Vtesse, Inc. a Mallinckrodt Pharmaceutical Company
NCT #NCT02534844

Clinical Research Protocol [redacted] Version 2.0

Protocol Synopsis for Parts A/B
Full protocol to be disclosed with Part C Results

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:	[redacted] – Version 2.0
Version Date:	18 October 2019
Investigational Product:	VTS-270 (specific and well-characterized mixture of 2-hydroxypropyl-β-cyclodextrin [HP-β-CD])
IND Number:	[redacted]
EudraCT Number:	2015-002548-15
Development Phase:	2b/3
Sponsor:	Vtesse, Inc a Mallinckrodt Pharmaceutical Company 1425 US Route 206 Bedminster, NJ 07921
Co-Principal Investigator:	Name: [redacted] Telephone: [redacted] Fax: [redacted] E-mail: [redacted]
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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, Inc a Mallinckrodt Pharmaceutical Company 1425 US Route 206 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 will evaluate 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 will receive treatment with VTS-270 for up to 52 weeks (inclusive of Part A). Subjects who elect not to continue with Part C will have 26 weeks of follow-up. 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. Part A and B subjects who transition into Part C will receive treatment with VTS-270 until the investigator considers VTS-270 to no longer be beneficial, VTS-270 receives marketing authorization, or the development program is discontinued. 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, VTS-270 receives marketing authorization, or the development program is discontinued. A European site-specific substudy will be conducted as part of the Part C study. This substudy will 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

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	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 will also be conducted and include approximately 6 eligible subjects under Part C of the VTS301 study. Eligible subjects will have completed the device safety and tolerability substudy, i.e., received 9 consecutive doses of 900 mg VTS-270 via the device. In addition, after 6 subjects have completed the device safety and tolerability substudy, subjects in the main Part C study who are on a stable dose of 900 mg VTS-270 via LP and eligible for device insertion will be eligible to participate in the European site-specific device PK substudy. During a single dosing session using the device, blood and CSF samples will be collected just before VTS-270 infusion and 1, 2, 4, 6, 8, approximately 24, and approximately 30 hours after infusion. The 30-hour time point should be at least 6 hours after the 24 hour time point. Subjects who enter the device PK substudy from the main Part C study must receive at least 3 device infusions of 900 mg VTS-270 before PK assessments are performed. Following the full PK assessment visit, subjects will continue in the main Part C study and have CSF samples collected for measurement of trough 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) concentration prior to each subsequent device infusion of VTS-270.
Dose Reduction	The following are guidelines for which dose reduction on an individual subject basis is allowed in Part B: Subjects who, in the opinion of the investigator, experience a drug-related adverse event (AE) after any blinded IT treatment that is considered clinically relevant and impactful to the subject's function may 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 continues to experience AEs as described above, the subject's dose may 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 continues to experience a drug-related clinically relevant AE, the dose is NOT to be reduced further and the subject is 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	Under specific circumstances, and after discussion with and approval by the medical monitor, an investigator may be allowed to re-escalate the dose for an individual study subject in Part C. If a subject has had his/her dose reduced and is in Part C on a tolerable dose, the subject may be dose titrated back up (e.g., from 400 mg to 600 mg and from 600 mg to 900 mg) to a tolerable dose as determined by the investigator.
Rescue Option	Subjects who are enrolled in Part B and manifest significant disease progression according to predefined clinical criteria after 26 weeks or more of treatment will have the option to enter

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	Part C. The blinded medical monitor will notify the blinded Rescue Option Criteria Committee (ROCC). Alternatively, a blinded site clinician may contact the blinded medical monitor to request a blinded ROCC review if he/she feels the disease symptoms have progressed substantially since the beginning of the trial. If a subject still meets criteria for predefined worsening at the confirmatory visit, the ROCC will make a recommendation as to whether the subject has the option to enter the open-label extension study or to withdraw from the program.
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 is 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 NPC-SS composite which consists of the sum of 4 components of the Niemann Pick Type C Severity Scale (NPC-SS): ambulation, fine motor, cognition, and swallowing. • The blinded Clinician-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 VTS-270.
Secondary Objectives	**Part A:** There are no secondary objectives for Part A. **Part B:** The secondary objectives for Part B are divided into 2 categories: key secondary objective and other secondary objectives. The key secondary objective for Part B is 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 are 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 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 One Point Increase (Worsening) on the NPC-SS Composite Score

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	• the Annualized Rate of Change (Slope) of The NPC-SS Composite • 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 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).
Exploratory Objectives	**Part A:** There are no exploratory objectives for Part A. **Part B:** The exploratory study objectives in Part B are to: • Collect cerebrospinal fluid (CSF), urine, and plasma samples from the subjects receiving study drug, and urine and plasma samples from subjects randomized to sham control, will be collected at prespecified intervals and stored for exploratory biomarker analyses. • 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: 1. The composite NPC-SS in completers. 2. The composite NPC-SS outcome assuming data missing at random using a standard multiple imputation model 3. The composite NPC-SS using a pattern mixture model 4. 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** **Inclusion Criteria:** Subjects must meet the following criteria to be included: 1. Male or female subjects, 4 to 21 years of age at time of screening, with onset of neurological symptoms prior to 15 years of age. 2. Diagnosis of NPC1 determined by one of the following: a. Two NPC1 mutations; b. Positive filipin staining or oxysterol testing and at least one NPC1 mutation; c. Vertical supranuclear gaze palsy (VSNGP) in combination with either: i. One NPC1 mutation, or ii. Positive filipin staining or oxysterol levels consistent with NPC1 disease and no NPC2 mutations.

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	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. Ability to undergo a LP and IT drug administration under monitored anesthesia care (conscious sedation) or if medically necessary, general anesthesia. 5. An NPC-SS score of 0 through 4, inclusive, on the cognition component, and 1 through 4 in two or more of the following components: ambulation, fine motor skills, or swallowing. 6. Total NPC-SS score of 10 or greater. 7. Subjects with adequately controlled seizures may qualify for enrollment. Subjects with a history of seizures should have a stable pattern of seizure activity and be on a stable dose and regimen of antiepileptic medication during the 3 months prior to screening without change in dose or regimen up to and including Study Day 0. 8. If taking miglustat, must have been on a stable dose for the past 6 to 8 weeks and be willing to remain on a stable dose for the duration of participation in Parts A and B of the study. Alternatively, subjects may elect to discontinue miglustat use and be eligible for trial entry after undergoing a minimum 6-week washout period prior to Study Day 0. 9. Agree to discontinue all nonprescription supplements such as coenzyme Q10, curcumin, cinnamon, fish oil supplements, high-dose vitamin D (> 500 mIU/day), N-acetylcysteine, acetylleucine, or gingko biloba at least 1 month prior to first dose (Study Day 0). Note: Daily administration of an age-appropriate multivitamin is allowed. 10. Agree to discontinue any other investigational treatments for NPC including, for example, vorinostat or arimoclomol at least 3 months prior to first dose (Study Day 0). 11. 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, or abstinence. 12. Subject or caregiver must possess the ability, per the investigator, to understand and comply with protocol requirements including clinical outcome measurements and instructions for the entire duration of the study. 13. Caregiver, parent, guardian or responsible adult must be able and willing to accompany the subject to study visits. **Exclusion Criteria:** Subjects meeting any of the following criteria are to be excluded: 1. Exclusion criteria as assessed by NPC-SS: a. Unable to walk, wheelchair dependent (ambulation score = 5). b. Needs a nasogastric tube or gastric tube for all feedings (swallowing score = 5). Note: Nasogastric or gastric tube use for supplemental feeding or medication administration is permitted and will not exclude a subject from this trial. c. Severe dysmetria (fine motor score = 5). d. Minimal cognitive function (cognition score = 5). 2. Body weight < 15 kg.

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	3. Prior treatment with IV 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) for NPC1 disease, unless the subject has undergone a minimum 3-month washout period prior to Study Day 0. Note: Any prior IT administration of HP-β-CD for the treatment of NPC1 disease will exclude a subject from enrollment. Treatment of other medical conditions with drug preparations containing HP-β-CD as an excipient (inactive ingredient) is acceptable and will not exclude a subject from immediate entry into this trial (no washout period required). 4. Status epilepticus occurring within 3 months of screening and/or seizure frequency that cannot be quantified. 5. Subjects on typical or atypical antipsychotics for treatment of psychosis. Note: Use of antipsychotic medication for treatment of other disorders (e.g., attention deficit hyperactivity disorder) will not exclude a subject from this trial. 6. History of hypersensitivity reactions to any product containing HP-β-CD. 7. Prior treatment with any other investigational product within 3 months prior to first dose (Study Day 0). 8. Female subjects who are pregnant or nursing. 9. Subjects with suspected infection of the central nervous system (CNS) or any systemic infection. 10. Spinal deformity that could impact the ability to perform a LP. 11. Skin infection in the lumbar region within 2 months of study entry. 12. Neutropenia, defined as an absolute neutrophil count (ANC) of less than 1.5×10^9/L. 13. Thrombocytopenia (platelet count less than 75×10^9/L). 14. Activated partial thromboplastin time (aPTT) or prothrombin time (PT) prolonged by greater than 1.5 times the upper limit of normal (ULN) or known history of a bleeding disorder. 15. Evidence of obstructive hydrocephalus or normal pressure hydrocephalus. 16. Recent use of anticoagulants (in past 2 weeks prior to first dose [Study Day 0]). 17. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 4 times the ULN. 18. Anemia: hemoglobin more than 2 standard deviations below normal for age and gender. 19. Estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73m^2 calculated using the modified Schwartz formula (2009) for subjects aged 6 through 17 years old or using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for subjects aged 18 years or older. 20. Active pulmonary disease, oxygen requirement, or clinically significant history of decreased blood oxygen saturation, pulmonary therapy, or requiring active suction. 21. Subjects who, in the opinion of the investigator, are unable to comply with the protocol or have medical conditions that would potentially increase the risk of participation. 22. Life expectancy less than 1 year. **Part C** 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

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	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** The European site-specific device safety and tolerability substudy will evaluate approximately 6 subjects who are currently enrolled in VTS301 Part C. A subject must meet all 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.

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	Subject Exclusion Criteria for the European Site-Specific Device Safety and Tolerability Substudy The presence of any of the following excludes 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. aPTT or PT greater than 1.5 times the 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 intracranial pressure (ICP; opening ICP > 25.0 cm H_2O). 10. AST or ALT greater than 4 times the ULN, or total bilirubin greater than 2 times ULN. 11. Anemia: hemoglobin more than 2 standard deviations below normal for age and gender. 12. 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 CKD-EPI formula for subjects aged 18 years or 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 **Subject Inclusion Criteria for the European Site-Specific Device Pharmacokinetic (PK) Substudy** 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

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	Or 2. After 6 subjects have completed the device safety and tolerability substudy, subjects in the main Part C study who are receiving a stable dose of 900 mg VTS-270 via LP and are eligible for device implantation 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.
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 (e.g., 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, e.g., headphones for music or video games. <u>Device Administration (European Site-Specific Device Safety and Tolerability Substudy, Part C)</u>

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	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	**Parts A and B** Total duration of subject participation in Parts A and/or B will be approximately 58 weeks, to include a screening period of up to 45 days (maximum), and 52 weeks of serial IT injections or sham control procedures given on a 2-week cycle. An additional 26 weeks of post-treatment follow-up will be included for any subject who elects not to participate in Part C, for a total of 84 weeks. Below is a summary of the duration of Part A and B: • Up to 45 days screening • Up to 8 weeks in Part A • Up to 52 weeks of dosing, inclusive of the 8 weeks for subjects from Part A, for subjects enrolled in Part B. • Up to 26 weeks of follow-up for Part B subjects who elect not to participate in Part C. **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, VTS-270 receives marketing authorization, or the development program is discontinued.
Efficacy Evaluations	
Primary Endpoint	**Part B:** The co-primary efficacy analysis will be based on: • Change from baseline in NPC-SS composite score at Week 52 in the group treated with VTS-270 vs. the sham control group. • Blinded Clinician CGIC at Week 52 in the group treated with VTS-270 vs the sham control group.
Secondary Endpoints	**Part B:** The secondary outcomes for Part B are divided into 2 categories: Key secondary outcome and other secondary outcomes. The key secondary endpoints are • Change from baseline at Week 52 in the total NPC–SS score with the hearing domain and ABR modifiers removed in the group treated with VTS-270 vs. the sham control group.

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	• Proportion of Caregiver CGIC responders (defined as a score of no change, minimally improved, moderately improved or markedly improved) at Week 52 in the group treated with VTS-270 vs. the sham control group. <u>Other (non-key) secondary endpoints:</u> • Summary of AEs, concomitant medications, physical examinations, audiologic examination, and clinical laboratories • Change from baseline in the EQ-5D-3L questionnaire at Week 52 • Proportion of subjects in each group, treated for at least 6 months who qualified for the rescue option. • Change from baseline to Week 52 in each of the 9 clinical domains of the NPC-SS • Change from baseline to Week 52 in the total NPC-SS with hearing domain and ABR modifier included • Time to one point increase (worsening) in NPC-SS composite score • The composite NPC-SS mean annualized rate of change (slope) from baseline to Week 52 • Change from baseline in the TUG test at Week 52 • Change from baseline in the 9-hole peg test at Week 52 **Part C:** • 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 one 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 (e.g., calbindin D) biomarkers • CSF and plasma sterol biomarkers • Gene and protein expression
Safety Evaluations	• AEs • Audiologic testing

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	• 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**	**Analysis populations:** The intent-to-treat (ITT) population will include all randomized subjects categorized by their randomized treatment assignment. The modified intent-to-treat (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 primary efficacy assessment will be the mITT. The per-protocol (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 safety population will also consist of all randomized subjects who receive at least one dose of VTS-270 or sham control. The European site-specific device safety population will consist of all subjects who receive at least 1 dose of VTS-270 via the device. The PK population will consist of subjects enrolled in the device PK substudy and whose plasma and/or CSF drug concentrations will provide at least 1 of the PK parameters of interest. Subjects in the PK population will be used for all PK data summaries. **Primary outcome measure:** The co-primary efficacy endpoints are the change from baseline in NPC-SS composite score (sum of the ambulation, cognition, fine motor, and swallowing components of the NPC-SS) at Week 52 and the blinded Clinician CGIC at Week 52. The NPC-SS composite score is the sum of the ambulation, cognition, fine motor, and swallowing domains of the NPC-SS. For the primary efficacy analysis, any missing Week 52 assessments will be imputed. Subjects who take the rescue option will be considered dropouts and will need to have their missing Week 52 assessment imputed. The Clinician CGIC is a 7-point Likert scale. The scale requires assessment of change from a baseline level of disease activity, with anchors ranging from markedly improved, moderately improved, and minimally improved to no change and corresponding worsening (minimally, moderately, markedly). The analysis of the blinded Clinician CGIC at Week 52 will be conducted using the nonparametric Van Elteren method to test for the treatment effect using study part as a blocking variable. Average ranks will be assigned when there are ties within a block. Missing Week 52 assessments will be imputed. **Analysis of secondary endpoints:** The following key secondary endpoints comparing subjects treated with VTS-270 with the sham controls will be analyzed using a hierarchical testing, serial gatekeeping strategy based on the mITT population. • The change from baseline to Week 52 in total NPC-SS with the hearing domain and ABR modifiers removed. • Proportion of Caregiver CGIC responders (defined as a score of no change, minimally improved, moderately improved or markedly improved) at Week 52.