Vtesse LLC, a Mallinckrodt Pharmaceuticals Company

Clinical Research
Protocol Amendment 15.0

A Phase 2b/3 Prospective, Randomized, Double-blind, Sham-controlled Trial of VTS-270 (2-hydroxypropyl-β-cyclodextrin) in Subjects with Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease

Protocol Number:	**VTS301**
Version Number:	Amendment 15.0
Version Date:	23 June 2021
Investigational Product:	VTS-270 (specific and well-characterized mixture of 2-hydroxypropyl-β-cyclodextrin [HP-β-CD])
IND Number:	[redacted]
EudraCT Number:	[redacted]
Development Phase:	2b/3
Sponsor:	Vtesse LLC, a Mallinckrodt Pharmaceuticals Company 90 Washington Valley Road Bedminster, NJ 07921
Co-Principal Investigator:	Name: [redacted] Telephone: [redacted] Fax: [redacted] E-mail: [redacted]
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PROTOCOL AMENDMENT 15.0 CHANGES

The objective of this amendment is reinforce the need for the investigator to assess whether subjects treated with intrathecal adrabetadex for NPC1 is 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 patients 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 (SOC) for Amendment 15 is provided below.

SUMMARY OF CHANGES FOR AMENDMENT 15.0

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 June 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.
4. 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.

The relevant sections of protocol Amendment 15.0 where the above changes may apply, either in whole or in part, are provided in the Study Synopsis, Duration of Subject Participation and Duration of Study; Section 7.1, Risk/Benefit Assessment; Section 15.1, Evaluations by Visit - Part C; and Section 17.1, Early Discontinurion.

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.

SIGNATURE OF AGREEMENT FOR APPROVAL OF PROTOCOL AMENDMENT 15

Refer to the e-signature page.

Approved: _____ **Date:** _____

[redacted]
Mallinckrodt Pharmaceuticals

[redacted]

1. INVESTIGATOR PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Vtesse LLC, a Mallinckrodt Pharmaceuticals Company with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice principles and to abide by the terms of this protocol.

Protocol Number: VTS301 Amendment 15.0

Protocol Title: A Phase 2b/3 Prospective, Randomized, Double-Blind, Sham-Controlled Trial of VTS-270 (2-hydroxypropyl-β-cyclodextrin) in Subjects with Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease

Protocol Date: 23 June 2021

Investigator Signature	Date
Print Name and Title	

2. TABLE OF CONTENTS

3. LIST OF TABLES

4. LIST OF ABBREVIATIONS

Abbreviations	Description of Abbreviations
24(S)-HC	24-(S) hydroxycholesterol
ABR	Auditory brainstem response
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-versus-time curve
$AUC_{0\text{-last}}$	Area under the concentration-versus-time curve from 0 to the last measurable time point
$AUC_{0\text{-inf}}$	Area under the concentration-versus-time curve from time 0 extrapolated to infinity
BAER	Brain stem auditory evoked response
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Oral clearance
C_{max}	Maximum concentration
CNS	Central nervous system
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DPOAE	Distortion product otoacoustic emission(s)
DS	Degree of substitution
DSC	Dose Selection Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ET	Early termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HP-β-CD	2-hydroxypropyl-β-cyclodextrin

Abbreviations	Description of Abbreviations
IC	Intracisternal
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICP	Intracranial pressure
ICV	Intracerebroventricular(ly)
IEC	Independent Ethics Committee
iIND	Investigator-initiated Investigational New Drug Application
IRB	Institutional Review Board
IT	Intrathecal
ITT	Intent-to-treat
IV	Intravenous
LE/LY	Late endosomal/lysosomal
LP	Lumbar puncture
mITT	Modified intent-to-treat
NCATS	National Center for Advancing Translational Sciences
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NPC	Niemann-Pick type C
NPC1	Niemann-Pick type C1 (phenotype)
NPC1	Niemann-Pick type C1 cat phenotype
Npc1 or Npc1$^{-/-}$	Niemann-Pick type C1 mouse phenotype
NPC-SS	NPC Severity Scale
PIR	Product Incident Report
PK	Pharmacokinetic(s)
PP	Per protocol
PT	Prothrombin time
PTA	Pure tone audiometry
QoL	Quality of life
SAE	Serious adverse event
SC	Subcutaneous
SCr	Serum creatinine
SOP	Standard operating procedure
SUSAR	Serious and unexpected suspected adverse reaction
$t_{½}$	Apparent half-life
T_{max}	Time to maximum concentration
TUG	Timed up and go

Abbreviations	Description of Abbreviations
ULN	Upper limit of normal
US	United States

5. PROTOCOL SYNOPSIS

Title	A Phase 2b/3 Prospective, Randomized, Double-blind, Sham-controlled Trial of VTS-270 (2-hydroxypropyl-β-cyclodextrin) in Subjects with Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease
Sponsor	Vtesse LLC, a Mallinckrodt Pharmaceuticals Company 90 Washington Valley Road Bedminster, NJ 07921
Number of Sites	Approximately 24 sites worldwide
Study Design	This is a multicenter, multinational, prospective, randomized, double-blind, sham-controlled, 3-part, efficacy and safety trial of VTS-270 administered by the lumbar intrathecal (IT) route every 2 weeks, with a planned enrollment of approximately 51 subjects (in Parts A and B) with Niemann-Pick type C1 (NPC1) disease. The study will be conducted in 3 parts: Parts A, B, and C. Part A evaluated 3 different dose levels of VTS-270 versus sham control, administered as 4 lumbar IT injections every 2 weeks, to determine the dose level for Parts B and C. A total of 12 subjects were enrolled and have completed Part A. Part B evaluated the safety and efficacy of the dose selected from Part A, 900 mg, compared with sham control in approximately 51 subjects, including the 12 subjects from Part A. Subjects received treatment with VTS-270 for up to 52 weeks (inclusive of Part A). Subjects who elected not to continue with Part C had 26 weeks of follow-up. All subjects have completed Part B. Part C will be an open-label extension phase of the study. Subjects who complete Part B, meet the criteria for dose reduction for a second time, or meet the rescue therapy criteria after 6 months of participation in Part B are eligible to participate in Part C. Subjects who are currently active in the National Institutes of Health (NIH) phase 1 study (Protocol 13-CH 0001) will also be eligible to participate upon completion of their participation in the phase 1 study. Additionally, subjects who have received prior written authorization from Vtesse to enroll directly into Part C are eligible to participate. Parts A and B subjects and NIH phase 1/2a subjects who transition into Part C will receive treatment with VTS-270 until the investigator considers VTS-270 to no longer be beneficial to the subject, or the development program is discontinued. The development program for VTS270 has been discontinued and Part C of the study is being terminated by the Sponsor. A European site-specific substudy was conducted as part of the Part C study. This substudy was designed to assess the safety and tolerability of the B. Braun Celsite® Spinal Access Port System (hereafter generally referred to as the "device") for the administration of VTS-270 every 2 weeks. The device is CE marked in Europe and consists of a subdermal access port connected to a catheter that is positioned in the lumbar IT space. Given that VTS-270 does not penetrate the blood-brain barrier and requires IT administration, the ability to administer VTS-270 via the device will obviate the need for biweekly lumbar punctures (LPs), as well as anesthesia, thereby removing a significant burden for subjects and site personnel. In this device safety and tolerability substudy, approximately 6 eligible Part C subjects who have received at least 3 lumbar IT doses (900 mg VTS-270) in Part C will undergo baseline assessments approximately 3 days prior to implantation of the device (same day as their last administration of VTS-270 via LP). The device will be implanted in the hospital, and the subject will remain in the hospital for 2 additional days post implantation. During the 3-day confinement period (Day 1 surgery, Days 2 and 3), subjects will be given intravenous (IV) antibiotics, which are part of the routine implantation procedure. Subjects entering the European site-specific device safety and tolerability substudy will continue on their Part C schedule of assessments but will have additional device safety

	evaluations. After a minimum of 2 weeks after placement of the device and confirmation of catheter patency, subjects will receive their VTS-270 dose via device infusion. Dosing will continue every 2 weeks for a total of 9 doses via the device. Specific evaluations will be conducted during the treatment period to assess device safety. These visits, designated Visit D1 through Visit D9, will occur at the same time as the subject's Part C schedule. Where there is duplication of assessments with the Part C schedule, only 1 assessment will be conducted. Following 9 device infusions of VTS-270 and the specific device safety assessments conducted during the treatment period, subjects will either enter the device pharmacokinetic (PK) substudy described below or will remain in the main Part C study and continue to receive VTS-270 via the device to evaluate its long-term safety and tolerability. A European site-specific device PK substudy was planned, but no subjects consented.
Dose Reduction	The following are guidelines for which dose reduction on an individual subject basis was allowed in Part B: Subjects who, in the opinion of the investigator, experienced a drug-related adverse event (AE) after any blinded IT treatment that was considered clinically relevant and impactful to the subject's function could have their dose reduced to 600 mg per IT administration for subsequent IT dosing intervals following discussion with the unblinded medical monitor. If, following dose reduction to 600 mg, a subject continued to experience AEs as described above, the subject's dose could be further reduced to 400 mg per IT administration for subsequent dosing intervals following discussion with the unblinded medical monitor. If, following dose reduction to 400 mg, a subject continued to experience a drug-related clinically relevant AE, the dose was NOT to be reduced further and the subject was to be discontinued from Part B of the study, being given the option to transition into Part C at a lower dose, based on discussion with the unblinded medical monitor and on a case-by-case basis. During Part C, the same guidelines apply for dose reduction, with each subject for whom dose reduction is considered being individually reviewed with the medical monitor.
Dose Re-Escalation	Dose re-escalation is not permitted
Rescue Option	Not applicable for Part C
Primary Objective	**Part A:** The primary study objective in Part A was to select the dose of VTS-270 to be used in Part B and Part C. Dose selection criteria included safety and tolerability including a thorough audiologic evaluation. Preliminary efficacy data was provided to the Dose Selection Committee (DSC) to assist, if necessary, in dose selection. **Part B:** The primary study objective in Part B was to evaluate, in a double-blind sham-controlled design, the progression of the neurologic manifestations of NPC1 disease following 52 weeks of treatment for subjects treated with VTS-270 compared to sham control, using the following assessments: • The Neimann Pick Type C Severity Scale (NPC-SS) composite which consists of the sum of 4 components of the NPC-SS: ambulation, fine motor, cognition, and swallowing. • The blinded Clinician-Clinical Global Impression of Change (CGIC). **Part C:** The primary study objective in Part C is to evaluate the long-term safety, tolerability, and efficacy of VTS270.
Secondary Objectives	**Part A:** There were no secondary objectives for Part A.

	Part B: The secondary objectives for Part B were divided into 2 categories: key secondary objective and other secondary objectives. The key secondary objective for Part B was to evaluate the progression of the neurologic manifestations of NPC1 disease using the total NPC-SS score, excluding the hearing domain and auditory brainstem response (ABR) modifier results, following 52 weeks of treatment for subjects treated with VTS-270 compared to sham controls and the Caregiver-CGIC. Other secondary objectives were to: 1. Evaluate the safety and tolerability of VTS-270 administered IT via LP every 2 weeks, compared to sham control. 2. Assess quality of life (QoL) using the EQ-5D-3L following 52 weeks of treatment for subjects treated for 52 weeks with VTS-270 compared to sham controls. 3. Further assess the efficacy of VTS-270 on treating the neurologic symptoms of NPC1 by comparing subjects treated for 52 weeks with VTS-270 compared to sham control on: • Subjects who required rescue following at least 6 months of treatment. • The 9 major domains of the NPC-SS. • The total NPC-SS score (hearing domain and ABR modifier included). • Time to a 1-point increase (worsening) on the NPC-SS composite score. • The annualized rate of change (slope) of the NPC-SS composite score. • Timed up and go (TUG) test. • 9-Hole peg test. **Part C:** The secondary study objectives in Part C are to: 1. Assess the safety and tolerability of the B. Braun Celsite Spinal Access Port utilized to administer VTS-270 (device safety and tolerability substudy). 2. Assess the plasma and cerebrospinal fluid (CSF) PK of VTS-270 concentrations in subjects receiving the 900 mg dose of VTS-270 via the B. Braun Celsite Spinal Access Port (device PK substudy).
Exploratory Objectives	**Part A:** There are no exploratory objectives for Part A. **Part B:** The exploratory study objectives in Part B are to: 1. Collect CSF, urine, and plasma samples from the subjects receiving study drug, and urine and plasma samples from subjects randomized to sham control, at prespecified intervals. Samples will be stored for exploratory biomarker analyses. 2. Further evaluate the efficacy of VTS-270 on treating the neurologic symptoms of NPC1 by comparing subjects treated with VTS-270 compared to sham control on: • The composite NPC-SS in completers. • The composite NPC-SS outcome assuming data missing at random using a standard multiple imputation model. • The composite NPC-SS using a pattern mixture model. • Assigning individual subject changes (+1 if improved, 0 if unchanged, or -1 if worse relative to baseline). **Part C:** There are no exploratory objectives for Part C.

Number of Subjects	Approximately 51 in Parts A and B. Part C may enroll more than 51 subjects. Approximately 6 in the device safety and tolerability and device PK substudies.
Subject Selection Criteria	**Parts A and B – not applicable as Part A and B are completed.** **Part C – NO NEW SUBJECTS ARE ALLOWED TO ENTER THE STUDY AS OF 20 JANUARY 2021** Inclusion Criteria: 1. Subject has completed Part B, meets the criteria for dose reduction for a second time or meets the criteria for the rescue option. OR 2. Subject is a current participant in the NIH phase 1/2a open-label study and: a. Subject agrees to convert from the dose of VTS-270 currently receiving as a subject in the NIH phase 1/2a protocol to the dose chosen for Parts B and C of this study, 900 mg. b. Subject agrees to convert from the monthly dosing regimen used in the NIH phase 1/2a protocol to an every 2-week dosing regimen. c. In instances where NIH phase 1/2a subjects eligible to enroll into Part C are unable to convert from their current NIH phase 1/2a dose or monthly regimen, the investigator must receive prior written authorization from the sponsor for the subject to enter Part C of the study on an amended dose and/or regimen. OR 3. Subject has received prior written authorization from Vtesse to enroll directly into Part C. 4. 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. 5. 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. **Subject Inclusion Criteria for European Site-specific Device Safety and Tolerability Substudy – Not applicable – enrollment in the Device Substudy concluded Aug 2018.** **Subject Exclusion Criteria for the European Site-specific Device Safety and Tolerability Substudy – Not applicable - enrollment in the Device Substudy concluded Aug 2018.** **Subject Inclusion Criteria for the European Site-specific Device Pharmacokinetic (PK) Substudy – Not applicable – no subject consented to participate in the PK Substudy.**
Test and Control Product, Dose, and Route of Administration	VTS-270 will be provided in appropriately labeled vials, formulated as a 200 mg/mL injectable solution. An unblinded pharmacist/designee at each investigational site will be responsible for dispensing or preparing the assigned dosage of 900 mg for administration in 4.5 mL. In the case of dose reduction, the 600 mg dose is administered in 3 mL and the 400 mg dose is administered in 2 mL. <u>VTS-270 Administration via Lumbar Puncture and Sham Lumbar Puncture</u> In Part A, VTS-270 administration via LP and sham will be performed every 2 weeks for 4 administrations. In Part B, VTS-270 administration via LP and sham will be performed every 2 weeks for 52 weeks. In Part C, VTS-270 will be administered via LP or the device

	every 2 weeks. Instructions for administration via the device are presented in the following subsection. The LP and/or sham is to be performed under monitored anesthesia care (conscious sedation) with an appropriate oral or IV agent and performed by an unblinded study physician. General anesthesia will be allowed on a case-by-case basis, following discussion with the medical monitor, in those subjects for whom a medical condition necessitates it. Parents/caregivers will not be present in the room during lumbar IT or sham treatment. Thus, the subject and the parent will be blinded to treatment, the former a consequence of anesthesia. The *sham procedure* will consist of 1 to 2 small needle pricks on the lower back at the location where the LP and IT injection is normally made. The needle(s) will break the skin but no lumbar puncture or needle insertion will occur. The needle prick(s) will be covered with the same bandage that is used to cover the IT injection normally, thus simulating the appearance of an IT LP injection. To maintain the blind, a similar type of anesthesia, sedation, or minimal sedation (eg, a low dose of an anxiolytic) should be used for the sham procedure as for the subject receiving study drug, following institutional procedures. The subject will be kept in the procedure room for approximately 30 minutes, simulating the same amount of time that subjects administered study drug are kept for administration procedure. VTS-270 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 group. Prior to the VTS-270 injection, a volume of CSF fluid approximately equal to the VTS-270 dose is to be removed. Anesthesia or sedation will be used for the IT dosing procedure, following institutional guidelines and procedures. All subjects, sham and study drug, are required to lie flat with feet elevated for 30 to 45 minutes following dosing. For the 3 days following each procedure, subjects in both the sham and active treatment groups are to avoid acoustic overstimulation and minimize exposure to loud noises, eg, headphones for music or video games. <u>Device Administration (European Site-specific Device Safety and Tolerability Substudy, Part C)</u> VTS-270 administration via the device will be conducted every 2 weeks. There are no adjustments for weight or subject age. The device area will be prepared for sterile manipulation following standard site procedures. Cerebrospinal fluid will be withdrawn through the port of the device. The first 1 mL will be discarded, and then at least 3 mL will be collected for clinical laboratory tests (approximately 2 mL) and VTS-270 concentration (approximately 1-2 mL). The volume of CSF to be removed should be approximately equal to that being administered. VTS-270 will be administered as a slow bolus over 1 to 2 minutes with a maximum rate of infusion of 4.5 mL/minute. Non-coring needles adapted for use with the device should be used. Normal hypodermic needles will damage the port septum and may cause leakage of the system or blockage due to small silicone particles from the septum. Subjects are to receive the same dose of VTS-270 administered during Study VTS301 Part C by IT LP. Following the infusion of VTS-270, the system should be flushed with 1.5 mL of preservative-free 0.9% saline solution. For 30 to 45 minutes following dosing, subjects should lie flat with feet elevated.

Duration of Subject Participation and Duration of Study	**Part C** Part C is an open-label extension. The total duration of subject participation is until the investigator considers VTS-270 to no longer be beneficial to the subject, or the development program is discontinued. The Sponsor has discontinued the VTS-270 development program following determination of a negative benefit/risk balance. Treatment with VTS-270 should be discontinued as soon as possible; in consideration of the need to determine a transition plan, treatment with VTS-270 will be permitted for up to an additional 9 months (20 October 2021). The potential extension of treatment is contingent upon reconsent of the subject and approval by their applicable IRB/EC and health authority. After 21 June 2021, subjects may not continue to receive IT 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 patients treated with adrabetadex and sham-treated patients on any efficacy measures in this randomized, controlled trial.
Efficacy Evaluations	
Primary Endpoint	**Part B:** Not applicable, as Part A/B is complete.
Secondary Endpoints	**Part B:** Not applicable as these analyses are complete. **Part C:** After 20 January 2021, efficacy endpoints for Part C will not be reported. • The change from baseline to each assessment in a composite outcome that is the sum of the ambulation, cognition, fine motor, and swallowing components of the NPC-SS. • The change from baseline to each assessment in total NPC-SS with the hearing domain and ABR modifiers removed. • Proportion of responders (defined as no change or improvement on NPC-SS total score with hearing domain and ABR modifiers removed) at each assessment. • Proportion of blinded Clinician-CGIC responders (defined as a score of no change, minimally improved, moderately improved, or markedly improved) at each assessment compared to baseline. • Summary of AEs, concomitant medications, physical examinations, audiologic examination, and clinical laboratories. • Change from baseline in the EQ-5D-3L questionnaire at each assessment. • Change from baseline to each assessment in each of the 9 clinical domains of the NPC-SS. • Change from baseline to each assessment in the total NPC-SS with hearing domain and ABR modifier included. • Time to 1-point increase (worsening) in NPC-SS composite score. • The composite NPC-SS mean annualized rate of change (slope) from baseline to each assessment.
Other Evaluations	• CSF, urine, and plasma protein (eg, calbindin D) biomarkers. • CSF and plasma sterol biomarkers. • Gene and protein expression.
Safety Evaluations	• AEs. • Audiologic testing.

	• Clinical laboratory tests (hematology, chemistry, coagulation, urinalysis). • Vital signs. • Physical and neurological examinations. • Electrocardiograms (ECGs). • Wound check/port and catheter track check for device safety and tolerability. • Intracranial pressure via LP for subjects with device. • CSF routine laboratory tests for subjects with device.
Statistics: Primary Analysis Plan	Not applicable, Part A/B completed and reported.
Rationale for Number of Subjects	The sample size for this study is approximately 51 subjects in Parts A and B combined. The rationale for the sample was based on both practical and statistical considerations. The sample size was determined based on the potential number of available subjects for this ultra-rare disorder. Based on the comparison of the NIH phase 1 subjects and similar subjects in the NIH natural history data set, approximately 51 subjects, 16 on sham and 35 on active treatment, will allow for the detection of clinically relevant difference of the sum of the 4 NPC-SS score domains that make up the composite outcome. The assumptions applied in the power calculation provide 79% power to detect a difference between the VTS-270 and sham groups by ANCOVA.

6. BACKGROUND

6.1. NPC1 Disease

Niemann-Pick type C1 (NPC1) disease is a rare, neurodegenerative, inherited, autosomal recessive disorder which primarily manifests in children and teenagers. Niemann-Pick type C (NPC) disease is characterized by systemic disease (hepatic, splenic, pulmonary) and progressive neurologic manifestations including ataxia, dementia, and seizures resulting in early death by the age of 20 to 25 years. The prevalence of NPC disease is estimated to be 1 in 150,000 people in the United States (US) (Millat 1999) and 1 in 100,000 people in the European Union (EU) (Vanier 2010).

NPC1 disease is a result of mutations in the NPC1 gene whose protein normally functions in neurons and other cells to transport unesterified cholesterol and sphingolipids from the late endosomal/lysosomal (LE/LY) compartment. Cells have a complex trafficking system to control the cellular concentration of cholesterol, sphingolipids, and other lipids. Part of this system is the lipid efflux from LE/LY via the action of NPC1, at least in part. In individuals lacking or with deficient NPC1, cholesterol, bis-(monoacylglycerol) phosphate, and various sphingolipids accumulate to toxic concentrations in lysosomal storage organelles. Most of the evidence supports that the primary storage metabolite in NPC1 disease, especially in the peripheral tissues, is low-density lipoprotein-derived cholesterol (Rosenbaum & Maxfield 2011). Cholesterol and sphingolipids are important lipids in mammalian physiology; however, in excessive concentrations, both are toxic to cells resulting in cellular dysfunction and death. The neuropathological abnormalities in NPC patients that are caused by this block in cholesterol transport include brain atrophy, widespread neuronal cytoplasmic vacuolization, and neuronal loss, with the Purkinje cells being the most severely affected.

6.2. VTS-270 (A Unique Mixture of 2-hydroxypropyl-beta-cyclodextrin [HP-β-CD])

Cyclodextrins (CD), as well as 2-hydroxypropyl-β-cyclodextrins (HP-β-CDs) in general, have been used extensively to modulate cholesterol and other lipids' composition of model and biological membranes. Cyclodextrins are also being used extensively to solubilize pharmaceuticals, and various regulatory authorities have approved them as delivery agents. 2-hydroxypropyl-beta-cyclodextrin has been approved for use as an excipient in oral and intravenous (IV) pharmaceuticals for many years. VTS-270 is the first unique mixture of HP-β-CD being developed as an active pharmaceutical product for a specific disease.

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 VTS-270 is strictly controlled during manufacturing, resulting in a drug with a tightly controlled degree of substitution (DS) and a defined fingerprint of the different species present in the mixture. This unique fingerprint distinguishes VTS-270 from all other commercially available HP-β-CDs.

All HP-β-CDs are amorphous mixtures of different isomers, characterized by the DS, which represents the average substitution of the hydroxyl with propyl groups per HP-β-CD molecule. The active drug substance in Vtesse's investigational drug product (VTS-270) is KLEPTOSE® HPB parenteral grade, which has an average DS of 4.34.

The average DS and unique substitution fingerprint are critical quality attributes of the drug for safety and efficacy. Scientists at the National Center for Advancing Translational Sciences (NCATS) have demonstrated that the fingerprint pattern of different substituted species and the average DS of methylated betacyclodextrin have a dramatic effect on efficacy as measured by the ability to clear cholesterol sequestered in NPC cell lines and to restore normal lysosomal function and structure (Rosenbaum 2010). An extensive nonclinical safety and efficacy package has been generated specifically for VTS-270 to demonstrate that this unique version of HP-β-CD is suitable for intrathecal (IT) dosing in pediatric patients during clinical trials.

The therapeutic potential of HP-β-CD was discovered in 2009 when HP-β-CD, injected systemically to 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 LE/LY storage organelles where unesterified cholesterol accumulates in NPC 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 CoA:acyl transferase and subsequent efflux (Rosenbaum & Maxfield 2011; Abi-Mosleh 2009). 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.

6.3. Overview of Nonclinical Studies

Though multiple cellular processes may play a role in the pathogenesis of NPC1, including alterations in autophagy and sphingolipid homeostasis, impaired cholesterol mobilization from the lysosomal compartment is most likely the primary result of loss of NPC1 function and thus the main cause of the signs and symptoms in NPC1. Experiments have been conducted in vitro as well as in vivo in mouse and feline models of NPC1 and in humans that demonstrate the effects of HP-β-CD treatment on NPC1 deficiency. It has been shown that HP-β-CD works from inside endocytic organelles to reduce cholesterol storage and accumulation (Rosenbaum 2010), and that a portion of the cholesterol liberated from lysosomes is transferred to the endoplasmic reticulum for regulation of cholesterol homeostatic responses (Abi-Mosleh 2009). In vivo studies in animal models of NPC1 and in patients with NPC1 have shown that this redistribution of cholesterol modulates multiple pathways and improves NPC1 symptoms, including increasing lifespan (Tortelli 2014; Sidhu 2015; Maarup 2015).

Following its endocytosis into the lysosome, the cellular/molecular mechanism of HP-β-CD activity in the treatment of NPC disease is not known, but 3 potential mechanisms have been postulated.

The mouse and cat models of NPC disease are naturally occurring and genetically similar to the human disease (Walkley & Suzuki 2004). Recent studies in these 2 models have shown that administration of the drug either directly into the lateral ventricle (intracerebroventricularly

[ICV]) of mice or IT injection at the cerebellomedullary cistern of cats, or central nervous system (CNS) administration in combination with systemic treatment in cats and mice, greatly extends the lifespan of the animals and prevents or delays neurological symptoms (Aqul 2011; Vite 2015; Study Nos. Einstein-Mouse-001; Einstein-Mouse-002; Einstein-Mouse-003; 804000).

In studies conducted in the naturally occurring NPC1 cat (Vite 2008), investigators recognized a dose-dependent increase in hearing threshold associated with therapy as determined by brain stem auditory evoked response (BAER) testing. To further assess the effect of HP-β-CD on hearing threshold, normal cats were administered the drug subcutaneously (SC) at either 4000 mg/kg or 8000 mg/kg body weight, or IT at a dose of 4000 mg/kg brain weight. HP-β-CD caused a significant increase in hearing threshold following 1 dose of 8000 mg/kg SC or 120 mg IT and the effect was maintained for at least 12 weeks. Repeated weekly SC administration of 4000 mg/kg HP-β-CD resulted in a similar increase in hearing threshold. These studies are the first to describe a specific negative effect of HP-β-CD on the auditory system and suggest the need for auditory testing in subjects receiving similar doses of HP-β-CD (Ward 2010).

The safety of Kleptose HPB (VTS-270) has been demonstrated by nonclinical toxicology studies conducted to support the use of Kleptose HPB as a pharmaceutical excipient by Janssen Pharmaceutical Research (Janssen Drug Master File 9428) and with additional toxicology studies in cats and juvenile dogs conducted by the National Institutes of Health (NIH) Therapeutics for Rare and Neglected Diseases and collaborators to further support its use as an active drug product for the treatment of NPC disease. Kleptose HPB is the active ingredient in VTS-270.

VTS-270 has been safe and well tolerated in NPC cats treated every 2 weeks via the IT route. VTS-270 has also been administered IT in the United States in a NIH phase 1/2a study (13-CH-0001) and under investigator-initiated Investigational New Drug applications (iINDs), and is currently being administered IT in a global phase 2b/3 study (VTS301; the study described in this protocol).

6.3.1. Overview of Nonclinical Toxicology Studies

The pharmacological properties of HP-β-CD have been extensively studied in Npc1-/- mice and NPC1 cats. The pharmacokinetic (PK) properties have been studied in rats, dogs, Npc1-/- mice, and NPC1 cats. The safety of HP-β-CD was evaluated in a comprehensive toxicology program conducted by Janssen Research Foundation (Janssen) to support its use as a pharmaceutical excipient. Nonclinical toxicology studies included single and repeat-dose toxicity studies, in vitro and in vivo genotoxicity assays, carcinogenicity studies, reproductive and developmental toxicity (Segment I, II, and III) studies, and special toxicity (local tolerance and mechanistic toxicity) studies. HP-β-CD has been approved for use as an excipient in oral and IV pharmaceuticals for over a decade. Vtesse has obtained the rights to reference the Roquette Freres Type IV Drug Master File No. 9420 for HP-β-CD, the drug substance. HP-β-CD is being developed for the treatment of NPC1, a lethal, autosomal recessive, lysosomal storage disorder characterized by neurodegeneration in early childhood and death in adolescence. Since ICV administration was the intended route for clinical use, canine repeat-dose toxicity studies of 6 months were initiated. Clinical ICV administration using an Ommaya reservoir resulted in bacterial infections and therefore administration was shifted to IT delivery with testing of IT delivery of HP-β-CD in *NPC1* mutant cats. Further details of these nonclinical studies are presented in the Investigator's Brochure.

6.4. Overview of Clinical Studies

6.4.1. NIH Natural History Study

A natural history study is being conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) in Bethesda, MD, entitled "Evaluation of Biochemical Markers and Clinical Investigation of Niemann-Pick Disease, Type C". This study is ongoing and has enrolled 97 subjects with NPC disease as of November 2016 (NCT00344331). Disease progression is being tracked using the NPC Severity Scale (NPC-SS).

Planned assessments in this study include disease severity, neuropsychiatric, ophthalmological, audiological, speech, and language pathology evaluations. Planned laboratory evaluations include cholesterol metabolite measurements in blood, urine, and cerebrospinal fluid (CSF). Review of the data collected from 2006 to August 2014 has shown that the mean age at first symptoms and diagnosis was 3.8 and 9.2 years, respectively.

6.4.2. Phase 1/2a Study 13-CH-0001

Vtesse LLC, a Mallinckrodt Pharmaceuticals Company, in concert with its development partner at the NIH/NICHD, has recently completed a phase 1/2a, open-label, single-center, ascending, multiple-dose, cohort dose-escalation study of VTS-270 in 14 subjects with NPC1 disease (NCT01747135). The study was designed to characterize the feasibility, safety, tolerability, PK, and activity of VTS-270 administered monthly via lumbar injection to subjects with NPC1. Subjects with confirmed NPC1 disease have received monthly lumbar IT injections of VTS-270. This study applied safety data to guide dose escalation and plasma 24-S hydroxycholesterol (24[S]-HC) concentrations to potentially identify an effective dose of VTS-270.

The primary objectives of this study were:

- To assess the safety and tolerability of IT administration of VTS-270 with NPC1 disease.
- To examine plasma PK of VTS-270 after IT administration.
- To determine a biochemically active dose of VTS-270 as assessed by changes in plasma 24(S)-HC concentration.

Secondary objectives of this study were:

- To evaluate the use of candidate plasma and CSF biomarkers.
- To perform an exploratory evaluation of clinical outcome measures for possible use in further clinical development.

Since October 2013, 14 subjects, aged 4 to 23 years, enrolled in dosing cohorts of 3 subjects each and received VTS-270 doses ranging from 50 to 1200 mg monthly. The first 3 enrolled subjects received 50 mg ICV via an Ommaya reservoir. However, due to complications associated with the Ommaya device implantation procedure (ie, *Propionibacterium acnes* infections), subsequent subjects received doses ranging from 200 mg to 1200 mg monthly via the IT (lumbar) route.

6.4.2.1. Phase 1 Study - Safety Evaluation

Adverse Events Observed with ICV Administration

All adverse events (AEs) observed after ICV administration were considered unlikely to be related to study drug and included Common Terminology Criteria for Adverse Events (CTCAE) grade 1 AEs and 3 serious adverse events (SAEs). The SAEs involved the removal of the Ommaya reservoirs in 2 subjects in Cohort 1 due to *P. acnes* colonization/infection and a false positive CSF gram stain in 1 subject, which resulted in increased subject and parent anxiety and their request to remove the Ommaya reservoir. In the investigator's opinion, the complications leading to removal of the Ommaya reservoir were protocol related, not drug related.

Adverse Events Observed After ICV and IT Administration

Seven subjects have received 1200 mg IT, the highest dose tested.

Eleven subjects have received 900 mg IT, 9 subjects have received 600 mg IT, 7 subjects have received 400 mg IT, 9 subjects have received 300 mg IT, 8 subjects have received 200 mg IT, and 3 subjects have received 50 mg IT. All but 1 subject experienced at least 1 AE after IT administration. All AEs observed after ICV administration were considered unlikely to be related to study drug and included CTCAE grade 1 AEs and 3 SAEs.

All of the SAEs for ICV treatment were considered to be Ommaya related, not study-drug related. No deaths have been reported with VTS-270 administration. As of September 2015, there were 2 SAEs (Subject # [redacted] status epilepticus; Subject # [redacted] emesis and bloody stool) reported that were considered possibly related to VTS-270 in subjects administered study drug IT.

The most common AEs experienced by subjects involved the ear and labyrinth systems. Sensorineural hearing loss was reported in 57% (8/14 subjects) and tinnitus in 21% (3/14 subjects). Other AEs occurring in 2 or more subjects included headache, post lumbar puncture (LP) 57% (8/14 subjects); emesis 50% (7/14 subjects); elevated liver enzymes—pre and post drug 36% (5/14 subjects); fatigue after IT administration 29% (4/14 subjects); seizure, change in pattern or frequency 29% (4/14 subjects); fever 21% (3/14 subjects); tingling hands 14% (2/14 subjects); proteinuria 14% (2/14 subjects); urobilinogen 14% (2/14 subjects); discomfort at LP site 21% (3/14 subjects); and fecal incontinence 14% (2/14 subjects). Except for sensorineural hearing loss and aspiration event during anesthesia, all of the most frequently occurring AEs previously mentioned were grade 1 or grade 2, as were most of the AEs reported during the study. Of the 8 reported AEs of sensorineural hearing loss on audiometry, 3 AEs were grade 1, 1 AE was grade 2, and 4 AEs were grade 3, none of which were considered to be a clinical change in hearing.

Results of assessments of ambulation, ataxia, posture, gait, and swallowing have been largely unchanged at the doses of VTS-270 administered to date, in some cases with greater than a year of treatment on VTS-270. Preliminary analysis of the biomarker 24(S)-HC, an indicator of target engagement, has shown only modest increases with VTS-270 dose escalation.

6.4.3. VTS-270–Related Ototoxicity

Ototoxicity, an expected AE based on the feline model, was observed in the NIH phase 1/2a study (13-CH-0001) at doses of 200 mg and higher, as assessed by tonometric audiometry. These data track with murine and feline NPC models that show a dose-dependent hearing loss with VTS270 treatment; however, variable susceptibility has been seen, which is common in otopathology, and which suggests a number of factors may influence the ototoxic properties of VTS-270.

Additionally, the degree of recovery of ototoxicity between monthly IT treatments is unclear, and although data are limited, subjects have demonstrated partial, and in some cases, complete recovery on pure tone audiometry (PTA). Additionally, it should be noted that the interpretation of ototoxicity is confounded by the fact that hearing loss occurs naturally in the progression of NPC disease. Based on this, there is an expectation that some degree of ototoxicity may occur in subjects receiving VTS-270 with uncertain reversibility.

The hearing loss associated with VTS-270 is complex. In a phase 1 study, mid- to high-frequency hearing loss was documented in all participants (Ory 2017). The mechanism of hearing loss is not fully understood; however, based on preclinical data and our experience, it is possible that dose or duration of dosing may result in greater hearing changes.

6.4.4. Rush University iIND Studies

Approximately 23 subjects are being treated under an iIND at Rush University. These subjects have received VTS-270 doses ranging from 200 mg to 750 mg IT every 2 weeks. With the exception of hearing loss in 1 subject who had the VTS-270 dose de-escalated, no treatment-related severe or serious AEs were reported.

6.4.5. Efficacy Based on Comparison Data from Subjects Treated with VTS-270 with Comparable Subjects in the Natural History Study

To assess the effect of VTS-270 in NPC patients, the rate of change in the NPC-SS and its major domains was compared in a data set of subjects in the NIH phase 1/2a study with comparable age in the natural history study. Results of the latest data analysis are summarized below.

An effect of adrabetadex above that seen with miglustat cannot be demonstrated in a post-hoc comparison subsetted by baseline miglustat use.

6.5. Dose Rationale

In Part A, the dose-finding portion of this study, VTS-270 in a fixed-dose regimen at 900 mg, 1200 mg, or 1800 mg was administered to 3 subjects each by IT administration every 2 weeks for 4 dosing cycles. After the last subject in Part A received 4 IT infusions at the randomized dose level or sham including the 2 weeks observation following the 4th treatment, an independent Dose Selection Committee (DSC) reviewed the safety and efficacy data for dose selection. The dose of 900 mg was selected for Parts B and C based on evaluation of the safety, audiometric, and preliminary efficacy data of the 4 cycles of each of 3 doses tested in Part A. The fixed-dose regimen in Part A was chosen to allow for similar exposure and comparable safety and efficacy assessment across the study population.

The doses initially chosen for evaluation in Part A were based on the therapeutically effective ranges identified in the naturally occurring *NPC1* mutant cat model (intracisternal [IC] dosing) and on preliminary clinical data from the open-label iIND and NIH phase 1/2a clinical study (IT dosing).

Because the drug is administered directly into the CNS compartment, dosing is based on brain weight (mg VTS-270/kg brain weight). Brain weight in humans is similar from approximately 4 years of age (1200 g) through adulthood (1400 g) so there is no dose adjustment based on age or body size. Summary dosing and therapeutic effectiveness data from the *NPC1* mutant cat model and preliminary clinical data are shown in Table 1.

Table 1: Summary Dosing and Therapeutic Effectiveness Data

***NPC1* Mutant Cat 30 g Brain Weight**						**NPC Child 1200 g Brain Weight**			
HP-β-CD IC (mg)	**HP-β-CD IC (mg/kg) Brain**	**HP-β-CD IC (mg/mL) CSF**	**Purkinje Cell Survival**	**Delay of Ataxia**	**Otoxicity**	**HP-β-CD IT (mg)**	**HP-β-CD IT (mg/kg) Brain**	**HP-β-CD IT (mg/mL) CSF**	**Otoxicity**
3.8	127	0.9	+	+	-				
						200	166	1.5	-
7.5	250	1.8	NT	+	-	300	250	2.2	+
						400	333	2.9	+
15	500	3.7	NT	++	-	600	500	4.4	+
						900	750	6.5	+
30	1000	7.5	++	+++	++	1200	1000	8.7	+
						1800	1500	13.0	
Maximum Feasible Dose in Humans:						2000	1666	14.5	
60	2000	15	NT	++++	+++	2400	2000		
120	4000	30	++	+++++	+++	4800	4000		

CSF = cerebrospinal fluid; HP-β-CD = 2-hydroxypropyl-β-cyclodextrin; IC = intracisternal; IT = intrathecal; NPC = Niemann-Pick type C; NT = not tested.

7. STUDY RATIONALE

At present, no therapies are approved for use in the United States for patients with NPC1 disease. Miglustat (ZAVESCA®), an imino sugar, has been approved for the treatment of patients with NPC1 disease in many countries outside the United States, including many countries in Europe. The Food and Drug Administration (FDA) did not approve miglustat for the treatment of NPC1 in the United States; however, miglustat was approved by the FDA for a subset of patients with Gaucher's disease. To help address this significant unmet medical need, researchers have

identified the cholesterol-sequestering agent HP-β-CD as a potential treatment for patients with NPC1 disease.

In naturally occurring nonclinical models of NPC1 disease in the mouse and cat, HP-β-CD has been found to:

- Mobilize excess cellular cholesterol caused by the metabolic deficiency as demonstrated in both in vitro and in vivo models (Liu 2010; Ramirez 2010; Aqul 2011).
- Delay onset of signs and symptoms and prolong survival by ~ 100% in the mouse *Npc1* model (Ramirez 2010).
- Prolong survival by ~ 8-fold, decrease Purkinje cell loss, and improve gait in the cat *NPC1* model (Vite 2017).

On the basis of these findings, HP-β-CD has entered clinical evaluation in an NIH phase 1/2a study (13-CH-0001) to evaluate the safety of multiple escalating doses. This pivotal phase 2b/3 efficacy trial in subjects with NPC1 disease is designed to formally evaluate the efficacy of HP-β-CD (VTS-270) for the management of the neurologic manifestations of NPC1 disease.

7.1. 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, patients typically develop progressive cerebellar dysfunction, hearing loss, and motor and cognitive deterioration with death typically occurring during adolescence.

2-hydroxypropyl-β-cyclodextrin administered IT into the 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 iIND).

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 this study shows no benefit of adrabetadex on the pre-specified co-primary endpoints. A post-hoc analysis evaluating the effect of miglustat use showed that subjects receiving miglustat (with or without adrabetadex) show evidence of disease stabilization but subjects receiving adrabetadex without miglustat show 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 NIH 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 or SAEs, is supported, only in those subjects (or legally authorized representative):

- who appear to be benefiting from IT 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 patients treated with adrabetadex and sham-treated patients on any efficacy measures in this randomized, controlled trial.

7.2. Sham Procedure Rationale

The sham procedure control group for this pivotal study was carefully considered over the alternatives (ie, unblinded concurrent non-intervention control, historical control, or a blinded placebo control). The sham procedure control (monitored anesthesia care [conscious sedation] or if medically necessary, general anesthesia, and 1 to 2 skin needle pricks) minimizes both undue risk to the NPC1 subjects and the potential for bias. Because only the IT injection staff would be unblinded to treatment assignment, the assessment of the safety and efficacy of VTS-270 by the investigator, outcomes raters, and all other site staff is unbiased and no different than if the trial were fully placebo-controlled, but without taking the risks inherent in performing lumbar IT placebo injections every 2 weeks.

Subjects enrolled in the VTS301 study were randomly assigned in a 3:1 ratio (in Study Part A) or a 2:1 ratio (in Study Part B) to receive either IT administered VTS-270 or a sham control procedure. The intention of the sham procedure control group was to provide the most unbiased assessment of the efficacy and safety of VTS-270 in the intended population of patients with NPC1 disease in this phase 2b/3 pivotal study.

The sham procedure for this study specifically consisted of 1 to 2 needle skin pricks at the same site where a lumbar puncture would occur; the needle(s) were not inserted and no LP was performed in sham control subjects. In order to ensure that the sponsor, the investigator, key members of the investigator's staff involved in assessments of efficacy and safety, and the subject's parents/caregivers remained fully blinded to the treatment assignment, a separate treatment team was tasked with conducting the IT administration of VTS-270 or sham control procedures. This treatment team consisted of a specialist who was credentialed and experienced in performing IT injections in pediatric patients (ie, an anesthesiologist, neurologist, pediatric oncologist, interventional neuroradiologist, etc.) and an assistant (ie, nursing staff to monitor safety and help maintain sterile field). Besides their role on a treatment team, these individuals

were not involved in any study-specific clinical evaluations, including AE assessments; however, physicians in this role could serve as the treating physician/clinician. In this role, the treating physician/clinician was the primary point of contact for the subject and family for their overall medical care throughout the course of the trial. However, if the treating physician/clinician was the IT/sham administrator, a separate blinded clinician at the site (eg, physician, physician assistant, nurse practitioner) was responsible for querying and assessing any AEs. The procedure (sham procedure or IT injection) was performed in a separate procedure room away from the key study staff involved in efficacy and safety assessments and without the parents/caregivers present.

7.3. Rationale for Administration of VTS-270 via Spinal Intrathecal Access Port System

Given that VTS-270 does not penetrate the blood-brain barrier and requires IT administration, the ability to administer VTS-270 via a spinal IT access port system will obviate the need for biweekly LPs, as well as anesthesia, thereby removing a significant burden for subjects and site personnel. Part C of the study includes a substudy to assess the safety and tolerability of the B. Braun Celsite Spinal Access Port System, which is CE marked in the European Union, for the administration of VTS-270 every 2 weeks. An additional substudy of Part C will evaluate the PK of VTS-270 administered using the B. Braun Celsite Spinal Access Port System (hereafter generally referred to as the "device").

8. STUDY OBJECTIVES

8.1. Primary Objectives

8.1.1. Part C

The primary study objective in Part C is to evaluate the long-term safety, tolerability, and efficacy of VTS-270. Following a determination of a negative benefit/risk balance on 20 January 2021, the objective for Part C has been changed to evaluate only longer-term safety and tolerability.

8.2. Secondary Objectives

8.2.1. Part C

The secondary study objectives in Part C are to:

1. Assess the safety and tolerability of the B. Braun Celsite Spinal Access Port utilized to administer VTS-270 (device safety and tolerability substudy).
2. Assess the plasma and CSF PK of VTS-270 and trough HP-β-CD concentration in subjects receiving the 900 mg dose of VTS-270 via the B. Braun Celsite Spinal Access Port (device PK substudy).

8.3. Exploratory Objectives

8.3.1. Part C

There are no exploratory objectives in Part C.

9. INVESTIGATIONAL PLAN

9.1. Study Design

This is a multicenter, multinational, prospective, randomized, double-blind, sham-controlled, 3-part, efficacy and safety trial of VTS-270, administered IT every 2 weeks, with a planned enrollment of approximately 51 subjects (in Parts A and B) with NPC1 disease. The study is being conducted in 3 parts:

- Part A evaluated 3 different dose levels of VTS-270 versus sham to determine the dose level for Parts B and C of the study. A total of 12 subjects were enrolled and have completed Part A.
- Part B evaluated the safety and efficacy of the VTS-270 dose selected from Part A, 900 mg, compared with sham control in approximately 51 subjects including the 12 subjects from Part A. Subjects received treatment with VTS-270 for up to 52 weeks (inclusive of Part A).
- Part C will be an open-label extension phase of the study for those subjects who qualify; additionally:
  - A European site-specific substudy of the safety and tolerability of the device was conducted in subjects who met the eligibility criteria to have a device implanted for VTS-270 infusion. Device implantations were terminated in August 2018 following reports of the catheter tip migrating from the IT space in some subjects.
  - A European site-specific substudy of plasma and CSF PK of VTS-270 administered via the device was planned but not conducted under Part C, as no subjects consented.

The VTS270 development program has been terminated by the sponsor. No new subjects are permitted to enroll in the study.

9.2. Dose Reduction

As established by the DSC, a dose reduction regimen was available in Part B through which, under specific circumstances and after discussion with the unblinded medical monitor, an investigator could be allowed to reduce the dose for an individual study subject. Subjects who, in the opinion of the investigator, experienced a drug-related AE after any blinded IT treatment that was considered clinically relevant and impactful to the subject's function could have their dose of study drug reduced.

If a subject required dose reduction due to an AE meeting the above description, the dose was to be initially reduced from 900 mg to 600 mg per lumbar IT administration. If, following dose

reduction to 600 mg, a subject continued to experience an AE as described above, the subject's dose could be further reduced to 400 mg per lumbar IT administration. Following dose reduction to 400 mg, if a subject continued to experience AE(s) as described above, the dose was NOT to be reduced further, and the subject was to be discontinued from Part B of the study, being given the option to transition into Part C at a lower dose, based on discussion with the unblinded medical monitor and on a case-by-case basis.

Once the dose of VTS-270 had been reduced for a given subject in Part B, the dose could not be subsequently increased back to the dose selected for Part B (900 mg). In addition, dose reduction on an individual subject basis was separate from the Data Monitoring Committee (DMC) review of all subject safety data, which could result in dose reduction for all subjects enrolled in the trial.

The same guidelines apply for dose reduction in Part C, except that study drug will be open-label (not blinded) and the frequency of dosing may also be reduced. Each subject for whom dose reduction or dose frequency change is considered will be individually reviewed with the medical monitor.

9.3. Dose Re-escalation

Dose re-escalation is not permitted as of 20 January 2021.

9.4. Rescue Option

The rescue option was only applicable to Part B.

Please see Table 2 for overall study design, and refer to Section 23 for the Schedule of Assessments.

Table 2: Phase 2b/3 3-Part Study Design

	Part A			Part B			Part C		
Treatment	**Dose**	**N**	**DSC Assessment**	**Dose**	**N**	**Total**	**Dose**	**N**	**Total**
VTS-270	900 mg	3	Final Dose Selection	900 mg[a]	26	35	900 mg biweekly, or lower dose with possible reduced frequency	51 + up to 14 NIH phase 1	51-65?
	1200 mg	3							
	1800 mg	3							
Sham	Sham Control	3		Sham Control	13	16			
	Total	12			39	51			

[a] Subjects who received VTS-270 in Part A will continue on the selected Part B dose, and subjects who received sham in Part A will remain on sham for a total of 12 months.

DSC = dose selection committee; NIH = National Institutes of Health.

10. CRITERIA FOR EVALUATION

10.1. Part C (Including Substudies) Endpoints

10.1.1. Primary Endpoints in Part C

As of 20 January 2021 no efficacy analyses will be performed.

- The change from baseline to each assessment in a composite outcome that is the sum of the ambulation, cognition, fine motor, and swallowing components of the NPC-SS.
- The change from baseline to each assessment in total NPC-SS with the hearing domain and auditory brainstem response (ABR) modifiers removed.
- Proportion of responders (defined as no change or improvement on NPC-SS total score with hearing domain and ABR modifiers removed) at each assessment.
- Proportion of Blinded Clinician-Clinical Global Impression of Change (CGIC) (defined as a score of no change, minimally improved, moderately improved, or markedly improved) at each assessment compared to baseline.
- Summary of AEs, concomitant medications, physical examinations, audiologic examination, and clinical laboratories.
- Change from baseline in the EQ-5D-3L questionnaire at each assessment.
- Change from baseline to each assessment in each of the 9 clinical domains of the NPC-SS.
- Change from baseline to each assessment in the total NPC-SS with hearing domain and ABR modifier included.
- Time to 1-point increase (worsening) in NPC-SS composite score.
- The composite NPC-SS mean annualized rate of change (slope) from baseline to each assessment.

10.1.2. Secondary Endpoints in Part C

Secondary endpoints in Part C will be evaluated for the device safety and tolerability substudy for the first 9 port infusions:

- Summary of wound check, examination of port site and catheter track at access port infusion visits.
- Intracranial pressure (ICP) via LP.
- Summary of plasma and CSF pharmacokinetic parameters following a single dose of VTS-270.

11. SUBJECT SELECTION

11.1. Study Population

Subjects with a diagnosis of NPC disease who meet the inclusion and exclusion criteria will be eligible for participation in this study.

Eligibility criteria for Part A/Part B are not applicable as these parts have been completed.

As of 20 January 2021, no new subjects can be enrolled.

11.2. Inclusion Criteria Part C

No new subjects may be enrolled in the study.

1. Subject has completed Part B, meets the criteria for dose reduction for a second time (see Section 9.2), or meets the criteria for the rescue option (see Section 9.4).

   OR

2. Subject is a current participant in the NIH phase 1/2a open-label study and:
   a. Subject agrees to convert from the dose of VTS-270 currently receiving as a subject in the NIH phase 1/2a protocol to the dose chosen for Parts B and C of this study, 900 mg;
   b. Subject agrees to convert from the monthly dosing regimen used in the NIH phase 1/2a protocol to an every 2 weeks dosing regimen;
   c. In instances where NIH phase 1/2a subjects eligible to enroll into Part C are unable to convert from their current NIH phase 1/2a dose or monthly regimen, the investigator must receive prior written authorization from the sponsor for the subject to enter Part C of the study on an amended dose and/or regimen.

   OR

3. Subject has received prior written authorization from Vtesse to enroll directly into Part C.
4. 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.
5. 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.

11.3. Criteria for Part C European Site-specific Device Safety and Tolerability Substudy

This European site-specific VTS301 substudy investigated the safety and tolerability of the spinal IT access device in approximately 6 subjects who were currently enrolled in VTS301 Part C.

11.3.1. Inclusion Criteria for European Site-specific Device Safety and Tolerability Substudy

NOTE: Enrollment in the device substudy was terminated in August 2018.

A subject must have met all of the following inclusion criteria to be eligible to enroll in the substudy:

1. Subject must be enrolled in Study VTS301 Part C.
2. Subject must have received a minimum of 3 doses of VTS-270 (900 mg each) in Part C of Protocol VTS301 (frequency of every 2 weeks) and be on a stable dose to be eligible for device placement.
3. 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.
4. 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.
5. Subject or caregiver must possess the ability, in the judgment of the investigator, to understand and comply with protocol requirements, including clinical outcome measurements and instructions, for the entire duration of the study.
6. Caregiver, parent, guardian, or responsible adult must be able and willing to accompany the subject to study visits.

11.3.2. Exclusion Criteria for European Site-specific Device Safety and Tolerability Substudy

The presence of any of the following excluded a subject from substudy enrollment:

1. Musculoskeletal/spinal abnormality or other anatomic abnormality identified by symptoms, history, physical/neurological examination, and/or imaging studies that would impact placement and patency of the device (port and catheter).
2. Skin infection in the lumbar or abdominal region within 3 months prior to device placement.

3. Subjects who, in the opinion of the investigator, are unable to comply with the protocol or have disease severity or medical conditions that would potentially increase the risk of participation or confound study results.
4. Subjects with suspected or confirmed infection of the CNS or any systemic infection.
5. Absolute neutrophil count less than 1.5×10^9/L.
6. Platelet count less than 100×10^9/L.
7. Activated partial thromboplastin time (aPTT) or prothrombin time (PT) greater than 1.5 times the upper limit of normal (ULN) or known history of a bleeding disorder.
8. Requirement for anticoagulation therapy.
9. Evidence of obstructive hydrocephalus or normal pressure hydrocephalus based on symptoms, history, and physical/neurological examination, or elevated ICP (opening ICP > 25.0 cm H_2O).
10. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 4 times the ULN, or total bilirubin greater than 2 times ULN.
11. Hemoglobin more than 2 standard deviations below normal for age and gender.
12. Estimated glomerular filtration rate (eGFR) less than 60 mL/minute/1.73 m^2 calculated using the modified Schwartz formula (2009) for subjects aged 4 through 17 years or using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for subjects aged 18 years and older.
13. Active pulmonary disease, oxygen requirement, or clinically significant history of decreased blood oxygen saturation, pulmonary therapy, or requiring active suction.
14. Hypersensitivity to any materials contained in the device port or catheter.
15. Subjects with a CNS shunt.
16. Prior radiation therapy to the area for device placement.
17. Expected need for magnetic resonance imaging during participation in the study, with exception of the following allowable conditions for safe scanning immediately after device placement:
    a. Static magnetic field of 3 Tesla and 1.5 Tesla;
    b. Maximum spatial gradient magnetic field of 710 Gauss/cm or less;
    c. Maximum whole body averaged specific absorption rate of 2.9 W/kg for 15 minutes of scanning.

11.4. Inclusion Criteria for European Site-specific Device PK Substudy

The European site-specific device PK substudy will investigate plasma and CSF PK of VTS-270 administered via the IT access device. A subject must meet the following inclusion criteria to be eligible to enroll in the device PK substudy:

1. Subject has completed the device safety and tolerability substudy and received 9 consecutive doses of 900 mg VTS-270 via the device.

   OR

2. After 6 subjects have completed the device safety and tolerability substudy, subjects in Part C who are receiving a stable dose of 900 mg VTS-270 via LP and are eligible for implantation of the device per the above eligibility criteria for the device safety and tolerability substudy.
3. 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.

12. CONCOMITANT MEDICATIONS

All subjects should be maintained on the same medications throughout Parts A and B of the study, as medically feasible.

12.1. NPC Treatment-related Medications

- Allowed NPC treatment-related medications
  - Miglustat (ie, ZAVESCA or generic) maintained at a constant dose (dose adjustments for weight or as medically necessary are permitted).
- Prohibited NPC treatment-related medications
  - Any other investigational treatment for NPC including, for example, vorinostat or arimoclomol.

12.2. Allowed Medications and Treatments

- 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.

12.3. Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation:

- Nonprescription supplements (Section 11.2), which must be discontinued at least 1 month before screening and not used for the 12-month duration of the trial.
- Any other investigational or non-approved therapies.

13. STUDY TREATMENTS

13.1. Method of Assigning Subjects to Treatment Groups

13.1.1. Part C

All subjects will be assigned to receive VTS-270 at the dose level and frequency used in Part B of the study (900 mg every 2 weeks), unless otherwise allowed by the sponsor on an individual subject basis. Subjects who have prior written authorization from Vtesse to enroll directly into Part C will be assigned to receive 900 mg VTS-270 every 2 weeks, unless otherwise indicated by the sponsor on an individual subject basis.

13.1.1.1. Part C: European Site-specific Device Safety and Tolerability Substudy

Approximately 6 subjects meeting eligibility criteria for the device safety and tolerability substudy were assigned to receive VTS-270 at the dose level and frequency used in Part B of the study (900 mg every 2 weeks).

13.1.1.2. Part C: European Site-specific Device PK Substudy

All subjects in the device PK substudy will receive 900 mg VTS-270 every 2 weeks via the device.

13.2. Blinding

13.2.1. Parts A and B

Part A and Part B were blinded.

13.2.2. Part C

Part C is open label. There will be no blinding. Since there is no blinding for subjects in Part C, sedation for lumbar IT drug administration is not required and should be used only if in the judgment of the treating clinician it is medically warranted.

The substudies of Part C (device safety and tolerability substudy and device PK substudy) will also be open label. There will be no blinding.

13.3. Formulation of Test and Control Products

VTS-270 will be provided in appropriately labeled vials, formulated as a 200 mg/mL injectable solution. An unblinded pharmacist/designee at each investigational site will be responsible for dispensing or preparing the assigned dosage undiluted (the 900 mg dose will be administered in 4.5 mL, the 600 mg dose will be administered in 3 mL, and the 400 mg dose will be administered in 2 mL).

13.3.1. Formulation of Test Product

The formulation and filling of VTS-270 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 0.01N sodium hydroxide, and bringing to the final volume with water for injection. The product is a clear, colorless solution that is free from visible foreign matter. The product is then sterile filtered into vials (5 mL fill with a 1 mL overfill) 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.

13.3.2. Formulation of Control Product

There is no control product in this study.

13.3.3. Packaging and Labeling

Preparation, packaging, and labeling of all study medications will be in accordance with standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations. All investigational medication used in this study will be prepared, packaged, and labeled under the responsibility of Vtesse and their designees.

Labeling of the study drug will be in accordance with GMP, Manufacture of Investigational Medicinal Products, and local legislation. 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.

The labels on the outer package (carton) containing vials will include the following minimum information:

1. Study number.
2. Name of the responsible investigator/site number.
3. Number of vials containing 2-hydroxypropyl-β-cyclodextrin solution (VTS-270).
4. Volume of study drug in each vial.
5. Dosage and route of administration according to special instructions.
6. Storage conditions.
7. Expiry date.
8. Caution statement: For clinical trial use only.

9. Sponsor name, address, and phone number.
10. Manufactured by name.
11. Kit number.
12. Batch number.

The labels on the vials containing 2-hydroxypropyl-β-cyclodextrin (VTS-270) will include the following minimum information:

1. Study number.
2. Sponsor name and address.
3. Manufactured by name.
4. Subject number.
5. Investigator (site) number.
6. Administration route.
7. Single-use vial.
8. Volume of study drug in each vial.
9. Batch number.
10. 2-hydroxypropyl-β-cyclodextrin solution for injection.
11. Caution statement: For clinical trial use only.

The packaging will consist of 8 mL Type I white glass vial filled with 6 mL of VTS-270 (5 mL fill with a 1 mL overfill), 20 mm FIOLAX stopper, and plastic white flip-off caps coated with FluroTec.

13.4. Supply of Study Drug at the Site

The sponsor (or designee) will ship study drug to the investigational sites. The initial study drug shipment will be shipped after site 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 site request for resupply.

13.4.1. Dosage/Dosage Regimen

VTS-270 will be provided in labeled 8 mL Type I glass vials, formulated as a 200 mg/mL injectable solution (5 mL fill with a 1 mL overfill). The assigned dosage will be administered per the following:

- 900 mg dose will be administered in 4.5 mL.
- 600 mg dose will administered in 3 mL (if dose reduction required and authorized).
- 400 mg will be administered in 2 mL (if dose reduction required and authorized).

All doses are administered undiluted. Other doses less than 900 mg will also be administered undiluted. VTS-270 administration via LP and sham will be conducted every 2 weeks under

monitored anesthesia care (conscious sedation) or if medically necessary, general anesthesia, for 52 weeks in Parts A and B. Subjects in Part C will receive VTS-270 until the investigator considers VTS-270 to no longer be beneficial to the subject, or the development program is discontinued. There are no adjustments for weight or subject age.

The VTS270 development program has been terminated by the Sponsor following a determination of a negative benefit / risk balance. Although the Sponsor recommends discontinuing treatment with VTS270 as soon as possible, treatment for up to an additional 9 months (20 October 2021) will be permitted to allow for transition planning. This continuation of treatment is contingent upon subject re-consent and approval by the applicable IRB/EC and health authority.

13.4.2. Dispensing

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

13.4.3. VTS-270 Administration by Lumbar Puncture and Sham Lumbar Puncture

VTS-270 will be provided in appropriately labeled vials (8 mL Type I white glass vial filled with 6 mL of VTS-270, 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 investigational site 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 and 30°C, inclusive.

The IT dosing via LP or sham procedure will be conducted by dedicated study personnel who are unblinded to treatment group; this cannot involve any of the blinded key study site personnel responsible for the blinded efficacy ratings or AEs. Besides their role on a treatment team, these individuals will not be involved in any study-specific clinical evaluations, including AE assessments. Note that in those instances in which the IT/sham administrator is also serving as the treating physician/clinician for the subject and family, being responsible for their overall medical care throughout the course of the trial, a separate, blinded clinician at the site (eg, physician, physician assistant, nurse practitioner) will be responsible for querying and assessing AEs. The IT injection or sham procedure will be performed in a dedicated room and the key study personnel and the parents/caretakers will not be present during the procedure to ensure blinding.

For subjects randomized to drug treatment, VTS-270 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 group (Table 3). Prior to the VTS-270 injection, a volume of CSF approximately equal to the VTS-270 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: VTS-270 Dose, Injection Volume, and Concentration

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

For subjects randomized to the sham procedure control group, the sham procedure will consist of 1 to 2 small needle pricks on the lower back at the location where the LP and IT injection is normally made. The needle(s) will break the skin but no LP or needle insertion will occur. The needle prick(s) will be covered with the same bandage that is used to cover the IT injection normally, thus simulating the appearance of an IT LP injection. Anesthesia or sedation is used for the IT dosing procedure in VTS-270 treated subjects, in order to maintain the blind, a similar type of anesthesia, sedation, or minimal sedation (ie, a low dose of an anxiolytic) should be used for the sham procedure, following institutional procedures. The study subject will be kept in the procedure room for approximately 30 minutes, simulating the same amount of time that subjects administered study drug are kept for administration procedure. All subjects, sham and study drug, are required, if possible, to lie flat with feet elevated for 30 to 45 minutes following dosing.

For the 3 days following each procedure, subjects in both the sham and drug-treatment groups are to avoid acoustic overstimulation and minimize exposure to loud noises, eg, headphones for music or video games.

For additional details, refer to the Study Manual.

13.4.4. Study Drug Administration in the European Site-specific Device Substudies

The Celsite Spinal Access Port System should be accessed only by personnel experienced in the technical and clinical aspects of access ports.

The port should only be accessed using the non-coring Huber needles. Utilizing a standard needle will cause serious damage to the port and will require the system to be surgically explanted.

The port site and catheter track must be inspected prior to study drug administration. If abnormal swelling or redness is noted around the port or along the catheter site and infection is suspected, study drug should not be administered and appropriate evaluation of the device and catheter track should be undertaken to rule out malfunction or infection.

Subjects/caregivers participating in the European site-specific device substudies (safety and tolerability and/or PK) should report any of the following findings to the investigator as soon as possible:

- Significant changes in lower limb function (eg, muscle weakness, numbness).
- Significant changes in bladder or bowel control (eg, incontinence, inability to void).
- Severe back pain or sciatica.
- Persistent headache and/or stiff neck associated with fever.

VTS-270 administration via the device will be conducted every 2 weeks. There are no adjustments for weight or subject age. The access port area will be prepared for sterile manipulation following standard site procedures. Cerebrospinal fluid will be withdrawn through the port. The first 1 mL will be discarded, and then a volume of CSF approximately equal to that being administered (including study drug and a 1.5 mL flush with preservative-free- 0.9% saline solution) will be withdrawn. The volume of the study drug infusion is determined by the dose (Section 13.4). Subjects will receive the same dose of VTS-270 administered during Part C via LP. VTS-270 will be administered as a slow bolus over 1 to 2 minutes with a maximum rate of infusion of 4.5 mL/minute. Noncoring needles adapted for use with Celsite Spinal Access Port System should be used. Normal hypodermic needles will damage the port septum and may cause leakage of the system or blockage due to small silicone particles from the septum.

Following the infusion of VTS-270, the system should be flushed with 1.5 mL of preservative-free 0.9% saline solution. Heparin should not be used in an IT access port. If resistance to infusion is noted at any time during administration of VTS-270 or during the flush, or if swelling occurs around the port or along the catheter during infusion or flush, device malfunction should be suspected and device patency assessed as per Access Port Manual of Procedures.

Additional Procedures for Subjects in the European Site-specific Device PK Substudy

For subjects in the device PK substudy, paired blood and CSF sampling over time will be conducted before and after a single dose administration, which will be the first and only dose in the substudy for subjects entering the substudy from the device safety and tolerability substudy (Table 15), and the fourth dose for subjects entering the substudy from the main Part C study.

Just prior to VTS-270 administration, a blood sample (approximately 4 mL) for VTS-270 concentration and a volume of CSF approximately equal to the volume of VTS-270 to be administered (4.5 mL for the 900 mg dose) plus 1.5 mL for flush of the device will be withdrawn. The first 1 mL of CSF withdrawn from the port should be discarded. Approximately 2 mL of the CSF sample will be sent for routine clinical laboratory tests, and approximately 2.5 mL will be sent for VTS-270 assay. VTS-270 will then be administered via the device as a slow bolus over 1 to 2 minutes. Following drug infusion, the device will be flushed with 1.5 mL preservative-free 0.9% saline. Blood and CSF samples will then be obtained at 1 hour (± 5 minutes), 2 hours (± 5 minutes), 4 hours (± 5 minutes), 6 hours (± 30 minutes), 8 hours (± 30 minutes), approximately 24 hours, and approximately 30 hours after infusion. The 30-hour time point should be at least 6 hours after the 24-hour time point. See Section 14.2.10 for further details on the assessments for PK.

Anesthesia is not required for administration of VTS-270 via the device; however, as determined by the investigator and clinical staff, the clinical site has the option to give topical anesthetic agents based on a subject's condition.

All subjects should lie flat with feet elevated for 30 to 45 minutes following dosing.

13.5. Storage

Investigational product should be stored between 15°C and 30°C (59°F and 86°F), inclusive. For additional details, refer to the Pharmacy Manual.

13.6. Study Drug Accountability

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

13.7. Investigational Device (for European Site-specific Device Substudies)

13.7.1. Investigational Device Handling

It is the responsibility of the clinical site to ensure that a sufficient stock of port kits is available at the appropriate intervals based on subject enrollment. For each subject receiving an IT access port, 2 kits that have passed visual inspection are required. A surplus of at least one kit must be maintained in inventory at all times. Refer to the sponsor-supplied Access Port System Manual of Procedures for ordering, receiving, returning, and presurgical preparation of the device.

13.7.2. Investigational Device Implantation

The Celsite Spinal Access Port System (port and catheter) will be surgically implanted in subjects by personnel experienced in the technical and clinical aspects of access ports. Specific procedures for implantation of the device in NPC1 subjects are detailed in the sponsor-supplied Access Port Manual of Procedures for the Braun Celsite Access Ports (ST304-20G). The subject will begin a 3-day IV course of a fourth-generation cephalosporin antibiotic approximately one hour prior to surgery, which will be followed by an 11-day course of oral fourth-generation cephalosporin antibiotic (total of 14 days). If cephalosporin cannot be used, the physician will administer another appropriate antibiotic. The subject will be under general anesthesia for this procedure. Standard hospital procedures for surgery will be followed. An x-ray will be taken postoperatively to verify proper implantation of the port and to confirm the catheter was placed at the mid-thoracic level. The date the x-ray was taken and subsequently read will be documented in the electronic case report form (eCRF). A copy of the x-ray should be stored in the subject's study record. The investigator should take appropriate measures to protect subject privacy if the x-ray needs to be transferred outside the facility of origin, such as de-identification of the image.

The subject will remain in the hospital for 3 days, including the day of surgery. Sutures will be removed when deemed appropriate by the investigator and may need to be removed by the local treating physician. A minimum of 14 days following implantation of the device must elapse before it is used for VTS-270 administration.

13.7.3. Investigational Device Removal

For European site-specific subjects with the device, if the device becomes nonfunctional at any time during the study, it will be removed and may be replaced (a flowchart to assess the device malfunction is included in the Access Port Manual of Procedures; note that CSF sampling and VTS-270 administration can occur via LP injection while the malfunction is being evaluated). If the subject discontinues the study early, the device must be removed. See the sponsor-supplied Access Port Manual of Procedures for information regarding device removal. Device removal

and postoperative care will be conducted under standard medical practices, depending on the reason for the removal. The procedure for initiating a Product Incident Report (PIR) and return of the device is located in the sponsor-supplied Access Port Manual of Procedures.

Additional reasons for device removal include termination of the adrabetadex (VTS-270) clinical development program.

13.7.4. Investigational Device Accountability

Inventory and accountability records for the investigational devices will be kept by the investigator or designee.

The clinical site is responsible for providing by-subject accountability of the device components throughout the clinical study. To facilitate tracking the devices from the time of receipt to time of return to the vendor, the sponsor has supplied an Accountability Log. All information should be recorded in permanent black ink. Any corrections should be made by a using a single line to strike out any text, and the corrections should be initialed and dated by the staff member making the corrections. The Accountability Log will be added to the on-site Regulatory Binder and entered into the electronic data capture system. Please refer to the sponsor-supplied Access Port Manual of Procedures for detailed instructions.

13.7.5. Investigational Device Handling and Disposal

The Celsite Spinal Access Port System is for single subject use only; do not re-sterilize the product or any of the components, and destroy unused items after use. The device and its accessories are neither re-usable nor designed to be re-used. Any re-use will compromise the performance and safety of the device.

13.8. Measures of Treatment Compliance

Study drug or sham procedure will be administered at the study site by a study clinician. The amount of study drug infused will be recorded and overall treatment compliance will be calculated.

For European site-specific subjects with the Celsite Spinal Access Port System, the device will be surgically implanted by a qualified surgeon according to the sponsor-supplied Access Port Manual of Procedures which contains additional details beyond the Instructions for Use insert for the Braun Celsite Access Ports (ST304-20G). Proper implantation of the port and catheter location at the mid-thoracic level will be confirmed by radiograph on the day of implantation and as indicated by the investigator to determine device placement and/or integrity during the study. Catheter patency will be verified according to the discretion of the site. A qualified staff member (MD, nurse practitioner [NP], registered nurse [RN], or physician assistant [PA]) will inspect the port site and catheter track at each study visit following implantation for evidence of any malfunction or adverse reactions. At device infusion visits, this examination will occur prior to and during administration of study drug.

14. STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for Parts A, B, and C (including substudies) of the study is diagrammed in Section 23.

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

Part C European site-specific subjects who are eligible to participate in the device safety and tolerability substudy, or in the device PK substudy, will undergo a device baseline visit at the last LP IT infusion approximately 3 days prior to device placement. Following completion of the device safety and tolerability substudy, subjects will have the option to participate in the device PK substudy or will continue in the main Part C study. Following completion of the device PK substudy, subjects will continue in the main Part C study.

14.1. Overview of Study Procedures

See Table 10, Schedule of Assessments for Screening through Week 28. See Table 11, Schedule of Assessments for Week 30 through Week 52. See Table 12, Schedule of Assessments for Week 54 through Week 182. See Table 13, Schedule of Assessments for Week 183 and beyond. See Table 14, Schedule of Assessments for End of Study and Follow-up.

14.2. Clinical Assessments

14.2.1. Concomitant Medications

All concomitant medication and concurrent therapies will be documented at each study visit for Parts A, B, and C until end of study or early termination (ET), when applicable, as well as the follow-up visits. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

14.2.2. Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening for Parts A, B, and C.

14.2.3. Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases, will be recorded at Screening for Parts A, B, and C.

14.2.4. Adverse Events

Information regarding occurrence of AEs (including adverse device effects for European site-specific device subjects) will be captured throughout the study, ET, and follow-up visits 1, 2, and 3, except at the baseline visit. At device infusion visits, AE assessment will be completed prior to and after administration of study drug. Definitions associated with AEs and the procedures for reporting them are presented in Sections 16.1 and 16.2.

14.2.5. Physical Examination

At screening for Parts A, B, and C, a complete physical examination will be performed by either the investigator or a subinvestigator who is a physician. Subjects in Part B who do not continue into Part C will also undergo a complete physical examination at the Week 54 Follow-up Visit. Subjects in Part C will undergo a complete physical examination at ET and Follow-up Visit 1. Qualified staff (MD, NP, RN, or PA) may complete the abbreviated physical examination at all other visits (Part B: Weeks 24 and 52; Part C: every 6 months). New abnormal findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit, or earlier if clinically indicated.

In the European site-specific device safety and tolerability substudy, an abbreviated physical examination will be conducted during the device baseline visit, on confinement period Days 2 and 3, and at the first and ninth device infusion visits (D1 and D9). For subjects in the European site-specific device PK substudy who transitioned from the device safety and tolerability substudy, an abbreviated physical examination will be conducted at baseline. Subjects who enter the device PK substudy from the main Part C study will have an abbreviated physical examination at baseline of the substudy and on confinement period Days 2 and 3.

The abbreviated physical examination includes 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.

New abnormal skin or physical examination findings associated with the site of port and catheter implantation must be documented and followed up by a physician or other qualified staff at the next scheduled visit, or earlier if clinically indicated.

14.2.6. Wound Check and Examination of Port Site and Catheter Track for European Site-specific Device Subjects

For European site-specific subjects who have an implanted IT access device, immediately after implantation of the device, a qualified staff member (MD, NP, RN, or PA) will examine the port site and catheter track for any evidence of malfunction. On the day of the first VTS-270 infusion via the device, a qualified staff member will perform a check of the wound, port site, and catheter track. At all study visits after implantation of device, a qualified staff member will inspect the port site and catheter track for any evidence of infection or malfunction associated with the IT port system. This examination will include the following:

- A directed examination of the following areas:
  - The port abdominal implant site.
  - Surrounding skin along the entire path as well as the vertebral bodies adjacent to the catheter.
- The staff member will examine all of the above areas for any adverse changes such as but not limited to:

- Redness.
- Tenderness of skin and subcutaneous tissues.
- Swelling and/or fibrotic reaction.
- Increased warmth.
- Effusion or exudate (fluctuance and/or discharge).
- Poor healing/wound dehiscence.

At device infusion visits, this examination will occur prior to and during any administration of study drug, as well as after study drug administration, during the 30- to 45-minute recovery period. If any significant concerns are noted during the examination of the wound, port site, and/or catheter track such as abnormal swelling or redness around the port or along the catheter site, study drug should not be administered, the sponsor/medical monitor should be notified, and an appropriate evaluation of the device and catheter track, including imaging, should be undertaken to confirm the device and placement and to assess possible malfunction or infection (see Access Port Manual of Procedures). Abnormal port and catheter-related observations and the lack of integrity of the device or dislodgement will be reported as device-related AEs.

If the subject is terminating study participation, the device must be removed (see Section 13.7.3). A wound check should be performed at ET and all follow-up visits.

14.2.7. Vital Signs

Body temperature, blood pressure, pulse, and respirations will be performed after a 5-minute rest period at 2 different times during each study visit for Parts A, B, and C (including ET and Follow-up Visit 1): 1) prior to LP or sham, and 2) after recovery from LP or sham (every study visit). For non-dosing visits, perform and record vital signs including blood pressure following 5-minute rest in supine position.

In the European site-specific device safety and tolerability substudy, vital signs will be performed at baseline visit for device implantation and confinement period Days 1 through 3 for device implantation. At each port infusion visit in the substudy, vital signs will be measured before infusion and after a 30- to 45-minute recovery period following VTS-270 infusion.

For subjects in the European site-specific device PK substudy who transitioned from the device safety and tolerability substudy, vital signs will be measured at baseline, before infusion of VTS-270 using the device, and after a 30- to 45-minute recovery period following the infusion.

For subjects in the device PK substudy who transitioned from the main Part C study, vital signs will be performed at baseline visit for device implantation and confinement period Days 1 through 3 for device implantation. At each subsequent port infusion visit, vital signs will be measured before infusion and after a 30- to 45-minute recovery period following VTS-270 infusion.

14.2.8. Intracranial Pressure Measurement for European Site-specific Device Subjects

For subjects in the European site-specific device safety and tolerability substudy and subjects transitioning from Part C of the main study to the device PK substudy, ICP (cm H_2O) will be

measured via LP per standard hospital practice just prior to CSF collection at baseline of device implantation.

14.2.9. Clinical Laboratory Measurements

All clinical laboratory samples obtained will be sent to an outside central laboratory, unless stated otherwise. Refer to the Laboratory Manual for detailed instructions.

14.2.9.1. Hematology

Blood will be obtained and sent to the central laboratory for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count), and coagulation (PT and aPTT) at screening (Parts A, B, and C); at Weeks 12 (Part B), 24 (Part B), 26 (Part C), 40 (Part B), and 52 (Parts B and C); and every 6 months after Week 52 (Part C), including ET.

In the European site-specific device safety and tolerability substudy, blood will be collected for hematology and coagulation at the device baseline visit and at the ninth device infusion visit (Visit D9).

For subjects in the European site-specific device PK substudy, hematology and coagulation blood tests will be performed at the baseline visit.

14.2.9.2. Genetic Analysis – Day 0

Blood will be obtained and archived for genetic analysis (eg, exome or genome sequencing) and other research purposes.

14.2.9.3. Blood Chemistry Profile

Blood will be obtained for determination of serum sodium, potassium, chloride, bicarbonate, calcium, random glucose, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, and lactate dehydrogenase at Screening (Parts A, B, and C); at Weeks 12 (Part B), 24 (Part B), 26 (Part C), 40 (Part B), and 52 (Parts B and C); and every 6 months after Week 52 in Part C, including ET.

For subjects in the European site-specific device safety and tolerability study, blood will be collected for serum chemistry analyses at the device baseline visit and at the ninth device infusion visit (Visit D9).

For subjects in the European site-specific device PK substudy, blood for clinical chemistry tests will be collected at the baseline visit.

The eGFR will be calculated using either the revised Schwartz equation for subjects 4 through 17 years of age, or the CKD-EPI equation for subjects 18 years of age or older. The following formulas are appropriate when creatinine measurements are obtained using creatinine methods that have calibration traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure.

The revised Schwartz equation (Schwartz 2009) for subjects 4 through 17 years of age:

- When serum creatinine (SCr) is reported in mg/dL: GFR (mL/min/1.73 m^2) = (0.41 × Height in cm) / Creatinine in mg/dL).

- When SCr is reported in µmol/L: GFR (mL/min/1.73 m^2) = (36.2 × Height in cm) / Creatinine in µmol/L).

The CKD-EPI equation (Levey 2009) for subjects 18 through 21 years of age:

- When SCr is reported in mg/dL: GFR = 141 × min (SCr /κ, 1)$^{\alpha}$ × max(SCr /κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black]

  Where, SCr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr /κ or 1, and max indicates the maximum of SCr /κ or 1.

- When SCr is reported in µmol/L:

  GFR = 141 × min (SCr /κ, 1)$^{\alpha}$ × max(SCr /κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black]

  Where SCr is serum creatinine in µmol/L, κ is 61.9 for females and 79.6 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr /κ or 1, and max indicates the maximum of SCr /κ or 1.

The revised Schwartz and the CKD-EPI formulae are less likely to overestimate creatinine clearance than the more commonly used Cockcroft-Gault formula, as they take into account the reduced body size and muscle mass of individuals in the NPC1 patient population.

14.2.9.4. Pregnancy Test

A serum pregnancy test will be obtained from female subjects who are of childbearing potential at screening (Parts A, B, and C), at Study Visit 27 (Week 52, Parts B and C), and annually after Week 52 (Part C). For subjects who complete Part B but elect not to go into Part C, a urine pregnancy test will also be obtained at Follow-up Visit 1 (Week 54, Part B). For subjects in Part C, a urine pregnancy test will be obtained after ET at Follow-up Visit 1.

For female subjects of childbearing potential in the European site-specific device substudies (safety and tolerability and/or PK), a serum pregnancy test will be performed at baseline of each substudy.

14.2.9.5. Urinalysis

Urine will be obtained and sent to the central laboratory for determination of color, specific gravity, pH, protein, glucose, ketones, and blood. Urinalysis will be performed at screening (Parts A, B, and C); at Week 8 (Part A); at Weeks 12, 24, 40, and Week 52 (Part B); and every 6 months in Part C.

14.2.9.6. Cerebrospinal Fluid for Routine Clinical Laboratory Tests in Subjects With Intrathecal Access Device

A CSF sample (at least 2 mL) for routine laboratory tests will be collected at the following time points:

- Port and catheter implantation.

- Immediately prior to each infusion of study drug through the device (the first 1 mL of CSF withdrawn should be discarded); includes infusions through the device in the main Part C study after the subject completes the substudy (or substudies).
- End of study.

The following parameters will be assessed:

- Glucose.
- Protein.
- Red blood cell count.
- White blood cell count with differential.

14.2.9.7. Collection, Handling, and Storage of Samples for Clinical Laboratory Tests

Procedures for collection, storage, and shipment of blood and CSF will be detailed in a separate manual of procedures.

14.2.10. Plasma and CSF VTS-270 Concentrations

Sampling of CSF for Trough Concentrations of HP-β-CD

A portion of the CSF sample removed prior to VTS-270 infusion via LP in Parts A and B of the study (Section 14.2.11) will be analyzed for trough concentrations of HP-β-CD to assess the potential for accumulation with repeated dosing.

Subjects in the European site-specific device safety and tolerability substudy will have CSF samples collected for measurement of trough HP-β-CD concentration prior to the first through ninth infusions via the device (Visits D2 through D9). The CSF samples will come from the CSF routinely removed prior to administration of VTS-270 (Section 13.4.4).

In addition, subjects in the device PK substudy who transition from main Part C will have CSF samples collected for measurements of trough HP-β-CD concentration prior to the first, second, and third device infusions.

Lastly, subjects continuing in the main Part C study after completing either the European site-specific device safety and tolerability substudy or the device PK substudy will have CSF samples collected for measurement of trough HP-β-CD concentration just before each subsequent infusion of VTS270.

NOTE: Collection of CSF samples for trough HP-β-CD concentrations will no longer be performed.

Sampling of Blood and CSF for Full VTS-270 PK Profile (Device Subjects Only)

Not applicable as no subject provided consent for this substudy.

14.2.11. CSF, Urine, and Plasma Biomarker Assays

Not applicable for Part C.

14.2.12. Electrocardiogram

A 12-lead ECG will be obtained and interpreted locally (at the investigational sites) for safety monitoring at screening (Parts A, B, and C), at Week 52 in Parts B and C, and annually after Week 52 in Part C.

14.3. Audiologic Evaluation

Acoustic reflexes, PTA, and ABRs have been used to date to evaluate abnormalities that have been previously reported in NPC subjects (King 2014).

14.3.1. Audiologic Testing

Audiologic evaluations will be performed at defined intervals throughout the study in all subjects. In Part A, assessments will be performed at screening, first visit Study Day 0 (first study dose), and Weeks 2, 4, 6, and 8. In Part B, assessments will be performed at screening, and prior to dosing at Study Day 0, Weeks 8, 16, 24, 32, 40, 46, and 52. In Part C, assessments will be performed at screening and every 6 months thereafter, as well as ET and the follow-up visit. If a subject reports an increase in clinically significant hearing loss at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.

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 loss will be defined by a standard clinical pediatric scale (ie, slight, mild, moderate, moderately severe, severe, and profound).

14.3.2. Auditory Brainstem Response

The ABR will be used to assess functional integrity of the auditory nerve and auditory brainstem pathways. A hearing threshold will not be obtained, but the waveform morphology and latencies will be evaluated. ABR will be conducted at screening in Parts A, B, and C; at Week 8 for all subjects in Part A; at Week 52 in Parts B and C; and annually after Week 52 in Part C, and ET.

The ABR will not be performed as of 20 January 2021 (implemented in advance of amendment 14 as there is a direct impact to subject safety).

14.4. Blinded Clinician Clinical Global Impression of Change (Clinician-CGIC)

The Clinician-CGIC is to be conducted by an independent, blinded clinician, trained in performing neurological exams. This rater will meet with the subject/caregiver at the first visit Study Day 0 (Part A and B) and establish a clinical assessment of the subject based on input from both subject and caregiver according to a standardized review of clinical status and functionality. This assessment at the baseline visit prior to administration of the subject's first dose of study drug is to allow the rater to establish an overall clinical baseline assessment of the subject's status and functionality. These notes are to be kept separately by the blinded rater and segregated from all other data regarding a study subject.

The Clinician-CGIC will be conducted at the beginning of the following visits *prior to all other procedures and assessments.* After the baseline assessment, the blinded rater will have no access or knowledge to treatment assignment, clinical and laboratory AEs, laboratory tests, Caregiver-CGIC, timed up and go (TUG) test, 9-hole peg test, quality of life (QoL) assessment, or NPC-SS assessment. The Clinician-CGIC evaluated using a 7-point Likert scale ranging from 1 = marked improvement from screening to 7 = marked worsening from screening, will be assessed at Weeks 8, 16, 24, 32, 40, 46, and 52 in Parts A and B, plus at Follow-up Weeks 63 and 76 in Part B for subjects who elect not to participate in Part C. The rater should refer to their baseline assessment notes to make these periodic assessments. The same rater should conduct the Clinician-CGIC at all visits for a given subject. Additionally, if a subject is deemed to be improved or worsened on the 7-point Likert scale, the blinded rater is to indicate the major factor that led to said change in score.

NOTE: The Clinician-CGIC will no longer be performed.

14.5. Blinded NPC Clinical Severity Score Rating

Data for the NPC-SS rating will be collected at each site by a trained and blinded clinician separate from the centralized blinded rater who conducts the Clinician-CGIC. The trained clinician will collect the data using a directed source document to permit consistent collection of NPC specific domain information. This information will be provided to a centralized independent blinded rater who will analyze all NPC information for all subjects across all sites. This rater will be blinded to treatment assignment, clinical and laboratory AEs, laboratory tests, Clinician-CGIC and Caregiver-CGIC assessments, TUG and 9-hole peg test results, and the QoL assessment.

The NPC-SS score will be assessed at screening, at Study Day 0, and Weeks 8, 16, 24, 32, 40, 46, and 52 prior to sham or study drug treatment in Parts A and B, and at Follow-up Weeks 63 and 76 in Part B for subjects who elect not to participate in Part C.

For Part C, the NPC-SS score will be assessed every 6 months, ET, and the follow-up visit. All efforts will be made to have the same trained clinician complete the NPC-SS Intake Form assessment at all visits during Parts A and B of the study for a given subject.

NOTE: The NPC-SS Intake Form assessment will no longer be performed.

14.6. Neurological Examination

Neurological exams will be performed by the same independent, blinded clinician who performs the Clinician-CGIC. A complete neurological exam will be performed at screening (Parts A, B, and C), at Week 52 in Part B, at Week 52 of Part C, and ET in Part C.

An abbreviated neurological exam comprising assessments of eye movements, coordination, gait, and reflexes, will be conducted at Week 24 (Part B), at Week 26 (Part C), and every 6 months after Week 52 in Part C.

In Parts A and B, the neurological exams will be videotaped to provide a retrievable, visual record of the subjects' neuromotor status and functional capabilities at the 3 distinct evaluation time points (Screening, Week 24, and Week 52). Guidelines for obtaining standardized videotaped recordings of the neurological exams are provided in the Study Manual.

In the European site-specific device safety tolerability substudy in Part C, an abbreviated neurological examination will be conducted at the baseline visit and ninth IT device infusion visit (Visit D9). Additionally, subjects in the device safety tolerability substudy will follow their Part C schedule for abbreviated neurological examination (Week 26 of Part C participation) and complete neurological examination (Week 52 of Part C participation). Where there is duplication of assessments with the baseline and infusion visits of the safety and tolerability substudy, only 1 assessment will be conducted.

For subjects in the European site-specific device PK substudy who transitioned from the device safety and tolerability substudy, an abbreviated neurological examination will be conducted at the baseline visit. Subjects who enter the European site-specific device PK substudy from the main Part C study will have an abbreviated neurological examination at the baseline visit.

14.7. Caregiver Clinical Global Impression of Change (Caregiver-CGIC)

Not applicable for Part C.

14.8. TUG Test and 9-Hole Peg Test

Not applicable for Part C.

14.9. EQ-5D-3L Quality of Life Assessment

The EQ-5D-3L assessment is a self-reported, simple, descriptive system measuring 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

The EQ-5D-3L assessment will be conducted prior to dosing at Study Day 0, and at Weeks 8, 16, 24, 32, 40, 46, and 52 in Parts A and B. Caregiver proxy assessments will be obtained for all subjects.

For Part C, the EQ-5D-3L assessment will be conducted every 6 months and at ET.

NOTE: The EQ-5D-3L assessment will no longer be conducted.

15. EVALUATIONS BY VISIT

The collection period of AEs/SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

15.1. Part C

For the schedules of assessments, see

- Table 10 (Part C Schedule of Assessments – Screening through Week 28).
- Table 11 (Part C Schedule of Assessments – Week 30 through Week 52).
- Table 12 (Part C Schedule of Assessments – Week 54 through Week 182).
- Table 13 (Part C Schedule of Assessments – Beyond Week 182 Visit Number 92).

- Table 14 (Part C Schedule of Assessments – End of Study and Follow-up).
- Table 15 (Part C European Site-specific Device Safety and Tolerability Substudy Schedule of Assessments).

For patients continuing in the study after 21 June 2021, the investigator must assess whether the subject is benefiting from treatment with IT adrabetadex. 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 patients 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.

16. ADVERSE EVENT REPORTING AND DOCUMENTATION

Information regarding occurrence of AEs will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the eCRF.

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and Medical Dictionary for Regulatory Activities (MedDRA) classification term. Adverse events will be tabulated by treatment group and will include the number of subjects for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

16.1. Adverse Events

16.1.1. Definitions

16.1.1.1. Adverse Event

An AE (also known as an "adverse experience") 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] 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).

16.1.1.2. Suspected Adverse Reaction

A suspected adverse reaction is an AE 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. Suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction (21 CFR 312.32(a)).

16.1.1.3. Adverse Reaction

An adverse reaction is defined as any AE caused by a drug.

16.1.1.4. 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 investigational plan. 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. Such events are to be reported to the sponsor's representative (CTI) within 24 hours.

16.1.1.5. 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. 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. Notify the CTI within 24 hours of becoming aware of a SUSAR.

At each study site, a qualified clinician (eg, physician, physician assistant, nurse practitioner) will be specifically designated to assess and follow AEs for the study subjects enrolled in the trial. This clinician investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the subject's eCRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

16.1.2. Adverse Event Severity

The National Cancer Institute-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 loss (Section 16.1.4; Table 6), the guidelines shown in Table 4 should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 4: AE Severity Grading

Severity (Toxicity Grade)	Description
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)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
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.

16.1.3. Adverse Event Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 5.

Table 5: AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	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.
Probably	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.
Possibly	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.
Unlikely	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.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

16.1.4. Adverse Events of Special Interest

16.1.4.1. Clinically Significant Hearing Loss

NPC1 disease and VTS-270 are both associated with hearing loss. The severity and site of lesion of auditory damage may differ between VTS-270 and NPC1 disease induced hearing loss. As shown in Table 6, there are some overlapping sites of lesion (outer hair cells), but some more

likely only in NPC1 disease. In addition, NPC hearing loss appears to progress more slowly than drug induced hearing loss.

Table 6: Distinguishing VTS-270 from NPC1 Disease Induced Hearing Loss

Site of Lesion	VTS-270 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 loss (CTCAE grade 3 or higher), this AE will be reviewed in an open-label manner by the DSC (if occurring during Part A). Such individuals will have repeat PTA and distortion product otoacoustic emission (DPOAE) testing as part of the hearing loss AE evaluation.

16.1.5. Adverse Event Relationship to Investigational Device

For European site-specific subjects who have an IT access device, the investigator should assess relationship of all AEs to the investigational device based on the information in the Investigator's Brochure, the subject's medical history, and other interventions that preceded the event. Guidelines are included in Table 7.

Table 7: Adverse Relationship to Investigational Device

Related:	**The AE follows a reasonable temporal sequence following the administration of the investigational device. The AE follows a known or expected response pattern to the investigational device.**
Not related:	Sufficient information exists to indicate that the etiology of the AE is unrelated to the investigational device. The AE does not follow a reasonable temporal sequence following administration of the investigational device, and/or the AE is readily explained by the subject's clinical state and/or other therapies.

AE = adverse event.

16.1.6. Adverse Device and Intrathecal Effects of Special Interest

Adverse reactions of special interest are categorized as either device issues or issues associated with IT access. A list of potential adverse reactions is included below:

- **Device issues:** catheter disconnection, rupture, or fragmentation, erosion of portal/catheter through the skin, catheter occlusion, inflammatory/foreign body reaction, explanation of the port secondary to inflammatory reaction, fibrin sheath formation around catheter tip, hematoma, portal site or subcutaneous tract infection, malposition of catheter, or port/catheter migration.
- **Issues associated with IT access:** CSF leak, dura mater or epidural vein perforation, epidural or IT space infection, sepsis, inadvertent epidural placement, pain on

injection, spinal cord or nerve injury, spinal cord compression (which could lead to paralysis), or spinal headache.

In addition, subjects/caregivers should report any of the following findings to the investigator as soon as possible:

- Significant changes in lower limb function (eg, muscle weakness, numbness).
- Significant changes in bladder or bowel control (eg, incontinence, inability to void).
- Severe back pain or sciatica.
- Persistent headache and/or stiff neck associated with fever.

16.1.7. Actions for Potential Device Deficiency

A malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device according to local regulations. Note that a flowchart to assess the device malfunction is included in the Access Port Manual of Procedures; CSF sampling and VTS-270 administration can occur via LP injection as indicated by the investigator.

If the device becomes nonfunctional or is found to be deficient at any time during the study, it will be placed in quarantine and may be replaced. If any deficiency of the investigational device occurs, it must not be used. The responsible site staff member will contact the sponsor study monitor or the sponsor study director to initiate a PIR. Upon initiation of a PIR, the site will receive a package containing all the necessary items to safely return the quarantined item(s). The procedure for placing an item in quarantine and initiating a PIR is described in the sponsor-supplied Access Port Manual of Procedures.

16.2. Serious Adverse Event

An AE or suspected adverse reaction is considered ‘serious’ if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death.
- A 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.

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

16.2.1. Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) on an SAE Report Form. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

All SAE Report Forms will be reviewed by the site investigator and sent by fax within 24 hours of the site learning of the event. Sites will fax the SAE report to the appropriate CTI SAE fax number identified on the SAE Fax cover page.

The site will notify the CTI of additional information or follow-up to an initial SAE Report as soon as relevant information is available. Follow-up information is reported on an SAE Report Form.

In accordance with the SOPs and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

16.3. Medical Monitoring

Please refer to the study Operations Manual for medical monitor contact information.

17. DISCONTINUATION AND REPLACEMENT OF SUBJECTS

17.1. 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.

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 patients treated with adrabetadex and sham-treated patients on any efficacy measures.

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

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 for transition planning unless there are additional time restrictions mandated by an IRB/EC or health authority.

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 (EOS) visit and the safety follow-up visit are noted in Table 14.

Subjects with an implanted device will need to undergo device explanation.

Reasonable attempts will be made by the investigator 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.

17.2. Replacement of Subjects

Only subjects in Part A who discontinue or are discontinued from the study following randomization and did not receive sham/study drug or a subject who discontinued prior to receiving all scheduled doses of sham/study drug will be replaced by newly enrolled subjects, not to exceed 6 total replacements.

17.3. Protocol Violations

A protocol violation occurs when the subject or investigator fails to adhere to protocol requirements. Major protocol deviations are those that are:

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

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

18. DOSE SELECTION COMMITTEE AND DATA MONITORING COMMITTEE

After all subjects in Part A have received 4 IT infusions at the randomized dose levels or sham including 2 weeks of observation following the fourth dosing, all safety and efficacy data was provided to the DSC. The DSC included 2 neurologists with expertise in NPC1 disease who were also allowed to participate, in an unblinded role, in the conduct of the study. The DSC also included a physician who was not allowed to be otherwise involved in the conduct of the study.

The single dose selected for Parts B and C of the study was based on identification of the highest dose with acceptable safety and tolerability, including results of audiologic testing, as determined by the DSC. All data available through the 8-week time point was evaluated by the DSC in an unblinded fashion. These data included information on all AEs and SAEs through 8 weeks. Results of efficacy assessments also were provided to the committee.

If at any time following the second dose of study drug during Part A of the study, a subject was reported to have clinically significant hearing loss (CTCAE grade 3 or higher), this was to be reviewed in an unblinded manner by the DSC, which could have made recommendations in light of other available audiometric data from the study. Such individuals were to have repeat PTA and DPOAE testing as part of the hearing loss AE evaluation. Such recommendations could have included, for example, continuing on the current dose scheme, decreasing that subject's dose by 300 to 600 mg, decreasing all subjects in a specific dose cohort by 300 to 600 mg, discontinuing that subject from the study, or discontinuing that dose cohort.

In Part B, an independent DMC monitored safety in an ongoing basis. This committee consisted of a neurologist with expertise in lysosomal storage disease, a second neurologist and a

statistician, all of whom were not involved in the conduct of the trial. The DMC convened at least quarterly during the trial to review the cumulative blinded clinical safety and efficacy data. The DMC could make recommendations about continued enrollment based on safety. Data for Part B was provided to the DMC in a blinded format. Upon request, individual treatment codes could be disclosed to the DMC to assist in the evaluation of safety. If the DMC identified safety and tolerability issues, assessed in the context of the efficacy data in Part B, in subjects receiving study drug, they could recommend, for example, continuing the study as is, decreasing the VTS-270 dose level by 300 mg or 600 mg for all subjects receiving active treatment for the remainder of the study, or discontinuation of the study. There were no stopping rules for safety or for futility or superiority based on the efficacy data.

In Part C, an independent DMC will be re-convened to monitor safety on an ongoing basis. Details of the re-convened independent DMC constituency and remit can be found in the DMC charter. The responsibilities of the Rescue Option Criteria Committee are described in Section 9.4.

19. STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed statistical analysis plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below and therefore serves as the overriding document dictating the statistical analyses performed.

19.1. Analysis Populations

19.1.1. Intent-to-Treat Population

The ITT population will include all randomized subjects categorized by their randomized treatment assignment.

19.1.2. Modified Intent-to-Treat

The mITT population will consist of all randomized subjects who received at least one dose of VTS-270 infusion or sham control. The primary population for the co-primary efficacy assessment will be the mITT.

19.1.3. Per Protocol Population

The PP population will consist of all randomized subjects who had no major protocol deviation that would have had an impact on the primary outcome and who received at least 75% of their scheduled VTS-270 IT administrations. The major protocol deviations will be defined prior to database lock and unblinding. A blinded review of data will identify which subjects will be included in the PP populations prior to unblinding of the data.

19.1.4. Safety Population

The safety population will consist of all randomized subjects who receive at least 1 dose of VTS-270 or sham control.

19.1.5. European Site-specific Safety Population

The European site-specific safety population will consist of all randomized subjects who receive at least 1 dose of VTS-270 via the IT access device.

19.1.6. European Site-specific Device Pharmacokinetic Population

The PK population will consist of subjects enrolled in the device PK substudy who have received at least one dose administration of VTS-270 and have at least one quantifiable concentration value post dose. Subjects in the PK population will be used for all PK data summaries.

19.2. Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized by treatment group. Information to be summarized includes age in years, gender, race, ethnicity, height, weight, and body mass index, miglustat status (Yes/No), NPC-SS score category (10-19, 20+), seizures (Yes/No), and baseline NPC-SS total score, NPC-SS total score minus hearing components, and NPC-SS composite endpoint score.

19.3. Analysis of Pharmacokinetic Endpoints

Plasma and CSF PK parameters, AUC_{last}, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, CL/F, $t_{½}$, will be derived using noncompartmental analysis, if data permit. PK parameters except T_{max} will be summarized using descriptive statistics (geometric mean, arithmetic mean, standard deviation, coefficient of variation, sample size, minimum, maximum, and median). T_{max} will be only reported as sample size, minimum, maximum, and median. .

Other PK endpoints will be measured repeatedly over the course of the study and where possible, statistical analysis will be performed. With the exception of the CSF measures, outcome data will be collected for both groups. The CSF measures will not be collected in the sham group since no LPs are done in this group.

19.4. Interim Analysis

No interim analysis is planned.

A database lock is planned and will include data from Part A/B subjects who completed the double-blind portion of the study (or transitioned early to Part C for rescue), as well as Part C data collected up to the data cut-off date will be included in the analysis. All the data up to this time point will be reviewed, cleaned, and locked. This interim database lock is the final analysis lock for Part A/B data.

19.5. Sample Size and Randomization

The sample size for this study was approximately 51 subjects in Parts A and B combined. The rationale for the sample was based on both practical and statistical considerations. The sample size was determined based on the potential number of available subjects for this ultra-rare disorder. Based on the comparison of the NIH phase 1 subjects and similar subjects in the NIH natural history data set, approximately 51 subjects, 16 on sham and 35 on active treatment, would allow for the detection of clinically relevant difference of sum of the 4 NPC-SS score

domains that make up the composite outcome. The assumptions applied in the power calculation provide 79% power to detect a difference between the VTS-270 and sham groups by ANCOVA.

In Part B, at least 39 eligible subjects were to be randomly assigned to receive either VTS-270 or sham in a ratio of 2:1. The randomization was carried out using permuted blocks of size 3 and a total of 4 strata defined by miglustat use (yes or no) and baseline total NPC-SS score (10-19 or ≥ 20).

19.6. Stratification

The fact that subjects were not stratified in Part A but were stratified in Part B creates a unique situation. In order to understand the effect of stratification, the following stratification groups will be used in statistical analyses:

- Subjects randomized in Part A.
- Subjects randomized in Part B, miglustat use +, NPC-SS total score ≥ 20.
- Subjects randomized in Part B, miglustat use -, NPC-SS total score ≥ 20.
- Subjects randomized in Part B, miglustat use +, NPC-SS total score < 20.
- Subjects randomized in Part B, miglustat use -, NPC-SS total score < 20.

20. DATA COLLECTION, RETENTION, AND MONITORING

20.1. Data Collection Instruments

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. An electronic data capture system will be used to collect data in this study.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF when the information corresponding to that visit is available. Subjects 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, subject number, and initials.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating the eCRF data and create an electronic audit trail.

The investigator 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 investigator. A copy of the eCRF will remain at the investigator's site at the completion of the study.

20.2. Data Management Procedures

The data will be entered into a validated database. The data management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

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

20.3. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the electronic data capture system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

21. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number and initials only. 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 investigator must also comply with all applicable privacy regulations (eg, Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

21.1. Protocol Amendments

Any amendment to the protocol will be written by Vtesse LLC, a Mallinckrodt Pharmaceuticals Company. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRBs are notified within 5 working days.

21.2. Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the SOPs and policies of the IRB/IEC, and the investigator will keep the IRB/IEC informed as to the progress of the study. The investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC 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/IEC. The IRB/IEC's written unconditional approval of the study protocol and the informed consent form will be in the possession of the investigator before the study is

initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to Vtesse LLC, a Mallinckrodt Pharmaceuticals Company 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.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC 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/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the SOPs and policies of the IRB; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

21.3. Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25 [a, b], CFR 50.27, and CFR Part 56, Subpart A), HIPAA, and local regulations.

The investigator will prepare the informed consent form (ICF), assent, and HIPAA authorization and provide the documents to the sponsor or designee for approval prior to submission to the IRB/IEC. The ICF generated by the investigator must be acceptable to the sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The investigator will send an IRB/IEC-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 local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the ICF and the HIPAA authorization, 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.

21.4. Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

21.5. Investigator Responsibilities

By signing the Agreement of Investigator form, the investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
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 to 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 clinical 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 IND safety reports).
9. Seek IRB/IEC approval before any changes are made in the research 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.

21.6. Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (eg, production of interim reports and final reports), data for analysis are locked and cleaned per established procedures.

21.7. Availability and Retention of Investigational Records

The investigator must make study data accessible to the monitor, other authorized representatives of the sponsor (or designee), IRB/IEC, and regulatory agency (eg, FDA) inspectors upon request. A file for each subject must be maintained that includes the signed informed consent, confidentiality commitments (eg, HIPAA), Assent Form, and copies of all source documentation related to that subject. The investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

All study documents (subject files, signed informed consent forms, copies of eCRFs, Study File Notebook, etc.) must be kept secured for a period of 2 years following marketing of the investigational product or for 2 years after centers have been notified that the IND 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.

21.8. Monitoring

Monitoring visits will be conducted by representatives of the sponsor according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the investigator grants permission to the sponsor (or designee) and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

21.9. Subject Confidentiality

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

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23. APPENDICES

APPENDIX 1. STUDY PARTS A AND B SCHEDULE OF ASSESSMENTS

Table 8: Study Parts A and B Schedule of Assessments – Screening through Week 26

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Day	**Day -45 to Day -1**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**
Window (days)			**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point (Week)	**Screening**	**1st Study Dose**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**
Study Procedure															
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics, medical hx[a]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medication history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Collect urine[b]	X	-	-	-	-	X[#]	-	X	-	-	-	-	-	X	-
Pregnancy test	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical exam[c]	X	-	-	-	-	-	-	-	-	-	-	-	-	X	
Vital signs	X[d]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]	X[d,e]
Weight	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological examination[f]	X	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Clinical laboratory testing[g]	X	-	-	-	-	-	-	X	-	-	-	-	-	X	-
12-lead ECG	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Audiologic testing[h]	X	X	X[#]	X[#]	X[#]	X	-	-	-	X	-	-	-	X	-
Auditory brainstem response	X	-	-	-	-	X[#]	-	-	-	-	-	-	-		-
NPC Clinical Severity intake	X	X	-	-	-	X	-	-	-	X	-	-	-	X	-

Table 8: Study Parts A and B Schedule of Assessments – Screening through Week 26 (Continued)

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Day	**Day -45 to Day -1**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**
Window (days)			**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point (Week)	**Screening**	**1st Study Dose**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**
Clinician-CGIC[i] and Caregiver-CGIC	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
TUG Test	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
9-Hole Peg Test	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
EQ-5D-3L QoL	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Confirm subject eligibility	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Randomization[j]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Collect plasma biomarker samples[k]	-	X	-	-	-	X[#]	-	X	-	-	-	-	-	X	-
Sham or lumbar puncture and study drug administration	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect CSF samples(study drug subjects only)	-	X	-	-	-	X[#]	-	X	-	-	-	-	-	X	-
Collect whole blood for genetic testing[l]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Adverse events[m]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Medical history includes history of NPC1 disease, diagnosis date, and prior treatments.
[b] Urine will be obtained for urinalysis and biomarker testing.
[c] Full physical exam at Screening; abbreviated physical exam at all other visits.
[d] Vital signs, including blood pressure, will be recorded following a 5-minute rest in supine position.
[e] A second set of vital signs will be recorded following recovery of sedation from lumbar puncture or sham procedure.
[f] Full, videotaped neurological exam at Screening and Week 52; brief, videotaped neurological exam at Week 24.
[g] Clinical laboratory tests include chemistry, hematology, and coagulation.

[h] If a subject reports an increase in clinically significant hearing loss at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.
[i] Blinded Clinician to meet with subject and assess overall status and functionality that will form baseline for future Clinician-CGIC assessments.
[j] Randomization may occur on or before Study Visit 1, Day 0, after receipt of NPC Clinical Severity Score from central rater to confirm eligibility.
[k] Plasma samples for biomarkers should obtained prior to intrathecal or sham treatment.
[l] CSF samples for subjects on 900 mg VTS-270 may also be used for trough HP-β-CD measurements.
[m] The collection period of adverse events will begin after informed consent is obtained and end after procedures for the final study visit have completed.
[#] Part A participants ONLY.
CGIC = Clinical Global Impression of Change; CSF = cerebrospinal fluid; ECG = electrocardiogram; hx = history; NPC = Niemann-Pick disease, type C; NPC1 = Niemann-Pick disease, type C1; QoL = quality of life; TUG = timed up and go.

Table 9: Study Parts A and B Schedule of Assessments – Week 28 through Week 54

Visit Number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Follow-up[p]**			**ET[q]**
Study Day	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**441**	**532**	
Window (days)	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point (Week)	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**54**	**63**	**76**	
Study Procedure																	
Informed consent	-	-	-	-	-	-	-	-	-	-	-	-	X[n]	-	-	-	-
Demographics, medical history[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medication history	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Collect urine[b]	-	-	-	-	-	-	X	-	-	-	-	-	X	X[c]	-	-	-
Pregnancy test	-	-	-	-	-	-	-	-	-	-	-	-	X	X[c]	-	-	X
Physical exam[d]	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-	-	X
Vital signs[e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	-	-	X
Weight	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-
Neurological examination[h]	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	X
Clinical laboratory testing[i]	-	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	X[j]
12-lead ECG	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-
Audiologic testing[k]	-	-	X	-	-	-	X	-	-	X	-	-	X	-	-	-	X
Auditory brainstem response	-	-	-	-	-	-	-	-	-	-	-		X	-	-	-	X
NPC Clinical Severity Intake	-	-	X	-	-	-	X	-	-	X	-	-	X	-	X	X	X
Clinician-CGIC[l] and Caregiver-CGIC	-	-	X	-	-	-	X	-	-	X	-	-	X	-	X	X	X

Table 9: Study Parts A and B Schedule of Assessments – Week 28 through Week 54 (Continued)

Visit Number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Follow-up[p]**			**ET[q]**
Study Day	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**	**378**	**441**	**532**	
Window (days)	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point (Week)	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**54**	**63**	**76**	
TUG Test	-	-	X	-	-	-	X	-	-	X	-	-	X	-	-	-	X
9-Hole Peg Test	-	-	X	-	-	-	X	-	-	X	-	-	X	-	-	-	X
EQ-5D-3L QoL	-	-	X	-	-	-	X	-	-	X	-	-	X	-	-	-	X
Confirm subject eligibility	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Collect plasma biomarker samples[m]	-	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-
Sham or lumbar puncture and study drug administration	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	-	-	-	-
Collect CSF samples (study drug subjects only)[o]	-	-	-	-	-	-	X	-	-	-	-	-	X[n]	-	-	-	-
Adverse events[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	X

[a] Medical history includes history of NPC1 disease, diagnosis date, and prior treatments.
[b] Urine will be obtained for urinalysis and biomarker testing.
[c] Urine will be collected at Follow-up Visit 1 (Week 54) for pregnancy test. No other tests will be performed with urine.
[d] Full physical exam at Screening; abbreviated physical exam at all other visits.
[e] Vital signs, including blood pressure, will be recorded following a 5-minute rest in supine position.
[f] A second set of vital signs will be recorded following recovery of sedation from lumbar puncture or sham procedure.
[g] The second set of vital signs will only be recorded for subjects proceeding to Part C following recovery of sedation from lumbar puncture or sham procedure.
[h] Full, videotaped neurological exam at Screening and Week 52; brief, videotaped neurological exam at Week 24.
[i] Clinical laboratory tests include chemistry, hematology, and coagulation.
[j] Clinical laboratory tests include chemistry, hematology, coagulation, urinalysis, and pregnancy.
[k] If a subject reports an increase in clinically significant hearing loss at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.
[l] Blinded Clinician to meet with subject and assess overall status and functionality that will form baseline for future Clinician-CGIC assessments.

[m] Plasma samples for biomarkers should obtained prior to intrathecal or sham treatment.
[n] To be performed only for subjects proceeding to Part C.
[o] CSF samples for subjects on 900 mg VTS-270 may also be used for trough HP-β-CD measurements.
[p] Only subjects who will NOT be continuing into Part C, the open-label extension, will complete the Follow-up visits.
[q] All subjects who discontinue study treatment will be requested to return to the clinic to complete an Early Termination (ET) visit.
[r] The collection period of adverse events will begin after informed consent is obtained and end after procedures for the final study visit have completed.
CGIC = Clinical Global Impression of Change; CSF = cerebrospinal fluid; ECG = electrocardiogram; ET = early termination; NPC = Niemann-Pick disease, type C; NPC1 = Niemann-Pick disease, type C1; QoL = quality of life; TUG = timed up and go.

APPENDIX 2. STUDY PART C SCHEDULE OF ASSESSMENTS

Table 10: Study Part C Schedule of Assessments – Screening through Week 28

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Study Day	**Day –45 to Day –1**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**
Window (days)			**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point (Week)	**Screen[a]**	**1st Study Dose**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**
Study Procedure																
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics, medical history[b]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medication history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Collect urine[c]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Pregnancy test	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical exam[d]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Vital signs	X[e]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]
Weight	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological examination[g]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Wound check/port site exam for IT access port subjects[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	(X)	(X)	(X)
Clinical laboratory testing[i]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
12-lead ECG	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Audiologic testing[j]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Auditory brainstem response	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Study Day	**Day –45 to Day –1**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**
Window (days)			**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point (Week)	**Screen[a]**	**1st Study Dose**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**
Study Procedure																
Clinician-CGIC	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
NPC-SS intake	X	X	-	-	-	-	-	-	-	-	-	-	-	-	X	-
EQ-5D-3L	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-
Lumbar puncture and study drug administration	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IT access port study drug administration for IT access port subjects[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	(X)	(X)	(X)
CSF lab tests and trough HP-β-CD for IT access device subjects[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	(X)	(X)	(X)
Adverse events[k]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Screening visit is only for subjects newly enrolled at Part C; for subjects continuing from Part B, the Week 52 visit functions as the Screening visit for Part C.
[b] Medical history includes history of NPC1 disease, diagnosis date, and prior treatments.
[c] Urine will be obtained for urinalysis only.
[d] Full physical exam at Screening; abbreviated physical exam at all other visits.
[e] Vital signs, including blood pressure, will be recorded following a 5-minute rest in supine position.
[f] A second set of vital signs will be recorded following recovery of sedation from lumbar puncture or sham procedure.
[g] Full neurological exam at Screening and Week 52; brief, videotaped neurological exam at Week 24.
[h] Subjects participating in the European site-specific IT access port safety and tolerability assessment will remain in their Part C schedules and will add additional port-specific assessments as detailed in the device-specific schedule of events for the first nine port infusions (Table 15). Where there is duplication of assessments with Part C, only 1 assessment will be conducted. CSF samples for subjects on 900 mg VTS-270 may also be used for trough HP β CD measurements

[i] Clinical laboratory tests include chemistry, hematology, and coagulation.
[j] If a subject reports an increase in clinically significant hearing loss at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.
[k] The collection period of adverse events will begin after informed consent is obtained and end after procedures for the final study visit have completed.
CGIC = Clinical Global Impression of Change; CSF = cerebrospinal fluid; ECG = electrocardiogram; IT = intrathecal; NPC = Niemann-Pick disease, Type C; NPC-SS = NPC Severity Scale.

Table 11: Study Part C Schedule of Assessments – Week 30 through Week 52

Visit Number	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Study Day	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**
Window (days)	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point (Week)	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52[k]**
Study Procedure												
Informed consent[a]	-	-	-	-	-	-	-	-	-	-	-	-
Demographics, medical history[b]	-	-	-	-	-	-	-	-	-	-	-	-
Medication history	-	-	-	-	-	-	-	-	-	-	-	-
Collect urine[c]	-	-	-	-	-	-	-	-	-	-	-	X[k,l]
Pregnancy test	-	-	-	-	-	-	-	-	-	-	-	X[k,m]
Physical exam[d]	-	-	-	-	-	-	-	-	-	-	-	X[k,l]
Vital signs	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[e,f,k]
Weight	-	-	-	-	-	-	-	-	-	-	-	X
Neurological examination	-	-	-	-	-	-	-	-	-	-	-	X[k,l]
Wound check/port site exam for IT access port subjects[g]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Clinical laboratory testing[h]	-	-	-	-	-	-	-	-	-	-	-	X[k,l]
12-lead ECG	-	-	-	-	-	-	-	-	-	-	-	X[m]
Audiologic testing[i]	-	-	-	-	-	-	-	-	-	-	-	X[k,l]
Auditory brainstem response	-	-	-	-	-	-	-	-	-	-	-	X[k,m]
Clinican-CGIC assessment	-	-	-	-	-	-	-	-	-	-	-	X[k,l]
NPC-SS intake	-	-	-	-	-	-	-	-	-	-	-	X[k,l]
EQ-5D-3L assessment	-	-	-	-	-	-	-	-	-	-	-	X[k,l]

Table 11: Study Part C Schedule of Assessments – Week 30 through Week 52 (Continued)

Visit Number	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Study Day	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**
Window (days)	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point (Week)	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**[k]
Lumbar puncture and study drug administration [j]	X	X	X	X	X	X	X	X	X	X	X	X
IT access port study drug administration for IT access port subjects [g]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
CSF lab tests and trough HP-β-CD for device subjects [g]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Adverse events [n]	X	X	X	X	X	X	X	X	X	X	X	X[k]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X[k]

[a] Study Visit 1 only.
[b] Medical history includes history of NPC1 disease, diagnosis date, and prior treatments.
[c] Urine will be obtained for urinalysis only.
[d] Full physical exam at Screening; abbreviated physical exam at all other visits.
[e] Vital signs, including blood pressure, will be recorded following a 5-minute rest in supine position.
[f] A second set of vital signs will be recorded following recovery of sedation from LP procedure.
[g] Subjects participating in the European site-specific IT access port safety and tolerability assessment will remain in their Part C schedules and will add additional port-specific assessments as detailed in the device-specific schedule of events for the first nine port infusions (Table 15). Where there is duplication of assessments with Part C, only 1 assessment will be conducted.
[h] Clinical laboratory tests include chemistry, hematology, and coagulation.
[i] If a subject reports an increase in clinically significant hearing loss at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.
[j] Subjects who have transitioned from the NIH phase 1 study will continue to receive IT administration of VTS-270 every 2 weeks (or as per authorized amended dosing regimen).
[k] All subjects who discontinue study treatment will be requested to return to the clinic to complete an Early Termination (ET) visit comprising these evaluations.
[l] After Study Visit 27, record every 6 months thereafter.
[m] After Study Visit 27, record annually thereafter.
[n] The collection period of adverse events will begin after informed consent is obtained and end after procedures for the final study visit have completed.
CGIC = Clinical Global Impression of Change; CSF = cerebrospinal fluid; ECG = electrocardiogram; IT = intrathecal; LP = lumbar puncture; NIH = National Institutes of Health NPC1 = Niemann-Pick disease, type 1; NPC-SS = NPC Severity Scale.

Table 12: Study Part C Schedule of Assessments – Week 54 through Week 182

Visit Number	**28-39**	**40**	**41-52**	**53**	**54-65**	**66**	**67-78**	**79**	**80-91**	**92**
Study Day	**378-532**	**546**	**560-714**	**728**	**742-896**	**910**	**924-1078**	**1092**	**1106-1260**	**1274**
Window (days)	**(±7)**	**(±7**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point	**Wk 54-76 (>1 yr to <1.5 yr)**	**Wk 78**	**Wk 80-102 (>1.5 yr to <2 yr)**	**Wk 104**	**Wk 106-128 (>2 yr to <2.5 yr)**	**Wk 130**	**Wk 132-154 (>2.5 yr to <3 yr)**	**Wk 156 (3 yr)**	**Wk 158-180 (>3 yr to<3.5 yr)**	**Wk 182**
Study Procedure										
Collect urine[a]	-	X	-	X	-	X	-	X	-	X
Pregnancy test	-		-	X	-	-	-	X	-	--
Physical exam (abbreviated)	-	X	-	X	-	X	-	X	-	X
Wound check/port site and catheter track exam[b]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Vital signs[c,d]	X	X	X	X	X	X	X	X	X	X
Weight	-	-	-	X	-	-	-	X	-	-
Neurological examination	-	X	-	X	-	X	-	X	-	X
Clinical laboratory testing[e]	-	X	-	X	-	X	-	X	-	X
12-lead ECG	-	-	-	X	-	-	-	X	-	-
Audiologic testing[f]	-	X	-	X	-	X	-	X	-	X
Lumbar puncture and study drug administration	X	X	X	X	X	X	X	X	X	X
IT access port study drug administration[b]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
CSF lab tests	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Adverse events	X	X	X	X	X	X	X	X	X	X

Table 12: Study Part C Schedule of Assessments – Week 54 through Week 182 (Continued)

Visit Number	**28-39**	**40**	**41-52**	**53**	**54-65**	**66**	**67-78**	**79**	**80-91**	**92**
Study Day	**378-532**	**546**	**560-714**	**728**	**742-896**	**910**	**924-1078**	**1092**	**1106-1260**	**1274**
Window (days)	**(±7)**	**(±7**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Time Point	**Wk 54-76 (>1 yr to <1.5 yr)**	**Wk 78**	**Wk 80-102 (>1.5 yr to <2 yr)**	**Wk 104**	**Wk 106-128 (>2 yr to <2.5 yr)**	**Wk 130**	**Wk 132-154 (>2.5 yr to <3 yr)**	**Wk 156 (3 yr)**	**Wk 158-180 (>3 yr to<3.5 yr)**	**Wk 182**
Concomitant medications	X	X	X	X	X	X	X	X	X	X

[a] Urine will be obtained for urinalysis only.
[b] Subjects participating in the European site-specific IT access port safety and tolerability assessment will remain in their Part C schedules and will add additional port-specific assessments as detailed in the device-specific schedule of events for the first nine port infusions (Table 15). Where there is duplication of assessments with Part C, only 1 assessment will be conducted.
[c] Vital signs, including blood pressure, will be recorded following a 5-minute rest in supine position.
[d] A second set of vital signs will be recorded following recovery of sedation from lumbar puncture procedure.
[e] Clinical laboratory tests include chemistry, hematology, and coagulation.
[f] If a subject reports an increase in clinically significant hearing loss at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.
CSF = cerebrospinal fluid; ECG = electrocardiogram; IT = intrathecal; NPC = Niemann-Pick disease, type C; NPC-SS = NPC Severity Scale; Wk = week.

Table 13: Study Part C Schedule of Assessments – Beyond Week 182 Visit Number 92

Visit Number	**93-104, 106-117, 119-130, 132-143**	**118 & 144**	**105 & 131**
Week	**184-206, 210-232, 236-258, 262-284**	**234 & 286**	**208 & 260**
Window (days)	**(±7)**	**(±7)**	**(±7)**
Time Point	**Every 2 weeks except 6 monthly and yearly visits**	**Every 6 Months from Year 4.5 and beyond**	**Yearly visit from Year 4 and beyond**
Study Procedure			
Collect urine[a]	-	X	X
Pregnancy test	-	-	X
Physical exam (abbreviated)	-	X	X
Wound check/port site and catheter track exam[b]	X	X	X
Vital signs[c,d]	X	X	X
Weight	-	-	X
Neurological examination	-	X	X
Clinical laboratory testing[e]	-	X	X
12-lead ECG	-	-	X
Audiologic testing[f]		X	X
Lumbar puncture and study drug administration	X	X	X
IT access port study drug administration[b]	X	X	X
CSF lab tests	X	X	X
Adverse events	X	X	X
Concomitant medications	X	X	X

[a] Urine will be obtained for urinalysis only.
[b] Subjects participating in the European site-specific IT access port safety and tolerability assessment will remain in their Part C schedules and will add additional port-specific assessments as detailed in the device-specific schedule of events for the first nine port infusions (Table 15). Where there is duplication of assessments with Part C, only 1 assessment will be conducted.
[c] Vital signs, including blood pressure, will be recorded following a 5-minute rest in supine position.
[d] A second set of vital signs will be recorded following recovery of sedation from lumbar puncture procedure.
[e] Clinical laboratory tests include chemistry, hematology, and coagulation.
[f] If a subject reports an increase in clinically significant hearing loss at any post-baseline assessment, unscheduled audiologic evaluation visits will increase in regularity at the discretion of the Primary Investigator.
CSF = cerebrospinal fluid; ECG = electrocardiogram; IT = intrathecal.

Table 14: Study Part C Schedule of Assessments – End of Study and Follow-up

Study Day	**End of Study**	**Follow-up Visit**
Window (days)		**(±7)**
Time Point (Week)		**ET + 2W**
Study Procedure		
Adverse events	X	X
Concomitant medications	X	X
Audiologic testing	X	-
Complete physical exam	X	X
Vital signs[a]	X	X
Clinical laboratory testing[b]	X	-
Complete neurological examination	X	-
Urine pregnancy test	-	X
Port device removal[c]	X	-
Wound check	X	X

[a] Vital signs, including blood pressure, will be recorded following a 5-minute rest in supine position.
[b] Clinical laboratory tests include chemistry, hematology, and coagulation.
[c] For subjects with port device, remove device prior to termination.
ET = early termination; NPC = Niemann-Pick disease, type C; NPC-SS = NPC Severity Scale; W = week.

Table 15: Part C European Site-specific Device Safety and Tolerability Substudy Schedule of Assessments

Visit Number[a]				**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**
Device Substudy Day	**-7 to -3**	**1**[b]	**2 to 3**	**15**[c]	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127 or ET**[e]
Window (days)		**+3**	**NA**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**
Study Procedure / Time Point	**Baseline**	**Confinement Period / Surgery**		**Device Infusion Visits**								
				1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Consent/assent	X	-	-	-	-	-	-	-	-	-	-	-
Eligibility criteria	X	-	-	-	-	-	-	-	-	-	-	-
Demographics & medical history	X	-	-	-	-	-	-	-	-	-	-	-
Medication history	X	-	-	-	-	-	-	-	-	-	-	-
Adverse events[f]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[f]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[h]	X	-	X	X	-	-	-	-	-	-	-	X
Neurological examination[i]	X	-	-	-	-	-	-	-	-	-	-	X
Clinical lab tests [j]	X	-	-	-	-	-	-	-	-	-	-	X
Lumbar puncture and study drug administration[d]	X	-	-	-	-	-	-	-	-	-	-	-
Intracranial pressure collection	X	-	-	-	-	-	-	-	-	-	-	-

Table 15: Part C European Site-specific Device Safety and Tolerability Substudy Schedule of Assessments (Continued)

Visit Number[a]				**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**
Device Substudy Day	**-7 to -3**	**1**[b]	**2 to 3**	**15**[c]	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127 or ET**[e]
Window (days)		**+3**	**NA**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**
Study Procedure / Time Point	**Baseline**	**Confinement Period / Surgery**		**Device Infusion Visits**								
				1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Serum pregnancy test	X	-	-	-	-	-	-	-	-	-	-	-
CSF lab tests	-	X		X	X	X	X	X	X	X	X	X
Device implantation	-	X [k,l]	-	-	-	-	-	-	-	-	-	-
Radiograph of device placement[m]	-	X	-	-	-	-	-	-	-	-	-	-
Wound check[n, o]	-	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Inspect port site & catheter track[n]	-	X	X	X	X	X	X	X	X	X	X	X
VTS-270 device infusion[p]	-	-	-	X	X	X	X	X	X	X	X	X[q]

AE = adverse event; CSF = cerebrospinal fluid; EOS = end of study; ET = early termination; lab = laboratory; NA = not applicable; PK = pharmacokinetics

[a] Subjects will remain in their Part C schedules and will add additional device-specific assessments as detailed in the device-specific schedule of events for the first 9 device infusions (D1-D9). Where there is duplication of assessments with Part C, only 1 assessment will be conducted.

[b] Implantation surgery will be scheduled as close as possible to the last lumbar puncture (within approximately 3 days).

[c] A minimum of 14 days following device implantation must elapse before the device is used for VTS-270 administration.

[d] Subjects will also receive last dose of VTS-270 via lumbar puncture per VTS301 protocol.

[e] All subjects who complete the VTS301 Part C or discontinue study treatment early should return to the clinic to complete a EOS/ET Visit. If the subject completes the study and does not continue to receive VTS-270, the device will be removed; if the subject discontinues from the study early, the device will be removed. Adverse events and concomitant medications should be recorded post removal.

[f] Concomitant medications and AEs to be collected before and after infusion (through end of visit), where appropriate.

[g] Vital signs including pulse rate, blood pressure, respiratory rate, and oral temperature will be recorded following a 5-minute rest in supine position. Vital signs should be repeated after the 30- to 45-minute recovery period following VTS-270 infusion.

[h] An abbreviated physical examination will be performed at baseline, Day 2 and 3 confinement period, and at the first and ninth device infusion visits.
[i] An abbreviated neurological examination will be performed at baseline and the ninth device infusion visit.
[j] Testing includes hematology, serum chemistry, and coagulation tests.
[k] If the device becomes nonfunctional at any time during the study, it will be removed; replacement with a new device requires approval from the sponsor.
[l] Procedures for implantation and removal are detailed in the device sponsor-supplied Access Port Manual of Procedures.
[m] The investigator may obtain repeat radiographs as indicated during the study to determine device placement and/or integrity.
[n] If abnormal swelling or redness is noted around the port or along the catheter site and infection is suspected, study drug should not be administered and appropriate evaluation of the device and catheter track should be undertaken to rule out malfunction or infection.
[o] Check wound at first infusion visit and until healed.
[p] All evaluations on the days of device infusion, including inspection of the port site and catheter track, will occur prior to and during administration of study drug, as well as after study drug administration. Following infusion of VTS-270 via the device, all subjects are required, if possible, to lie flat with feet elevated for 30 to 45 minutes. Following the recovery, the subject will be reassessed for vital signs, any new AEs, and any new concomitant medications.
[q] If an early termination visit is needed, subjects will not be treated with VTS-270 via the device.

Signature Page for VV-CLIN-028279 v1.0

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