are no adjustments of dosing regimen for weight or subject age. Patients participating in this study should not expect additional access to adrabetadex beyond this study.

11.5. Adrabetadex Administration by Lumbar Puncture

Adrabetadex will be administered as an IT slow bolus (1 to 2 minutes, depending on the volume administered) LP injection (maximum rate of administration = 4.5 mL/minute). The volume of the injection will be approximately 10 mL (Table 1). Prior to the adrabetadex injection, a volume of cerebrospinal fluid approximately equal to the infusion volume is to be removed. Anesthesia or sedation will be used for the IT dosing procedure, following institutional guidelines and

procedures. Patients will be required, if possible, to lie flat for 30 to 45 minutes following dosing with feet elevated. For the 3 days following each procedure, subjects should avoid acoustic overstimulation and minimize exposure to loud noises, eg, headphones for music or video games.

Table 1: Adrabetadex Dose and Infusion Volume

Dose Group[a]	Adrabetadex Volume	Volume of 0.9% NaCL	Total Infusion Volume
400 mg	2.0 mL	8 mL	10 mL
600 mg	3.0 mL	7 mL	10 mL
900 mg	4.5 mL	5.5 mL	10 mL

[a] Doses other than those provided in the examples above will be prepared in the same manner.
NaCL = sodium chloride.

11.6. Measures of Treatment Compliance

Adrabetadex will be administered at the clinical site by a study clinician, and the amount of drug infused will be recorded in the dose preparation worksheet and maintained in the subject's medical record/source documents.

12. STUDY PROCEDURES AND GUIDELINES

A schedule of assessments and procedures by time point is presented in Section 22.

Prior to conducting any protocol-related activities, written informed consent must be signed and dated by the subject or the subject's legal representative. If appropriate, assent must also be obtained prior to conducting any protocol-related activities.

Patients who have been screened, meet eligibility criteria, and have provided signed written informed consent will be enrolled. Baseline assessments will be completed at Screening, as described in Table 4.

12.1. General Assessments

12.1.1. Demographic Information

Demographic information (eg, date of birth, gender, race, ethnicity) will be recorded at Screening.

12.1.2. Medical History

Relevant medical history, including history of NPC (eg, diagnosis date, prior treatments), other pertinent respiratory history, and information regarding underlying diseases, will be recorded at Screening.

12.2. Safety Assessments

12.2.1. Prior and Concomitant Medications

Any medications used to treat NPC in the past (no time limit) and any other medications taken within 30 days of the Screening Visit will be collected at Screening. All concomitant medication and concurrent therapies will be documented at each study visit through Follow-up Visit 3. Dose, route, unit, frequency of administration, indication for administration, and dates of treatment will be captured using the appropriate CRF.

12.2.2. Adverse Events

Information regarding occurrence of AEs will be captured throughout the study, beginning with the signing of informed consent and ending after procedures for Follow-up Visit 3. Information will be recorded on the appropriate CRFs. Definitions associated with AEs and the procedures for reporting them are presented in Section 14.1 and Section 14.2, respectively.

Any time a subject has a reported AE of special interest, ie, AE related to hearing impairment (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or higher), audiologic assessments need to be conducted. Audiologic assessments may also be conducted at the discretion of the investigator for hearing impairment AEs of CTCAE grade < 3(Section 12.2.6.1, Section 14.1.8).

12.2.3. Vital Signs

Blood pressure, pulse rate, respirations, and body temperature will be measured after a 5-minute rest in a supine position. At all visits when adrabetadex is administered, vital signs will be measured at two different times: 1) prior to LP and 2) after recovery from LP (as defined by institutional practices).

12.2.4. Physical Examination

At Screening, a complete physical examination will be performed by either the clinician or a designee who is a physician. Qualified staff (physician, nurse practitioner, registered nurse, or physician assistant) may complete an abbreviated physical examination at all other visits (every 6 months after first dose; first 6-month time point = Week 26). This abbreviated examination focuses on body systems with a change in health or new symptoms. New abnormal findings must be documented, captured as AEs, and followed by a physician or other qualified staff until the abnormality resolves or stabilizes, or until the subject discontinues from the study for reasons other than the AE. Weight will be collected at every visit.

12.2.5. Neurological Examination

A complete neurological examination will be performed by an experienced clinician at Screening and then every 12 months after first dose. An abbreviated neurological examination comprising assessments of eye movements, coordination, gait, and reflexes, will be conducted at every 6 months in between. A complete neurological examination will be conducted at End of Study/Early Termination. Clinically significant changes in the neurological examination will be identified by the investigator, captured as AEs (if not related to medical history, underlying disease or to another existing AE), and followed by a physician or other qualified staff until the abnormality resolves or stabilizes, or until the subject discontinues from the study for reasons other than the AE.

12.2.6. Audiologic Evaluation

Acoustic reflexes, pure tone audiometry (PTA), and auditory brainstem responses (ABRs) have been used to date to evaluate abnormalities that have been previously reported in NPC subjects (King 2014). As of 20 January 2021, ABRs will not be collected, as the potential risks with the procedure outweigh the potential benefit of the data.

12.2.6.1. Audiologic Testing

Audiologic evaluations will be performed at the time points specified in Table 4.

Audiologic assessments will include:

- Evaluation of middle ear function (tympanometry).
- Air conduction PTA.
- Speech reception threshold.

- Bone conduction PTA (only at Screening and when a clinically significant change in hearing is observed in air conduction PTA).

  A clinically significant change is defined as:

  - ≥20 dB increase at any one test frequency relative to baseline measure.
  - ≥10 dB increase at any two adjacent test frequencies relative to baseline measure.
  - Loss of response at three consecutive test frequencies where responses were previously obtained (specifically the highest frequencies tested) on baseline measure.

12.2.7. Clinical Laboratory Measurements

All clinical laboratory samples obtained will be sent to central or local laboratories as specified in the Laboratory Manual.

12.2.7.1. Hematology

Blood will be obtained for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count), and coagulation studies (PT and aPTT) at Screening and every 6 months after first dose (first 6-month time point = Week 26). If platelet count is below 75×10^9/L, the platelet count should be repeated and the clinician will need to make a clinical determination whether the subject can be dosed or should be discontinued from the study.

12.2.7.2. Blood Chemistry Profile

Blood will be obtained for determination of serum sodium, potassium, chloride, bicarbonate, calcium, random glucose, blood urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin, albumin, and lactate dehydrogenase at Screening and every 6 months after first dose (first 6-month time point = Week 26).

12.2.7.3. Urinalysis

Urine will be obtained for determination of color, specific gravity, pH, protein, glucose, ketones, and blood. Urinalysis will be performed at Screening and every 6 months after first dose (first 6-month time point = Week 26).

12.2.7.4. Cerebrospinal Fluid for Routine Clinical Laboratory Tests

At the time of first treatment with adrabetadex in the study, a sample of CSF will be collected from treatment-naïve subjects just prior to adrabetadex infusion to be used for routine CSF analysis (red blood cell count, white blood cell count, white blood cell differential, glucose, and protein).

12.2.7.5. Pregnancy Test

For female subjects who are of childbearing potential, a serum pregnancy test will be obtained at Screening, and a urine pregnancy test will be obtained every 6 months after the first dose (first 6-month time point = Week 26).

12.2.8. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be obtained and interpreted locally (at the study sites) for baseline screening/safety monitoring at the Screening visit.

12.3. Efficacy and Quality of Life Assessments

Efficacy assessments (NPC severity scale [NPC-SS], Clinician Clinical Global Impression of Change [CGIC]) and self-reported outcomes (EuroQol five-dimensional three-level version [EQ-5D-3L]) will not be collected.

13. EVALUATIONS BY VISIT

See Table 4, Schedule of Assessments and Procedures.

For subjects continuing in the study after 21 June 2021, the investigator must assess whether the subject is benefiting from treatment with intrathecal adrabetadex. For those subjectss who appear to benefit from treatment, the investigator must review with them the risks associated with adrabetadex, including hearing loss, and the data from the randomized, controlled trial that demonstrated no significant differences between subjectss treated with adrabetadex and sham-treated subjectss on any efficacy measures. This discussion should be documented in the subject's medical record and only those subjects (or legally authorized representative) who have demonstrated an understanding of the risk/benefit of adrabetadex treatment should be permitted to continue in the study.

14. ADVERSE EVENTS – DEFINITIONS AND REPORTING

14.1. Definitions

This section defines the different categories of AEs. The procedures for reporting AEs are described in Section 14.2.

14.1.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (Code of Federal Regulations [CFR] Title 21 Part 312.32).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without any judgment about causality (GCP definition).

14.1.2. Suspected Adverse Reaction

A suspected adverse reaction is a subset of all AEs for which there is reasonable possibility (ie, evidence to suggest a causal relationship between the drug and the AE) that the drug caused the event (21 CFR 312.32).

14.1.3. Serious Adverse Event

An AE or suspected adverse reaction is considered serious if, in the view of either the clinician or sponsor, it results in any of the following outcomes (21 CFR 312.32):

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization (hospitalizations for less than 24 hours with no admission are not considered “hospitalization”)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Other important medical events may also be considered SAEs when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

Procedures for reporting SAEs are described in Section 14.2.

14.1.4. Unexpected Adverse Event/Unexpected Suspected Adverse Reaction

An unexpected AE (or unexpected suspected adverse reaction) is any AE or suspected adverse reaction that is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed if an Investigator’s Brochure is not required/available, or is not consistent with the risk information described in the general treatment plan (21 CFR 312.32). This also refers to AEs or suspected adverse reactions mentioned in the Investigator’s Brochure

as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the investigational product.

14.1.5. Serious and Unexpected Suspected Adverse Reaction

A serious and unexpected suspected adverse reaction (SUSAR) is any SAE related to investigational product, the specificity or severity of which is not consistent with those noted in the current protocol, Investigator's Brochure, or product labeling (no labeling exists for adrabetadex since it has not been approved for marketing). This also refers to AEs or suspected adverse reactions mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the investigational product.

14.1.6. Adverse Event Severity

The CTCAE, Version 4.03 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the AE is not covered by the grading in the CTCAE, the general guidelines of the CTCAE grades should be applied (see Table 2) for grading the severity.

Table 2: Adverse Event Severity Grading

Severity (Toxicity Grade)	Description
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 instrument 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.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
ADL = activities of daily living; AE=adverse event.

14.1.7. Adverse Event Relationship to Investigational Drug

The relationship of an AE to the investigational drug should be assessed using the following guidelines in Table 3.

Table 3: AE Relationship to Investigational Drug

Relationship to Drug	Comment
Definite	The AE follows a reasonable sequence from the time of study drug administration, follows a known response pattern of the study drug class, is confirmed by improvement on stopping the study drug, and/or the study drug definitely causes the event.
Probable	The AE follows a reasonable sequence from the time of study drug administration, follows a known response pattern of the study drug class, is confirmed by improvement on stopping the study drug, and/or is the most likely of all causes.
Possible	The AE follows a reasonable sequence from the time of study drug administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
Unrelated	Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE.

AE=adverse event.

14.1.8. Adverse Events of Special Interest – Clinically Significant Hearing Impairment

NPC and adrabetadex are both associated with hearing impairment. The severity and site of lesion of auditory damage may differ between adrabetadex- and NPC-induced hearing impairment; some lesion sites overlap, whereas some are more likely only in NPC. In addition, NPC hearing impairment progresses more slowly than drug-induced hearing impairment, which may occur abruptly within 24 hours of infusion at a given dose.

Any time a subject has a reported clinical AE of special interest, ie, AE of hearing impairment (CTCAE grade 3 or higher) audiologic assessments need to be conducted. Audiologic assessments may also be conducted at the discretion of the investigator for hearing impairment AEs of CTCAE grade < 3. Hearing impairment AE evaluation is described in Section 12.2.6.1.

14.2. Reporting of Adverse Events and Pregnancies

14.2.1. Reporting Adverse Events

Information regarding occurrence of AEs will be captured throughout the study beginning with signing of the informed consent form (ICF) and ending with Follow-up Visit 3. A qualified clinician (eg, physician, physician assistant, nurse practitioner) will be specifically designated to assess and follow AEs for the subject being treated with adrabetadex. This clinician will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the subject's medical record/source documents. Duration (start and stop dates and times), severity/grade (Section 14.1.6), outcome, treatment, relationship to investigational

drug (Section 14.1.7), and any corrective actions taken will be recorded on CRFs. Each AE should also be categorized as "serious" or "non-serious."

14.2.2. Reporting Serious Adverse Events

Clinical sites will document all SAEs that occur (whether or not related to adrabetadex) in the subject's medical record/source documents *and* on the appropriate CRFs. Information regarding occurrence of SAEs will be captured throughout the study beginning with signing of the ICF and ending with Follow-up Visit 3.

All SAEs will be reviewed by the site clinician, and reported within 24 hours of the site learning of the event. Sites will report applicable SAE information to the sponsor or designee according to the instructions in the Operations Manual.

The site will notify the sponsor or designee of additional information on the SAE, or follow-up information on the initial SAE report, as soon as relevant information is available.

In accordance with the standard operating procedures and policies of the IRB, the site clinician will report SAEs to the IRB.

14.2.3. Reporting Pregnancy

The sponsor must be informed within 24 hours upon learning that a subject, or a male subject's partner, has become pregnant any time after the first dose of adrabetadex until 60 days after the last dose of adrabetadex. The pregnancy form should be used to report the pregnancy to the sponsor or designee. The pregnant subject should be discontinued from the study per the exclusion criteria (Section 9.2). Pregnancy is not generally considered an AE; however, subject pregnancies (or pregnancy of a male subject's partner) must be followed until termination of pregnancy or the birth of the child. The pregnancy outcome form should be used to report information regarding the status of the infant and mother.

Patients who become pregnant will be discontinued from treatment.

15. DISCONTINUATION AND REPLACEMENT OF PATIENTS

15.1. Early Discontinuation

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the sponsor feels that it is not in the subject's best interest to continue.

The sponsor has made a determination of a negative benefit/risk balance for adrabetadex. Subjects in this study will be allowed to continue treatment until 20 October 2021 to allow time to start alternative treatment unless there are additional time restrictions mandated by an IRB/EC or health authority.

After 21 June 2021, subjects must be discontinued from the study if the investigator does not consider them to be benefiting from treatment and/or they do not understand the risks associated with adrabetadex, including hearing loss, and that the data from the randomized, controlled trial did not demonstrate significant differences between subjects treated with adrabetadex and sham-treated subjects on any efficacy measures. This discussion should be documented in the subject's medical record and only those subjects (or legally authorized representative) who have demonstrated an understanding of the risk/benefit of adrabetadex treatment should be permitted to continue in the study.

Following the last dose of adrabetadex, subjects will be asked to return to the clinic for a follow-up safety visit. Procedures for the End of Study visit and the safety follow-up visit are noted in Table 5.

If a subject is withdrawn from treatment due to an AE, the subject will be followed and treated by the clinician until the abnormal parameter or symptom has resolved or stabilized.

Reasonable attempts will be made by the clinician to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

15.2. Replacement of Patients

Patients who discontinue from the study will not be replaced.

16. PROTOCOL DEVIATIONS

A protocol deviation occurs when the subject or clinician fails to adhere to study requirements. Major protocol deviations are those that involve:

1. Deviations from the required consent procedure.
2. Failure to meet inclusion or exclusion criteria.
3. Wrong treatment or incorrect dose.
4. Failure to follow any other protocol-specified procedure that, in the opinion of the clinician, sponsor, or sponsor representative, impacts the integrity of the study or puts the study subjects at increased risk.

All major protocol deviations will be reported to the IRB as the IRB regulations dictate.

17. DATA MONITORING COMMITTEE

No data monitoring committee will be used in this study.

18. STATISTICAL METHODS AND CONSIDERATIONS

Study data will be summarized using descriptive statistics. No hypothesis testing will be conducted. Descriptive statistics (N, mean, median, standard deviation) will be provided for continuous variables and counts and proportions (N, %) will be provided for categorical variables. All analyses will be based on available data. Missing data will not be imputed.

Data generated in this study may be pooled with others in the adrabetadex clinical program or from historical cohort for comparison. Details of any pooled analysis will be prospectively documented in a separate statistical analysis plan.

Summary of Safety Endpoints

Treatment-emergent AEs (TEAEs) are defined as those AEs that are not present at Day 1 of study or represent the exacerbation of a pre-existing condition during the treatment period.

All AEs reported in this study will be coded using version 23.1 of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term, and the primary system organ class will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of subjects with at least 1 TEAE by system organ class and preferred term.
- TEAEs by severity, presented by system organ class and preferred term.
- TEAEs by relationship to treatment (related, not related), presented by system organ class and preferred term.

Deaths and other SAEs will be listed and summarized. TEAEs leading to permanent treatment discontinuation will be listed and summarized.

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest. Listings will be provided with flags indicating the out of laboratory range values.

Vital signs (body temperature, pulse rate, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Changes in audiologic testing will be summarized by visit based on accumulated data at the time of analysis.

19. DATA COLLECTION, RETENTION, AND MONITORING

19.1. Data Collection Instruments

The clinician will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the investigational drug. Case report forms will be used to collect study data.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the CRF when the information corresponding to that visit is available. Patients will not be identified by name in the study database or on any study documents to be collected by the sponsor (or designee), but will be identified by a site number and subject identification number.

If a correction is required in the CRF, it should be made by a using a single line to strike out any text. The staff member making the correction should initial and date the correction. All corrections in study-related documents must follow ALCOA (ie, attributable, legible, contemporaneous, original, accurate) data integrity principals.

The clinician is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the clinician.

19.2. Data Management Procedures

The data will be entered into the subject's medical records/source documents and CRFs. The sponsor or designee will be responsible for data processing, in accordance with procedural documentation.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH and EU guidelines for the handling and analysis of data for clinical trials.

19.3. Availability and Retention of Study Records

The clinician must make study data accessible to the monitor, other authorized representatives of the sponsor (or designee), IRB, and regulatory agency inspectors upon request. A file for each subject must be maintained that includes the signed ICF, confidentiality commitments, assent form, and copies of all source documentation related to that subject. The clinician must ensure the reliability and availability of source documents from which the information in the CRF was derived.

All study documents (subject files, signed ICFs, copies of CRFs, etc.) must be kept secured for a period of 2 years following marketing of the investigational product or for 2 years after sites have been notified that the Investigational New Drug application has been discontinued. There may be other circumstances for which the sponsor is required to maintain study records and, therefore, the sponsor should be contacted prior to removing study records for any reason.

19.4. Monitoring

Monitoring of data will be conducted by the sponsor or designee according to ICH Guidelines for GCP (E6). By signing this protocol, the clinician grants permission to the sponsor (or

designee) and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

19.5. Patient Confidentiality

In order to maintain subject confidentiality, only a site number and subject identification number will identify all study subjects on documentation submitted to the sponsor. Additional subject confidentiality issues (if applicable) are covered in the Study Agreement.

20. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, IRB requirements, and local regulations.

To maintain confidentiality, all laboratory specimens, CRFs, reports, and other records will be identified by a coded number. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the applicable regulatory authority. The clinician must also comply with all applicable privacy regulations (eg, Health Insurance Portability and Accountability Act of 1996, European Union Data Protection Directive 95/46/EC).

20.1. Protocol Amendments

Any amendment to the study protocol will be written by the sponsor. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to subjects. A study amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRBs are notified as soon as possible.

20.2. Institutional Review Boards

The protocol and consent form will be reviewed and approved by the IRB of each participating site prior to study initiation. Serious adverse events regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the clinician will keep the IRB informed as to the progress of the study. The clinician will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study and the ICF will be in the possession of the clinician before the study is initiated. The IRB's unconditional approval statement will be transmitted by the clinician to the sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Study and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse events occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect

adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

20.3. Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, and local regulations.

The informed consent document will contain the elements required by the ICH and will also comply with 21 CFR Part 50. The clinician will send an IRB-approved copy of the ICF to the sponsor (or designee) for the study file.

A properly executed, written ICF will be obtained from each subject prior to entering the subject into the study. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the IRB, assent from the subject will also be obtained. If a subject is unable to sign the ICF and privacy authorization (if applicable), a legal representative may sign for the subject. A copy of the signed ICF (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

Separate consent (on the same ICF) will be obtained from subjects providing blood samples to use for research on plasma bile acid biomarkers.

20.4. Publications

The sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results.

Terms and provisions of the investigator's publication rights are governed by the Publication Section in the Clinical Trial Agreement.

20.5. Clinician Responsibilities

By signing the Agreement of Clinician form, the clinician agrees to:

1. Conduct the study in accordance with the protocol and make changes only after notifying the sponsor (or designee), except when to protect the safety, rights, or welfare of subjects.
2. Personally conduct or supervise the study.
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in 21 CFR, Parts 50 and 56.
4. Report to the sponsor or designee any AEs that occur in the course of the study, in accordance with 21 CFR 312.64.
5. Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with 21 CFR 312.62 and make those records available for inspection with the sponsor (or designee).

7. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the study.
8. Promptly report to the IRB and the sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and required safety reports).
9. Seek IRB approval before any changes are made in the study, except when necessary to eliminate hazards to the subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in 21 CFR Part 312.

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22. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 4: Schedule of Assessments and Procedures – Screening through Week 26

Visit Number		**1**	**2 – 13**	**14**
Day	**–45 through –1**	**1**	**15 – 169**	**183**
Window (weeks)			**(± 1)**	**(± 1)**
Time Point or Frequency	**Screening**	**1st Dose[a]**	**Every 2 weeks (Weeks 2 – 24)**	**Week 26**
Procedure				
Informed consent	X			
Confirm patient eligibility	X	X		
Demographics	X			
Medical history [b]	X			
Clinician-CGIC assessment [c]	X			X
NPC-SS Intake [c]	X			X
EQ-5D-3L assessment [c]	X			X
Height	X			
Weight	X	X	X	X
Vital signs [d,e]	X	X[f]	X[f]	X[f]
Physical examination [g]	X			X
Urinalysis	X			X
Serum pregnancy test	X			
Urine pregnancy test				X
12-lead ECG	X			
Neurological examination [h]	X			X
Audiologic testing [i]	X			X
Diagnostic threshold auditory brainstem response [j]	X			

Visit Number		1	2 – 13	14
Day	–45 through –1	1	15 – 169	183
Window (weeks)			(± 1)	(± 1)
Time Point or Frequency	Screening	1st Dose[a]	Every 2 weeks (Weeks 2 – 24)	Week 26
Procedure				
Blood for clinical laboratory tests [k]	X			X
Blood for plasma bile acids [l]	X			X
LP and adrabetadex administration[m]		X	X	X
CSF for routine CSF analysis [n]		X		
Adverse events [e]	X	X	X	X
Prior and concomitant medications/therapies [e]	X [o]	X	X	X

[a] Patients who are already receiving adrabetadex may be screened and enrolled (receive first dose) on the same day.
[b] Medical history includes history of NPC, diagnosis date, and prior NPC treatments.
[c] The efficacy assessments (Clinician-CGIC, NPC-SS, and EQ-5D-3L) should be performed *prior to other assessments and procedures*. In addition, the Clinician-CGIC should be conducted prior to other efficacy assessments.
[d] Vital signs (blood pressure, pulse rate, respirations, and body temperature) will be recorded following a 5-minute rest in supine position.
[e] The collection period of adverse events, and concomitant medications will begin after informed consent is obtained and end at Follow-up Visit 3; the collection of vital signs will begin after informed consent is obtained and end at Follow-up Visit 1 (see Table 6).
[f] A second set of vital signs will be recorded following recovery from LP.
[g] Complete physical examination at Screening; abbreviated physical examination at all other visits.
[h] Complete neurological examination at Screening; abbreviated neurological examination at Week 26. A complete neurological examination will be conducted at End of Study/ Early Termination.
[i] Audiologic evaluations will also be performed prior to each dose escalation (within72 hours prior with results available at the study visit), within 72 hours prior to the subsequent visit following a dose escalation (with results available at the study visit) per Section 7.2, at 1-month intervals following a change in hearing until stable hearing is confirmed; and when indicated by a subjective hearing impairment AE of CTCAE grade 3 or higher, or at the discretion of the investigator for subjective hearing impairment AE of CTCAE grade < 3 (Section 14.1.8) Hearing impairment AE evaluation will be performed as described in Section 12.2.6.1.
[j] Only collected for subjects unable to provide reliable behavioral PTA results. For these subjects, Diagnostic ABR will be collected at Screening, within 72 hours prior to dose escalation and within 72 hours prior to the visit subsequent to dose escalation, once every 2 months after a clinically significant change in hearing is observed until hearing is reported to be stable, and once per year when hearing is otherwise thought to be stable. For subjects who are unable to provide reliable behavioral PTA results at the 6-month interval, this evaluation will not be performed.

Visit Number		1	2 – 13	14
Day	–45 through –1	1	15 – 169	183
Window (weeks)			(± 1)	(± 1)
Time Point or Frequency	Screening	1st Dose[a]	Every 2 weeks (Weeks 2 – 24)	Week 26
Procedure				

[k] Clinical laboratory blood tests include chemistry, hematology, and coagulation.
[l] Only for subjects who provide separate consent for this assessment.
[m] Prior to each dose escalation, an audiology examination should be performed (within 72 hours) to assess for hearing impairment. If hearing impairment is observed, dose escalation should not proceed. An audiology examination should also be performed within 72 hours prior to the subsequent visit following a dose escalation (with results available at the study visit) to see if the subject can continue at the same dose.
[n] Collected from treatment-naïve subjects only. Red blood cell count, white blood cell count, white blood cell differential, glucose, and protein.
[o] Any medications used to treat NPC in the past (no time limit) and any other medications taken within 30 days of the Screening Visit will be recorded at the Screening Visit.
CGIC = Clinical Global Impression of Change; CSF = cerebrospinal fluid; ECG = electrocardiogram; LP = lumbar puncture; NPC = Niemann-Pick type C disease; NPC-SS = Niemann-Pick Type C Disease Severity Scale

Table 5: Schedule of Assessments and Procedures – Week 28 and Thereafter, Including End of Study/Early Termination

Window (weeks)	**(± 1)**	**(± 1)**	**(± 1)**	**(+ 1)**
Frequency (starting at Week 28) or Time Point	**Every 2 Weeks After 1st Dose (Weeks 28, 30, 32, etc.)**	**Every 6 Months After 1st Dose (Weeks 52, 78, 104, 130, 156, 182, etc.)**	**Additional Assessment Every 12 Months After 1st Dose (Weeks 52, 104, 156, 208, etc.)**	**End of Study/ Early Termination**
Procedure				
Clinician-CGIC assessment [a]		_[b]		
NPC-SS Intake [a]		_[b]		
EQ-5D-3L assessment [a]		_[b]		
Weight	X	X		X
Vital signs [c,b,d]	X [e]	X [e]		
Abbreviated physical examination		X		X
Urinalysis		X		X
Urine pregnancy test		X		X
Neurological examination [f]		X		X
Audiologic testing [g]		X		X
Diagnostic threshold auditory brainstem response [h]		_[h]	-[h]	_[h]
Blood for clinical laboratory tests[j,i]		X		X
Blood for plasma bile acids [k,j]		_[b]		
LP and adrabetadex administration[k]	X	X		
Adverse events [d]	X	X		X

Window (weeks)	**(± 1)**	**(± 1)**	**(± 1)**	**(+ 1)**
Frequency (starting at Week 28) or Time Point	**Every 2 Weeks After 1st Dose (Weeks 28, 30, 32, etc.)**	**Every 6 Months After 1st Dose (Weeks 52, 78, 104, 130, 156, 182, etc.)**	**Additional Assessment Every 12 Months After 1st Dose (Weeks 52, 104, 156, 208, etc.)**	**End of Study/ Early Termination**
Procedure				
Concomitant medications/therapies [d]	X	X		X
All subjects who discontinue protocol treatment will be requested to return to the clinic to complete an Early Termination Visit.				

Note: Any assessment done every 6 months is, by definition, done every 12 months.
[a] The efficacy assessments (Clinician-CGIC, NPC-SS, and EQ-5D-3L) should be performed *prior to other assessments and procedures*. In addition, the Clinician-CGIC should be conducted prior to other efficacy assessments.
[b] Procedure(s) should not be performed starting when the protocol amendment is approved by the respective IRB/Ethics Committee.
[c] Vital signs (blood pressure, pulse rate, respirations, and body temperature) will be recorded following a 5-minute rest in supine position.
[d] The collection period of adverse events, and concomitant medications will begin after informed consent is obtained (see Table 4) and end at Follow-up Visit 3; the collection of vital signs will begin after informed consent is obtained and end at Follow-up Visit 1 (see Table 6).
[e] A second set of vital signs will be recorded following recovery from LP.
[f] Complete neurological examination every 12 months after first dose (starting at Week 52 in this table) and abbreviated neurological examination every 6 months in between. A complete neurological examination will be conducted at End of Study/Early Termination.
[g] Audiologic evaluations will also be performed prior to each dose escalation (within 72 hours prior with results available at the study visit), within 72 hours prior to the subsequent visit following a dose escalation (with results available at the study visit) per Section 7.2, at 1-month intervals following a change in hearing until stable hearing is confirmed; and when indicated by a subjective hearing impairment AE of CTCAE grade 3 or higher, or at the discretion of the investigator for subjective hearing impairment AE of CTCAE grade < 3 (Section 14.1.8). Hearing impairment AE evaluation will be performed as described in Section 12.2.6.1.
[h] Do not perform starting 20 January 2021 (implemented in advance of amendment 2 as there is a direct impact to subject safety).
[i] Clinical laboratory blood tests include chemistry, hematology, and coagulation.
[j] Only for subjects who provide separate consent for this assessment.
[k] Before each dose escalation, an audiology examination should be performed (within 72 hours) to assess for hearing impairment. If hearing impairment is observed, dose escalation should not proceed. An audiology examination should also be performed within 72 hours prior to the subsequent visit following a dose escalation (with results available at the study visit) to see if the subject can continue at the same dose.
CGIC = Clinical Global Impression of Change; ECG = electrocardiogram; LP = lumbar puncture;
NPC-SS = Niemann-Pick Type C Disease Severity Scale

Table 6: Follow-up Visit

Window (weeks)	(± 1)
Procedure	**Follow-up Visit[a] (2 weeks after EOS/ET visit)**
Complete physical examination	X
Vital signs[b]	X
Urine pregnancy test	X
Audiologic testing[c]	X
Adverse events	X
Concomitant medications/therapies	X

[a] Follow-up visits not required for subjects who transition to another sponsor study.
[b] Vital signs (blood pressure, pulse rate, respirations, and body temperature) will be recorded following a 5-minute rest in supine position.
[c] Diagnostic ABR testing will not be performed after 20 January 2021.
EOS = End of Study; ET = Early Termination

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