# CLINICAL STUDY PROTOCOL

## A Phase 2b/3 Open-label Trial of VTS-270 (2-hydropropyl-β-cyclodextrin) in Subjects with Neurologic Manifestations of Niemann-Pick Type C1 Disease Previously Treated Under Protocol VTS301

Regulatory Agency Identification Number: IND #113273

Protocol Number: VTS-270-302

Date of Protocol Amendment 2 Version 2: 10 February 2021

Date of Protocol Amendment 1 Version 1: 03 December 2019

Date of Original Protocol: 23 October 2018

Vtesse LLC, a Mallinckrodt Pharmaceuticals Company

90 Washington Valley Road

Bedminster, NJ 07921

# SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2

The Summary of Changes (SOC) reflects the changes made in Amendment 2 for VTS270-302 from Amendment 1 dated 03 December 2019. Key changes in Version 2.0 included updating the benefit / risk balance assessment of adrabetadex to negative, resulting in a recommendation effective 20 January 2021 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 patient/family to develop a transition plan. Continued treatment with adrabetadex is contingent upon a discussion between the treating physician and patient/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. The study objectives/endpoints/outcome measures were revised to delete all efficacy assessments and their analysis. A full description of the changes to this amendment can be found in the Summary of Changes document for VTS302 protocol amendment 2. A high-level description of the changes includes the following:

1. The benefit / risk information was updated to state that the sponsor has made a determination that the benefit / risk balance was negative.
2. Treatment with adrabetadex may be continued until 20 October 2021 as needed to allow time to start alternative treatment unless there are additional time restrictions mandated by an IRB/EC or health authority. Subjects may stop treatment at any time before 20 October 2021.
3. Efficacy assessments will not be performed and existing efficacy data will not be analyzed.
4. Auditory brainstem response (ABR) evaluation will not be performed effective 20 January 2021. As this procedure often requires sedation, the risks of performing it are outweighed by any potential benefit. (Note: As this is a safety issue, this information was communicated to investigators before Amendment 2 was implemented.)
5. Appropriate changes were made in Table 1 (Schedule of Study Events) to reflect the changes made by this amendment.
6. Follow-up visits 2 and 3 were removed from Table 2 (End of Study and Follow-up from Last Dose).

## SPONSOR SIGNATURE

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 (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.

| Sponsor Signature | Date of Signature<br>(DD Month YYYY) |
|---|---|

[redacted]

## INVESTIGATOR SIGNATURE

My signature confirms 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 US Code of Federal Regulations (where appropriate), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles such as the Declaration of Helsinki.

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

| | |
|---|---|
| Investigator's Signature | Date of Signature<br>(DD Month YYYY) |
| Investigator's Name and Title (print) | |

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## ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | Adverse event |
| ABR | Auditory brainstem response |
| ALT | Alanine aminotransferase |
| CGIC | Clinical Global Impression of Change |
| DPOAE | Distortion product of acoustic emissions |
| eCRF | Electronic case report form |
| EQ-5D-3L | EuroQol-5 Dimension-3 Level |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IT | Intrathecal |
| LP | Lumbar puncture |
| MM | Medical monitor |
| NPC | Niemann-Pick Type C |
| NPC1 | Niemann-Pick Type C1 |
| NPC-SS | Niemann-Pick Type C Severity Scale |
| PI | Principal investigator |

| Abbreviation | Term |
|---|---|
| PTA | Pure tone audiometry |
| SAE | Serious adverse event |
| ULN | Upper limit of normal |
| US | United States |

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

| **Study Title: A Phase 2b/3 Open-label Trial of VTS-270 (2-hydroxypropyl-β-cyclodextrin) in Subjects With Neurologic Manifestations of Niemann-Pick Type C1 Disease Previously Treated Under Protocol VTS301** | |
|---|---|
| **Protocol Number:** VTS-270-302 | **Type:** Interventional - Phase 2b/3 |
| **Condition/Disease:** Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease | |
| **Approximate Number of Subjects:** 7 | **Approximate Duration of Subject Participation:** Up to 3 years (Note: the last day of study drug administration can be no later than 20 October 2021. A follow-up visit will be conducted after that date.) |

**Rationale:**

At present, there are no therapies approved for use in the United States (US) for subjects with NPC1 disease. Miglustat (Zavesca®), an imino sugar, has been approved for the treatment of subjects with NPC1 disease in many countries outside the US, including the European Union; off-label use in the US is available. The efficacy of Miglustat is modest at best, and development of effective treatments for NPC1 is required to address the significant unmet need for this fatal disease.

This study is designed to enable subjects who have completed the treatment phase of Study VTS301 with an assessment by the treating principal investigator (PI) of Study VTS301 of continued benefit to have continued treatment with adrabetadex (VTS-270) and consensus of the PI in this study. A completer is defined as a subject who has completed Visit 27/Week 52 or completed at least through Visit 13/Week 24 and required rescue option, and is continuing in Part C of Study VTS301. Subjects will enter this study at the same dose and regimen they were taking upon exiting Study VTS301.

**Objectives and Endpoints:**

| **Primary Objective** | **Endpoints** |
|---|---|
| To evaluate the long-term safety and tolerability of adrabetadex in subjects transitioning from Study VTS301. | Primary baseline values are collected from the first assessment gathered in the Study VTS301, which is before the first dose of adrabetadex in Study VTS301.<br>Baseline values of the current study at Visit 1 are from evaluations gathered within the study period of Study VTS302 to account for newer raters in the study. These values will reflect evaluations by the Primary Investigator of the current study, performed within the study sites described in the Overall Design.<br>Endpoints will be assessed at Weeks 26, 52, 78, 104, 130, and/or 156 (end of study). (Note: The last possible date of treatment is 20 October 2021. A follow-up visit will be conducted after that date.)<br>Summary of general safety profile, including adverse events (AEs) (serious and nonserious), vital signs, change in annual weight, and laboratory parameters. |

| **Study Title: A Phase 2b/3 Open-label Trial of VTS-270 (2-hydroxypropyl-β-cyclodextrin) in Subjects With Neurologic Manifestations of Niemann-Pick Type C1 Disease Previously Treated Under Protocol VTS301** |
|---|
| **Overall Design:**<br>This is a multicenter, multinational, open-label study of adrabetadex, with intrathecal (IT) administration by lumbar puncture (LP) every 2 weeks. To qualify for participation in this study, subjects will have participated in Study VTS301 and completed the treatment phase of the study, with an assessment by the treating PI in Study VTS301 of continued benefit to treatment with adrabetadex and consensus of the PI in Study VTS-270-302. A completer is defined as a subject who has completed Visit 27/Week 52 or completed at least through Visit 13/Week 24 and required rescue option, and is continuing in Part C of Study VTS301.<br>Eligible subjects who transition into this study will receive treatment with adrabetadex at the last dose level administered in Study VTS301, administered IT via LP infusion every 2 weeks, for up to a total duration of 3 years or until the investigator considers adrabetadex to be no longer beneficial to the subject, or the adrabetadex development program is discontinued. |
| **Number of Subjects:**<br>Approximately 7 subjects who travelled and/or relocated to participate in Study VTS301 and who continue to have benefit from adrabetadex treatment, and are willing to continue treatment and observation at a study center that is in closer proximity to where they reside. Any country may serve as a location for an activated study site, including but not limited to Costa Rica, Mexico, and China. |
| **Treatment Groups and Duration:**<br>All subjects will receive adrabetadex. The total duration of subject participation is up to 3 years or until the investigator considers adrabetadex to be no longer beneficial to the subject or the adrabetadex development program is discontinued. |

## 1.2. Schedule of Study Events

**Table 1: Schedule of Study Events**

| | Visit 1 (Baseline of Current Study) | Visits Occur Every 2 Weeks Starting From Visit 2 (Week 2) Until the End of the Study at Visit 79 (Week 156) [q] | Unscheduled Visit |
|---|---|---|---|
| **Window (days)** | **(+14)** | **Window for Visits 2 to 6 (Weeks 2 to 10) ± 3 days; for all other visits ± 7 days** | |
| **Time Point (Week)** | **0** | **Week 2 to Week 156 (every 2 weeks)** | |
| **Study Procedure** | | | |
| Informed consent[a] | X | | |
| Review eligibility | X | | |
| Demographics, medical history[b] | X | | |
| Medication history | X | | |
| Current medical condition[c] | X | X | X |
| Collect urine[d] | X | Every 6 months starting from Visit 14 (Week 26) | X |
| Pregnancy test[e] | X | Every 6 months starting from Visit 14 (Week 26) | |
| Physical examination[f] | X | Every 6 months starting from Visit 14 (Week 26) | X |
| Vital signs | X[g,h] | X[f, g] | X[f,g] |
| Weight and height[i] | X | Every 12 months until end of study Visit 79 (Week 156) | |
| Neurological examination[j] | X | Every 6 months starting from Visit 14 (Week 26) | |
| Clinical laboratory testing[k] | X | Every 6 months starting from Visit 14 (Week 26) | |

| | Visit 1 (Baseline of Current Study) | Visits Occur Every 2 Weeks Starting From Visit 2 (Week 2) Until the End of the Study at Visit 79 (Week 156) [q] | Unscheduled Visit |
|---|---|---|---|
| **Window (days)** | **(+14)** | **Window for Visits 2 to 6 (Weeks 2 to 10) ± 3 days; for all other visits ± 7 days** | |
| **Time Point (Week)** | **0** | **Week 2 to Week 156 (every 2 weeks)** | |
| Audiologic testing[l,m] | X | Every 6 months starting from Visit 14 (Week 26) | |
| ABR[l] | X | Do not perform starting 20 January 2021 (implemented in advance of amendment 2, as there is a direct impact to subject safety) | |
| Clinician-CGIC | X | Do not perform starting 10 February 2021 | |
| NPC-SS intake | X | Do not perform starting 10 February 2021 | |
| EQ-5D-3L[n] | X | Do not perform starting 10 February 2021 | |
| Lumbar puncture and study drug administration[o] | X | X | X |
| AEs[p] | X | X | X |
| Concomitant medications | X | X | X |

[a] Baseline Visit only (and at times as may be required by the study or when changes are made to the consent form).
[b] Medical history includes history of NPC1 disease, diagnosis date, and prior treatments.
[c] Assessment of current medical condition will be obtained from the last visit of Study VTS301 Part C. Current medical condition will only be recollected if the assessment from Study VTS301 exceeds 12 weeks from Visit 1 (Baseline of Current Study).
[d] Urine will be obtained for urinalysis only. If completed in Study VTS301 within the past 12 weeks, it does not need to be repeated.
[e] Urine pregnancy test at Baseline of the Current Study Visit (Visit 1) and every 6 months except at final visit, which should be a serum pregnancy test.
[f] Full physical examination at Baseline of the Current Study Visit (Visit 1); abbreviated physical examination at all other visits. If a full physical examination is completed in Study VTS301 within the past 12 weeks, it does not need to be repeated. ECG assessment is to be performed annually.
[g] Vital signs, including blood pressure, will be recorded following a 5-minute rest in a supine position.
[h] A second set of vital signs will be recorded following recovery of sedation from lumbar puncture procedure.

[i] Height is to be measured once at the Baseline of Current Study Visit (Visit 1).
[j] Full neurological examination at the Baseline Visit and End of Study Visit; abbreviated neurological examination at all other visits.
[k] Clinical laboratory tests include chemistry, hematology, and coagulation. If completed in Study VTS301 within the past 12 weeks, it does not need to be repeated.
[l] If audiology and ABR were obtained at Study VTS301 site within 12 weeks of the Baseline of the Current Study Visit (Visit 1), it does not have to be repeated.
[m] If a subject reports an increase in clinically significant hearing impairment at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.
[n] If the subject is unable to provide feedback for the EQ-5D-3L assessment, a parent or legal guardian can serve as proxy. The same parent or legal guardian from Study VT301 should make their best attempt to serve as proxy for all EQ-5D-3L assessment visits in the current study.
[o] All procedures must be completed prior to first dose of study drug.
[p] The collection period of AEs will begin after informed consent is obtained and end after procedures for the final study visit have completed.
[q] End of Study and Follow-up Visit should follow the procedures detailed in Table 2.

**Table 2: End of Study and Follow-up from Last Dose**

| | EOS | Follow-up Visit[a] |
|---|---|---|
| **Window (days)** | | **(±14)** |
| **Time Point (Week)** | | **EOS+2W** |
| **Study Procedure** | | |
| Adverse events | X | X |
| Concomitant medications | X | X |
| Audiologic testing[b] | X | - |
| Complete physical exam | X | - |
| Vital signs[c] | X | - |
| Clinical laboratory testing[d] | X | - |
| Complete Neurological examination | X | - |
| Urine Pregnancy Test | X | - |

EOS = End of Study; W = weeks.
[a] The follow-up visit is required for all subjects who complete their final dose of treatment or undergo early termination from the study. The visit may be conducted over the telephone.
[b] If a subject reports an increase in clinically significant hearing impairment at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.
[c] Vital signs, including blood pressure, will be recorded following a 5-minute rest in supine position.
[d] Clinical laboratory tests include chemistry, hematology, and coagulation.

# 2. INTRODUCTION

## 2.1. Background

Adrabetadex (VTS-270) is a specific and well-characterized mixture of HP-β-CD, a cyclic oligosaccharide with a distinctive truncated cone configuration containing 7-cyclo-α-(1,4)-anhydroglucose units with hydroxypropyl groups randomly substituted onto the C-2, C-3, and C-5 positions of the molecule. The level of hydroxypropylation in adrabetadex is strictly controlled during manufacturing, resulting in a drug with a tightly controlled degree of substitution and a defined fingerprint of the different species present in the mixture. This unique fingerprint distinguishes adrabetadex from all other commercially available HP-β-CDs.

The therapeutic potential of HP-β-CD was discovered in 2009 when HP-β-CD, injected systemically to Niemann-Pick Type C1 (NPC1) -/- mice beginning at either postnatal Day 7 or 21 and continuing every other day, delayed onset of clinical symptoms, reduced intraneuronal cholesterol and glycosphingolipid storage, reduced markers of neurodegeneration, and increased animal survival (Davidson, 2009). HP-β-CD enters cells by the endocytic pathway and is delivered to the late endosomal/lysosomal storage organelles where unesterified cholesterol accumulates in NPC1 deficiency. HP-β-CD replaces the function of NPC1 protein and promotes transport of the accumulated unesterified cholesterol to the endoplasmic reticulum for esterification by acetyl coenzyme A:acyl transferase and subsequent efflux (Abi, 2009; Rosenbaum, 2011). While the precise mechanism of HP-β-CD action to bypass or replace NPC1 function is not defined, HP-β-CD normalizes intracellular cholesterol trafficking by binding the hydrophobic moieties of cholesterol and other lipids.

A detailed description of the chemistry, pharmacology, efficacy, and safety of adrabetadex is provided in the Investigator's Brochure.

## 2.2. Study Rationale

At present, there are no therapies approved for use in the United States (US) for subjects with NPC1 disease. Miglustat (Zavesca®), an imino sugar, has been approved for the treatment of subjects with NPC1 disease in many countries outside the US, including the European Union; off-label use in the United States (US) is available. The efficacy of Miglustat is modest at best, and development of effective treatments for NPC1 is required to address the significant unmet need for this fatal disease.

This study is designed to enable subjects who have completed the treatment phase of Study VTS301 with an assessment by the treating principal investigator in Study VTS301 of continued benefit to have continued treatment with adrabetadex and consensus of the principal investigator (PI) in the current study. A completer is defined as a subject who has completed Visit 27/Week 52 or completed at least through Visit 13/Week 24 and required rescue option,

and is continuing in Part C of Study VTS301. Subjects will enter this study at the same dose and regimen they were taking upon exiting Study VTS301.

## 2.3. Assessment of Potential Benefits and Risks

NPC1 is a fatal disorder with both systemic and central nervous system signs and symptoms. Although age of onset varies, subjects typically develop progressive cerebellar dysfunction, hearing impairment, and motor and cognitive deterioration with death typically occurring during adolescence.

Ototoxicity, an expected AE based on the feline model, was observed in Study 13-CH-0001 at doses of 200 mg and higher, as assessed by tonometric audiometry. The clinical assessment of drug-related ototoxicity is confounded by disease related ototoxicity occurring as the course of Niemann-Pick Type C (NPC) progresses. Regardless, data in murine and feline NPC models show a dose-dependent hearing impairment with adrabetadex treatment, with variable susceptibility as is common in otopathology, suggesting that a number of external factors may influence the ototoxic properties of adrabetadex (Davidson, 2009;Ory, 2017;Ward, 2010).

The degree of recovery from ototoxicity in adrabetadex treated subjects has not been clearly documented due to limited clinical data. Pure-tone audiometry has indicated partial, and in some cases, complete recovery. Therefore, some degree of ototoxicity with uncertain reversibility may occur in subjects receiving adrabetadex. The mechanism of ototoxicity is not fully understood; however, based on preclinical and clinical data, it is possible that higher doses or longer duration of dosing may result in further hearing impairments. It should be noted that subjects with decreased hearing may benefit from use of assisted hearing devices such as hearing aids or cochlear implants. The overall preclinical and clinical data suggest that there is risk of hearing impairment associated with the administration of adrabetadex. Animal data suggest that the potential mechanism of adrabetadex-induced hearing impairment is a loss of outer hair cells in the cochlea of the inner ear, which amplify low-level sounds reaching the cochlea(Crumling, 2017;Ward, 2010). Moreover, in a clinical setting, fatigue-like symptoms, balance disorders and pyrexia were observed in the Study VTS301 and Study 13-CH-001 and may be associated with the administration of adrabetadex.

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 patient/family to develop a transition plan. Continued treatment with adrabetadex is contingent upon a discussion between the treating

physician and patient/family and re-consent. Likewise, continuation of treatment is also contingent upon approval by the respective Institutional Review Board / Ethics Committee and health authority.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs can be found in the Investigator's Brochure.

# 3. OBJECTIVES AND ENDPOINTS

## 3.1. Primary Objective(s)/Endpoint(s)

| Primary Objective | Endpoint |
|---|---|
| To evaluate the long-term safety and tolerability of adrabetadex in subjects transitioning from Study VTS301. | Primary baseline values are collected from the first assessment gathered in the Study VTS301, which is before the first dose of adrabetadex in Study VTS301.<br>Baseline values of the current study at Visit 1 are from evaluations gathered within the study period of Study VTS302 to account for newer raters in the study. These values will reflect evaluations by the Primary Investigator of the current study, performed within the study sites described in the Overall Design.<br>Endpoints will be assessed at Weeks 26, 52, 78, 104, 130, and/or 156 (end of study) (Note: The last possible date of treatment is 20 October 2021. A follow-up visit will be conducted after that date.)<br>Summary of general safety profile, including AEs (serious and nonserious), vital signs, change in annual weight, and laboratory parameters. |

## 3.2. Secondary Objectives/Endpoints

There are no secondary objectives for this study.

## 3.3. Exploratory Objectives/Endpoints

There are no exploratory objectives for this study.

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a multicenter, multinational, open-label study of adrabetadex, with intrathecal (IT) administration by lumbar puncture (LP) every 2 weeks. To qualify for participation in this study, subjects will have participated in Study VTS301 and completed the treatment phase of the study, with assessment by the treating PI in Study VTS301 of continued benefit from treatment with adrabetadex and consensus of the PI in the current study. A completer is defined as a subject who has completed Visit 27/Week 52 or completed at least through Visit 13/Week 24 and required rescue option, and is continuing in Part C of Study VTS301.

Eligible subjects who transition into this study will receive treatment with adrabetadex at the last dose level administered in Study VTS301, administered IT via LP infusion every 2 weeks, for up to a total duration of 3 years or until the investigator considers adrabetadex to be no longer beneficial to the subject, or the adrabetadex development program is discontinued.

This study is intended as open-label treatment for approximately 7 subjects who completed Part B of Study VTS301. This represents subjects who travelled and/or relocated to participate in Study VTS301 and who are willing to continue treatment and observation at a study center that is in closer proximity to where they reside. Any country may serve as a location for an activated study site, including but not limited to Costa Rica, Mexico, and China.

## 4.2. Study Design Rationale

Adrabetadex is being developed for pediatric use. The typical onset of NPC symptoms is in early childhood. Owing to different clinical presentations and course of disease, NPC is typically categorized as early-infantile onset (less than 2 years of age), late-infantile onset (2 to less than 6 years of age), juvenile onset (6 to less than 15 years of age) and adolescent/adult onset (at least 15 years of age).

Due to the shorter life-span (death is usually within 5 years for early-infantile onset and between 7 and 12 years for late-infantile onset), and the difficulty in making a diagnosis in those subjects with infantile onset forms of NPC, the focus of this drug development program has been for those 4 to 21 years of age with onset of neurologic symptoms before the age of 15. The disease has a relatively slow progression in those with adult onset.

This study is being conducted with the goal of obtaining longitudinal safety and efficacy data; as of the approval of Amendment 2, only safety data will be collected.

## 4.3. Treatment/Dose Rationale

Subjects in Study VTS301 may have had dosage adjustment based on tolerability. In transition to the current study, the maximum titrated dose established in Study VTS301 will be used as the starting dose. Should tolerability issues occur in the current study, dose reduction is permitted (see Table 4).

Adrabetadex is administered IT via LP every 2 weeks.

## 4.4. End of Study Definition

The end of the study is defined as the completion of the final assessment for the last subject enrolled in the study.

# 5. STUDY POPULATION

No new patients can be enrolled in the study.

Prospective approval of protocol deviations in recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

## 5.1. Inclusion Criteria

To be eligible to participate in the study, at the Baseline Visit (except as noted below):

1. Subject completed Part B of Study VTS301 (defined as having completed Visit 27/Week 52 or completed at least through Visit 13/Week 24 and required rescue option) and is continuing in Part C of Study VTS301.
2. Subject, in the opinion of the PI, should continue treatment with adrabetadex.
3. Females of childbearing potential (not surgically sterile) 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.
4. Subject 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.

## 5.2. Exclusion Criteria

A subject is ineligible for study participation if, at the Baseline Visit:

1. Subjects discontinued from Study VTS301 for AEs or perceived lack of efficacy.
2. Subject has an unresolved SAE for which treatment with adrabetadex has been halted.
3. Female subjects who are pregnant or nursing.
4. Subjects with suspected infection of the central nervous system or any systemic infection.
5. Subjects with a spinal deformity that could impact the ability to perform a LP.
6. Subjects with a skin infection in the lumbar region within 2 months of study entry.
7. Any of the following laboratory abnormalities at the Baseline Visit:
    a. Neutropenia, defined as an absolute neutrophil count of less than $1.5 \times 10^9$/L.
    b. Thrombocytopenia (platelet count of less than $75 \times 10^9$/L).
    c. Activated partial thromboplastin time or prothrombin time prolonged by greater than 1.5 × the upper limit of normal (ULN) or known history of a bleeding disorder.
    d. Aspartate aminotransferase or alanine aminotransferase (ALT) greater than 4 × ULN.

e. Anemia: hemoglobin greater than 2 standard deviations below normal for age and gender.
f. Estimated glomerular filtration rate less than 60 mL/minute/1.73 $m^2$ calculated using the modified Schwartz formula (Schwartz, 2009) for subjects aged 4 through 17 years old or using the Chronic Kidney Disease Epidemiology Collaboration equation formula for subjects aged 18 years or older.

8. Evidence of obstructive hydrocephalus or normal pressure hydrocephalus.
9. Recent use of anticoagulants (in past 2 weeks prior to first dose [Study Day 0]).
10. Active pulmonary disease, oxygen requirement, or clinically significant history of decreased blood oxygen saturation, pulmonary therapy, or requiring active suction.
11. Subjects who, in the opinion of the investigator, are unable to comply with the protocol or have medical conditions that would potentially increase the risk of participation.

## 5.3. Lifestyle Considerations

For the 3 days following each dosing procedure, subjects should avoid acoustic overstimulation and minimize exposure to loud noises (eg, headphones for music or video games).

# 6. STUDY TREATMENT

Study treatment is defined as any investigational treatment, marketed product, placebo, or device intended to be administered to a study subject according to the study protocol.

The formulation and filling of adrabetadex involves dissolving the active pharmaceutical ingredient in water for injection, adding sodium chloride to 0.9% 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 (10 mL vial with sufficient overfill to facilitate a 4.5 mL withdrawal) and autoclaved. The final formulation and fill process will be transferred to a third-party contract manufacturer for future commercial manufacturing. This will be carried out under a formal technology transfer protocol and product comparability will be assessed. The product is a clear, colorless solution that is free from visible foreign matter.

## 6.1. Treatment Administration

No new patients can be enrolled in the study.

Eligible subjects who transition into this study will receive treatment with adrabetadex at the last dose level administered in Study VTS301; adrabetadex will be administered IT via LP infusion every 2 weeks, for up to 3 years or until the investigator considers adrabetadex to be no longer beneficial to the subject, or the adrabetadex development program is discontinued. The IT dosing via LP will be conducted by dedicated study personnel in a dedicated room.

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 is determined by the dose level (see Table 3). Prior to adrabetadex injection, a volume of cerebrospinal fluid approximately equal to the adrabetadex dose is to be removed. Anesthesia or sedation will be used for the IT dosing procedure, following institutional guidelines and procedures. Subjects will be required, if possible, to lie flat for 30 to 45 minutes following dosing with feet elevated.

**Table 3: Adrabetadex Dose, Injection Volume, and Concentration**

| Dose Level (mg) | Injection Volume (mL) | Concentration (mg/mL) |
|---|---|---|
| 900 | 4.5 | 200 |
| 600 | 3.0 | 200 |
| 400 | 2.0 | 200 |

There is no control product in this study. For additional details, refer to the study manual.

## 6.2. Study Treatment Preparation/Handling/Storage/Accountability

Study treatment will be provided by the sponsor or sponsor's representative.

Labeling of the study drug will be in accordance with Good Manufacturing Practice and as required by local and national regulations.

The sponsor (or designee) will ship study drug to the study center. The initial study drug shipment will be shipped after study center activation (ie, all required regulatory documentation has been received by the sponsor and a contract has been executed). Subsequent study drug shipments will be made after study center request for resupply.

Adrabetadex will be provided in appropriately labeled vials (10 mL Type I white glass vial filled with 4.5 mL of adrabetadex, 20 mm FIOLAX stopper, and plastic white flip-off caps coated with FluroTec, or similar vial) formulated as a 200 mg/mL injectable solution. A pharmacist/designee at each study center will be responsible for preparing the assigned dose undiluted (ie, a 900 mg dose will be administered in 4.5 mL, a 600 mg dose will be administered in 3 mL, and a 400 mg dose will be administered in 2 mL). Study drug should be stored between 15°C and 25°C, inclusive.

The investigator or designee will confirm that appropriate temperature control conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved prior to study treatment administration.

The study treatment will be maintained in a monitored, environmentally controlled (in accordance with treatment labeling), secure, locked area with restricted access at the study center.

During the study, the study drug will not at any time be handed out to the subjects. The designated study personnel will be responsible for the handling and administration of the study drug during the study.

In accordance with the International Council for Harmonisation (ICH) requirements, at all times the investigator will be able to account for all study drug furnished to the study center. An accountability record will be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of study drug received, to whom it was administered (subject-by-subject accounting) and accounts of any study drug accidentally or deliberately destroyed. All unused study drug not involved in immediate subject treatment will be maintained under locked, temperature-controlled storage at the study center.

Please refer to the Pharmacy Manual for complete information regarding handling, storage, preparation, and accountability of study drug.

## 6.3. Measures to Minimize Bias

This is an open-label study; no measures to minimize bias are being employed.

## 6.4. Study Treatment Compliance

Adrabetadex will be administered at the study center by a study clinician. The amount of adrabetadex administered will be recorded and overall treatment compliance will be calculated.

## 6.5. Prior and Concomitant Therapy

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior and concomitant medications and non-drug therapies received will be recorded. All treatments (lifetime) for NPC will be recorded.

### 6.5.1. Prohibited Concomitant Therapies

The following treatments will not be permitted during the study:

- Anticoagulants.
- Investigational treatments (exclusive of adrabetadex).
- Any investigational drug, device, or procedure administered as part of a research study.

If any prohibited medication is taken during the study, all pertinent information will be recorded in source documents and the electronic case report form (eCRF). The designated study medical monitor (MM) must be informed immediately so the sponsor may determine whether to continue the subject in the study.

### 6.5.2. Permitted Concomitant Therapies

The following treatments will be permitted during the study:

- Miglustat (ie, Zavesca or generic) maintained at a constant dose (dose adjustments for weight or as medically necessary are permitted).
- Age-appropriate multivitamins.
- Other required chronic medications as prescribed by a physician should be maintained at a constant dose throughout the study (dose adjustments for weight or as medically necessary are permitted).
- Short-term course of other medication for treatment of, eg, otitis, urinary tract infection, pain, upper respiratory infection.

## 6.6. Study Treatment Modification

Subjects who, in the opinion of the investigator, experience a drug-related AE after any IT treatment that is considered clinically relevant and impactful to the subject's function may have their dose of adrabetadex reduced (see Table 4).

Dose reductions should be considered for subjects who experience a drug-related AE of hearing impairment, asthenia, fatigue, lethargy, marked behavioral disturbance, ataxia, or gait difficulty that:

- Occurs after any IT treatment AND
- Is of moderate or severe intensity AND
- Does not resolve within 48 hours after dosing.

If a subject requires dose reduction due to an AE meeting the above criteria, and if a subject continues to experience an AE of note after dose reduction, the subject's dose may be reduced as described in Table 4.

**Table 4: Adrabetadex Dose Reductions Due to Drug-Related Adverse Events**

| Dose Level (mg) at Time of Adverse Event | Reduced Dose (mg): |
|---|---|
| 900 | 600 |
| 600 | 400 |
| 400 | Dose may only be reduced after discussion with MM on a case-by-case basis, with a lower limit of 200 mg. |

The AE that led to the dose reduction must be fully documented.

# 7. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Treatment

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 transition off of treatment unless there are additional time restrictions mandated by an IRB/EC or health authority. Subjects can stop treatment at any time before 20 October 2021.

Following the last dose of adrabetadex, subjects will be asked to return to the clinic or participate in a telemedicine visit for a follow-up safety visit. Procedures for the End of Study (EOS) visit and the safety follow-up visit are noted in Table 2.

Permanent study treatment discontinuation is required for any of the following:

- The subject develops a concurrent medical condition that precludes further participation.
- The subject's parent or guardian, withdraws consent/assent to receive any further administration of adrabetadex.
- Subject is lost to follow-up.
- Start of new treatment/therapy for the underlying disease outside the scope of this protocol.
- The subject becomes pregnant during the active treatment phase of the study.

Additionally, the sponsor reserves the right to terminate the study at any time. Following termination of this study, there is no guarantee of continued access to adrabetadex.

Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicate a potential health hazard to subjects.
- Emergence of any efficacy information that could significantly affect the benefit:risk ratio.
- Any unforeseen problems with the drug, including manufacturing, sourcing, etc.
- Any government health and regulatory agencies request termination.
- Violation of Good Clinical Practice (GCP), protocol, or the contract by study center staff or treating physician.
- Commercial drug becomes available for the subject within the respective region.

Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a subject meets one of the conditions outlined in Section 10.5.

During the annual electrocardiogram, if a clinically significant cardiac finding is identified (including but not limited to changes from baseline in QT interval corrected using Fridericia's formula) after the start of study treatment, the investigator or a qualified designee will determine if the subject can continue in the study and if any change in management is needed.

The reason for study treatment discontinuation will be recorded.

A Follow-up Visit is required for all subjects who complete their final dose of treatment or undergo early termination from the study.

### 7.1.1. End of Study Visit

1. Review and record any AEs or experiences.
2. Record changes to concomitant medications.
3. Perform complete physical examination.
4. Perform and record vital signs including blood pressure following 5-minute rest in supine position.
5. Perform complete neurological evaluation.
6. Perform audiologic testing.
7. Collect blood for clinical laboratory tests (chemistry, hematology, coagulation).

### 7.1.2. Follow-up Visit

1. Review and record any AEs or experiences.
2. Record changes to concomitant medications.

## 7.2. Subject Discontinuation/Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent. If a subject withdraws from the study, the subject may request destruction of any samples taken and not tested and the investigator must document this in the study center study records.

The reason for study discontinuation/withdrawal will be recorded. A subject may be discontinued from the study for the following medical or administrative reasons.

### 7.2.1. Withdrawal by Subject

Subjects will be free to discontinue from the study at any time.

### 7.2.2. Adverse Event

If a dosed subject suffers an AE that, in the judgment of the investigator, sponsor, or MM; presents an unacceptable consequence or risk to the subject, the subject will be discontinued from study drug.

### 7.2.3. Death

In the event that a subject dies during the study, death will be the reason for discontinuation and the cause of death will be reported as a serious AE.

### 7.2.4. Lost to Follow-up

Every effort should be used to maintain contact with subjects during their participation in the study. A subject may be considered lost to follow-up if there is no response to at least 3 attempts to reach the subject by telephone and no response to a certified letter (or equivalent) sent to the last known address of the subject, if possible. Efforts to contact the subject should be noted in the source documentation.

### 7.2.5. Met Withdrawal Criteria

Discontinuation for safety and/or tolerability issues as outlined in Section 7.1.

### 7.2.6. Worsening of Disease Activity

Subjects may be withdrawn if, in the opinion of the investigator, there is a lack of efficacy during the study.

### 7.2.7. Other

If the above reasons are not applicable, please use the “Other” option in the eCRF and provide the appropriate reason for subject withdrawal.

# 8. STUDY ASSESSMENTS AND PROCEDURES

Efficacy assessments (NPC-SS, Clinician CGIC) and self-reported outcomes (EQ-5D-3L) will not be collected.

## 8.1. Audiologic Evaluation

### 8.1.1. Audiologic Testing

Audiologic evaluations will be performed at times outlined in the Schedule of Study Events (Table 1).

Audiologic assessments will include: 1) behavioral assessment of pure-tone and speech thresholds, and air conduction and bone conduction thresholds, when indicated; 2) word recognition ability using test techniques appropriate for age and condition; 3) evaluation of middle ear function (tympanometry); and 4) otoacoustic emissions (cochlear function). The degree of any hearing impairment will be defined by a standard clinical pediatric scale (ie, slight, mild, moderate, moderately severe, severe, and profound). If a subject reports an increase in clinically significant hearing impairment at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.

## 8.2. Safety Assessments

All safety assessments will be performed at times outlined in the Schedule of Study Events (Table 1). Additional (unscheduled) safety assessments may be performed as needed.

### 8.2.1. Medical and Surgical History

Medical and surgical history will be obtained at the Baseline Visit for Study VTS301. Medical history will be reviewed for this study. This will include a review of the following systems: general, dermatological, respiratory, cardiovascular, gastrointestinal, genitourinary, gynecological, endocrine, musculoskeletal, hematological, neuropsychological, immune (allergies), and head, eyes, ears, nose, and throat. Historical and current medical conditions will be recorded.

### 8.2.2. Neurological Examination

Neurological examinations will be performed. A complete neurological examination will be performed at the Baseline Visit and at Early Termination (Table 2).

An abbreviated neurological examination comprising assessments of eye movements, coordination, gait, and reflexes, will be conducted at other visits as noted in the Schedule of Study Events (Table 1).

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 patient discontinues from the study for reasons other than the AE.

### 8.2.3. Physical Examination

A complete physical examination will be performed at the Baseline of the Current Study Visit (Visit 1), End of Study Visit, and Follow-up Visit. This will include evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart (ECG), peripheral pulses, and presence or absence of edema), genitourinary system, lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles) neurological system (including cranial nerves, reflexes, sensation, strength), skin, extremities, and other conditions of note.

An abbreviated physical examination will be performed at visits after baseline as specified in the Schedule of Study Events (Table 1) and will include evaluation of the following:

- Skin – general examination of exposed skin
- Chest – auscultation and percussion of lungs; auscultation of the heart
- Abdomen – palpation and auscultation
- Extremities – visual inspection

The findings of the physical examinations will be recorded. Any change from the Primary Baseline Visit physical examination that is considered clinically significant by the investigator will be recorded as an AE.

### 8.2.4. Weight and Height

Weight and height will be collected as outlined in the Schedule of Study Events (Table 1). Any change from the Primary Baseline Visit in subject weight that is considered by the investigator to be clinically significant will be recorded as an AE.

### 8.2.5. Vital Signs

Vital signs will be obtained after the subject has been in the supine position for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded. Any change from the Primary Baseline Visit vital signs that is considered clinically significant by the investigator will be recorded as an AE.

Vital signs will be measured twice (prior to LP and after recovery from LP) during each study visit.

### 8.2.6. Clinical Laboratory Tests

Required clinical laboratory tests are listed in Section 10.2. Specific instructions for collection, processing, storage, and shipment of clinical laboratory samples will be provided in separate laboratory manual(s).

Samples for laboratory testing at all visits may be collected under fasted or nonfasted conditions. Fasting early morning samples are preferred, but a random daytime sample is acceptable. The date and time of the sample collection must be documented on the laboratory report. Investigators must review and sign laboratory reports and document the clinical significance of each laboratory abnormality. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs.

Hematology with differential, serum chemistry, coagulation, and urinalysis samples will be collected as outlined in the Schedule of Study Events (Table 1).

In addition, all female subjects of childbearing potential will have serum and/or urine pregnancy tests at the time points outlined in the Schedule of Study Events (Table 1). Any positive urine pregnancy test will be confirmed with a serum pregnancy test. Results must be available prior to protocol mandated study treatment. Subjects with positive results at the Baseline Visit will be ineligible for study entry. Any female subject that becomes pregnant during the study will be immediately withdrawn and will have the pregnancy reported as per Section 10.4.

If applicable, the subject's agreement to use contraception throughout study participation and for 28 days after ending study participation will be documented.

## 8.3. Adverse Events

AEs will be recorded from signing of the informed consent form (ICF) and for 28 days after any active treatment period, and will be followed by the investigator until the AE is resolved or stabilized. All safety measures (which includes standard of care activities) should be provided by the study center to the subject. Any study center follow-up should be documented.

Refer to Section 10.3 for additional details on the handling of AEs and SAEs.

## 8.4. Treatment Overdose

For this study, any dose greater than the dose to be administered per protocol, within a 24 (± 1) hour period, will be considered an overdose.

The effects of an overdose of adrabetadex are not known. In the event of overdose, subjects should be observed and appropriate supportive treatment should be given. There is no known specific treatment in case of overdose.

The highest dose of adrabetadex administered in humans is 1800 mg, as described in the Investigator's Brochure. Side effects seen at this dose were similar to those seen at other doses, with increased intensity, severity, and duration.

In the event of an overdose, the investigator or designee should:

- Contact the MM immediately.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities should be recorded.
- Document the quantity of the excess dose, as well as the duration of the overdose.

# 9. STATISTICAL CONSIDERATIONS

## 9.1. Sample Size Determination

The sample size for this study is approximately 7 subjects. The sample size was determined based on the potential number of subjects eligible to transition from Study VTS301.

## 9.2. Populations for Analysis

For the purposes of analysis, the following populations are defined:

- The Intent-to-Treat population will include all enrolled subjects.
- The Safety population will include all subjects who receive at least one dose of adrabetadex, which will be inclusive of all enrolled subjects within this study.

## 9.3. Statistical Hypothesis and Analyses

This section provides a general summary of the statistical methods to be used in analyzing study data.

### 9.3.1. Efficacy Analyses

Efficacy data will be provided in data listings and no analyses are planned.

### 9.3.2. Safety Analyses

The Safety population will consist of all enrolled subjects who receive at least 1 dose of adrabetadex, which will be inclusive of all enrolled subjects within this study.

AEs will be coded using the Medical Dictionary for Regulatory Activities by preferred term within system organ class. All AE data will be provided in data listings. Other safety data will be listed.

### 9.3.3. Interim Analysis

There is no planned interim analysis for this study.

### 9.3.4. Handling Missing Data

No imputation will be performed.

### 9.3.5. Multiplicity

Not applicable.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

The study will be conducted in full compliance with applicable international, national, and local regulatory requirements; US Food and Drug Administration (FDA) regulations including 21 Code of Federal Regulations 314.106 and 312.120, (where applicable), ICH guidelines for GCP, in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and European regulation 536/2014/EU (where applicable).

It is the responsibility of the investigator to obtain the approval of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before the start of the study. A copy of the approval letter along with a roster of IRB/IEC members and compliance letter and/or the US Department of Health and Human Services general assurance number (if applicable) will be provided to the sponsor and retained as part of the study records. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. The investigator will notify the IRB/IEC of SAEs or other significant safety findings per IRB/IEC guidelines. The study protocol, ICF, advertisements (if any), and amendments (if any) will be approved by the IRB/IEC in conformance with international, national, and local regulatory requirements.

Any change in the study plan requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame, if appropriate.

### 10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after the end of the study.

### 10.1.3. Subject Information and Consent

The ICF must be approved by the sponsor and the IRB/IEC before any subject provides consent. The investigator will provide the sponsor with a copy of the IRB/IEC-approved ICF and a copy of the IRB/IEC written approval before the start of the study.

At the Baseline Visit (and at other times as may be required by the study or when changes are made to the consent form), subjects will read the consent form(s) and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form), if applicable after being given an explanation of the study. Before signing the consent form(s) and the privacy authorization form (if applicable), subjects will have an opportunity to discuss the contents of these forms with study center personnel.

Subjects must assent understanding of and voluntarily sign these forms in compliance with ICH GCP and all applicable national and international regulations, before participating in any study related procedures. Subjects will be made aware that they may withdraw from the study at any time. Subjects unable to give written informed consent must orally assent to the procedures, and written informed consent must be obtained from a legally authorized representative in accordance with national and local laws, as applicable.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations including confidentiality. All versions of each subject's signed ICF must be kept on file by the study center for possible inspection by regulatory authorities and/or authorized sponsor personnel. Signed copies of the consent form(s) and the HIPAA authorization form, if applicable, will be given to the subject.

The subjects will be made aware of their right to see and copy their records related to the study for as long as the investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

### 10.1.4. Data Protection

Study subjects will be assigned a unique identifier by the sponsor or designee. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make a subject identifiable will not be transferred.

The subjects must be informed that their personal study related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure (in accordance with local and/or national law) must also be explained to the subjects.

The subjects must be informed that their 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.

### 10.1.5. Committees Structure

No monitoring committees will be used for this study.

### 10.1.6. Dissemination of Clinical Study Data

Aggregate results data will be provided to the study centers that actively enrolled subjects into this study after the clinical study report is finalized.

Study results and de-identified individual subject data will be released as required by local and/or national regulation.

### 10.1.7. Data Quality Assurance

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the Investigator's Brochure, the eCRF and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study.

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to original source data and documents.

Each subject's eCRF should be fully completed and submitted to the sponsor in a timely fashion.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

Any significant changes in study personnel will require an updated Statement of Investigator (ie, FDA form 1572) to be filed with the sponsor.

The investigator must notify the IRB/IEC of protocol deviations in accordance with local regulatory and IRB/IEC requirements.

The eCRF data are stored in a database and processed electronically. The sponsor's MM reviews the data for safety information. The data are reviewed for completeness, and logical consistency. Automated validation programs will identify missing data, out-of-range data, and other data inconsistencies. In addition, clinical laboratory data will be processed electronically. Requests for data clarification are forwarded to the study center for resolution.

### 10.1.8. Source Documents

All subject information recorded in the eCRF will be attributable to source data from the study center.

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 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 medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by

an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

### 10.1.9. Study and Study Center Closure

The sponsor may suspend or terminate the study or part of the study at any time for any reason. If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations. Study termination and follow-up will be performed in compliance with the sponsor or designee standard operating procedures.

The sponsor, investigator, or local and national regulatory authorities may discover conditions during the study that indicate that the study or study center should be terminated. This action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study/study center include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- The decision on the part of the sponsor to suspend or discontinue testing or evaluation of the study drug.
- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulations.
- Submission of knowingly false information from the study center to the sponsor, study monitor, or local and national regulatory authorities.
- Insufficient adherence to protocol requirements.

### 10.1.10. Publication Policy

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 Study Agreement.

## 10.2. Appendix 2: Clinical Laboratory Tests

| | |
|---|---|
| **Serum Chemistry** | |
| Alanine aminotransferase (ALT) | Chloride |
| Albumin (total) | Creatinine |
| Alkaline phosphatase | Glucose |
| Aspartate aminotransferase (AST) | Phosphorus |
| Bilirubin (total) | Potassium |
| Blood urea nitrogen | Protein, total |
| Calcium | Sodium |
| Bicarbonate | Uric acid |
| **Hematology Assays** | |
| Hematocrit | Platelet count |
| Hemoglobin | Red blood cell count |
| White blood cell count, including differential | |
| **Coagulation** | |
| Prothrombin time | Activated partial thromboplastin time |
| **Urinalysis** | |
| Color | Ketones |
| Clarity | Protein |
| Albumin | pH |
| Bilirubin | Specific gravity |
| Blood | Urea |
| Creatinine | Microscopy (white blood cell/ high power field, red blood cell/high power field and urinary casts) |
| Glucose | |
| **Hormones** | |
| Serum and urine beta-human chorionic gonadotropin (pregnancy test) | |

## 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

### 10.3.1. Safety

For safety information about adrabetadex, refer to the most recent version of the Investigator's Brochure.

### 10.3.2. Definitions

Adverse Event

An AE is any untoward or undesirable medical occurrence in a subject who is administered a study treatment, which does not necessarily have to have a causal relationship with this treatment. Examples of AEs include but are not limited to:

- Clinically significant laboratory findings.
- Clinically significant changes in physical or neurological examination findings.
- An AE occurring due to study drug overdose whether accidental or intentional.
- An AE occurring from study drug abuse.
- An AE associated with study drug withdrawal.
- An unexpected AE.

An unexpected AE is defined as an AE, the nature and severity of which is not consistent with the applicable product information in the most recent version of the Investigator's Brochure.

Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose results in any of the following outcomes:

- Death.
- Life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

***Death***

Death is an outcome of an event. The cause of death should be recorded and reported on the SAE Form. All causes of death must be reported as SAEs. The investigator should make every effort

to obtain and send death certificates and autopsy reports to the sponsor or designee, or state not available.

***Life-Threatening Event***

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

***Hospitalization***

Hospitalization is defined as an official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious. The following situations should not be reported as SAEs:

A hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.

A hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.

A hospitalization for a pre-existing condition that has not worsened.

***Important Medical Events***

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

AEs (serious or nonserious) that commonly occur in the study population or background regimen will be considered anticipated events. Such events include known consequences of the condition under investigation (eg, symptoms, disease progression) and other events that may be common in this study population. Anticipated events are to be recorded on the eCRF and reported as SAEs when serious. These SAEs will not be expedited to health authorities, but rather, included in aggregate safety reports.

### 10.3.3. Adverse Event and Serious Adverse Event Classifications

***Study Drug Relatedness***

Table 5 summarizes the classifications to be used when evaluating the relationship of AEs or SAEs to study treatment.

**Table 5: Adverse Event Relationships to Study Treatment**

| Relationship | Definition |
|---|---|
| Unrelated | An event that can be determined with certainty to have no relationship to the study drug. |
| Unlikely Related | An event with a temporal sequence from administration of the drug that makes a relationship improbable (but not impossible); underlying disease or other concurrent therapies provide plausible explanation. |
| Possibly Related | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors. |
| Probably Related | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions. |
| Definitely Related | Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis. |

***Severity Assessment***

The NCI-CTCAE Version 4.03 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the AEs of special interest/hearing impairment (special interest hyperlink), the guidelines shown in Table 6 should be used to grade severity.

**Table 6: Adverse Event Severity Grades**

| Grade | Definition |
|---|---|
| Mild (1) | Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well. |
| Moderate (2) | Mild to moderate limitation in activity, no or minimal medical intervention/therapy required. |
| Severe (3) | Interferes significantly with subject's usual function and activities. |
| Life-threatening (4) | The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe. |

To ensure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical importance (such as a severe headache). This is not the same as "serious," which is based on the subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

If an AE increases in severity (eg, from moderate to severe); decreases in severity (eg, changes from moderate to mild); or if there is a change in seriousness, a new AE will be opened and the original AE will be closed. If an AE is still ongoing at the time of a subject's completion of the Follow-up Visit, the resolution/stop date and time is left blank.

### 10.3.4. Adverse Event and Serious Adverse Event Recording and Reporting

AEs and SAEs will be recorded from signing of the ICF through completion of the last Follow-up Visit. The investigator is required to record the AE or SAE regardless of the severity of the event or its relationship to study treatment. The investigator must follow up on all AEs and SAEs reported to have occurred through the last Follow-up Visit until the event has resolved or stabilized or at such time the investigator refers the subject to a nonstudy physician. The investigator will document the further follow-up information in the subject's source document.

During the period specified above, the investigator will:

- Record all AEs and SAEs from the signing of the ICF through the completion of the last Follow-up Visit.
- Report all SAEs on an SAE Report Form to Mallinckrodt Global Pharmacovigilance or designee.
- Report all pregnancies to Mallinckrodt Global Pharmacovigilance or designee on the appropriate form.
- Submit any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction from Mallinckrodt Global Pharmacovigilance or designee to the IRB/IEC.

The reporting requirements for AEs are summarized in Table 7.

**Table 7: Reporting Requirements for Adverse Events**

| Seriousness | Reporting Time | Type of Report |
|---|---|---|
| All Serious | Within 24 hours of first knowledge of event | Initial report on the SAE Form, appropriate eCRF, and source document |
| | Within 24 hours of receipt of follow-up information | Follow-up report on the SAE Form, appropriate eCRF, and source document |
| Nonserious | Per eCRF submission procedure | Appropriate eCRF and source document |

### 10.3.5. Adverse Events of Special Interest

#### 10.3.5.1. Clinically Significant Hearing Impairment

NPC1 disease and adrabetadex are both associated with hearing impairment. The severity and site of lesion of auditory damage may differ between adrabetadex and NPC1 disease induced hearing impairment. As shown in Table 8, there are some overlapping sites of lesion (outer hair cells), but some more likely only in NPC1 disease. In addition, NPC hearing impairment appears to progress more slowly than drug induced hearing impairment.

**Table 8: Distinguishing Adrabetadex from NPC1 Disease Inducing Hearing Impairment**

| Site of Lesion | Adrabetadex Toxicity | NPC1 Disease | Test(s) to Detect |
|---|---|---|---|
| Outer hair cells | Yes | Yes | PTA, DPOAE |
| Inner hair cells | Maybe | Maybe | PTA, ABR |
| Hair cell synapses | Unknown | Maybe | PTA, ABR |
| Neuronal dysfunction | Unknown | Maybe | PTA, ABR |

ABR = auditory brainstem responses; DPOAE = distortion product otoacoustic emissions; NPC1 = Niemann-Pick type C1; PTA = pure tone audiometry.

If at any time a subject is reported to have clinically significant hearing impairment (CTCAE Grade 3 or higher). Such individuals will have repeat PTA and DPOAE testing as part of the hearing impairment AE evaluation. ABR will not be performed after 20 January 2021.

## 10.4. Appendix 4: Pregnancy Reporting

Certain information regarding pregnancy, although not considered an SAE, must be recorded, reported, and followed up as indicated. This includes the following:

Subjects should not become pregnant during the study. If a female subject, or the female partner of a male subject, becomes pregnant during any active treatment period, study treatment must be discontinued immediately and the investigator must report the pregnancy by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance, or designee, within 24 hours of confirmation of a pregnancy (ie, positive serum pregnancy test result). The outcome of pregnancy (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) must be reported by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance, or designee, within 24 hours of the pregnancy outcome being submitted to the study center. If the pregnancy results in a live birth, a postdelivery follow-up will be performed at least 28 days after the baby is born and must be reported to Mallinckrodt Global Pharmacovigilance, or designee, within 24 hours of the study center becoming aware of the follow-up information.

## 10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

All events of ALT ≥ 3 × ULN and with total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio > 1.5 (if international normalized ratio measured) which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE as outlined in Section 10.3.4 (excluding studies of hepatic impairment or cirrhosis).

Subjects with confirmed Hy's Law liver injury will be immediately withdrawn from study treatment and no rechallenge will be allowed.

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