# Restoration of cholesterol trafficking results in decreased markers of neuronal damage in individuals with Niemann-Pick Disease Type C1

Poster S250

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## Background

### Disease Overview

Niemann-Pick Disease Type C (NPC) is a rare, autosomal-recessive, neurodegenerative disorder caused by pathogenic variants in *NPC1* (~95% of cases) or *NPC2*, which encode proteins essential for intracellular cholesterol transport.[1-3] Impaired cholesterol trafficking results in toxic accumulation of unesterified cholesterol in lysosomes and a relative deficiency of cytoplasmic cholesterol needed for normal cellular function. This imbalance leads to dysfunction across multiple organs—particularly the brain—ultimately causing progressive neurological decline and premature mortality.[1-3]

### Biomarkers of Cholesterol Dysregulation and Neuronal Injury

CNS markers related to NPC neuropathology include:[3-7]

- 24(S)-hydroxycholesterol (24[S]-OHC): neuron-derived oxysterol produced as the main route for eliminating excess brain cholesterol; reduced in CSF and plasma in participants with NPC, reflecting impaired cholesterol trafficking
- Calbindin D: calcium-binding protein especially enriched in Purkinje neurons; increased in CSF of individuals with NPC, reflecting cerebellar neuronal loss
- Fatty acid–binding protein 3 (FABP3): cytosolic protein involved in membrane dynamics and synapse formation; increased in CSF of participants with NPC as a marker of neuronal damage and death

### Adrabetadex Investigational Therapy

Adrabetadex (VTS-270) is a proprietary mixture of 2-hydroxypropyl-β-cyclodextrin (HPβCD) isomers that addresses the core pathology of NPC by replacing the function of *NPC1/NPC2* and re-establishing cholesterol trafficking.[6,8-10] In a Phase 1/2a study, adrabetadex was shown to restore cholesterol trafficking, reduce markers of neuronal damage and death, and improve neurological outcomes.[6] In addition, preclinical data have shown that HPβCD improved cholesterol distribution, increased Purkinje neuron survival, and improved survival in animal models.[8-15] Improved overall survival outcomes were observed in infantile-onset NPC participants from clinical studies and an Expanded Access Program (Poster S249).

Adrabetadex was evaluated in a randomized, sham-controlled, Phase 2b/3 trial of participants with NPC; the study did not meet the co-primary endpoints (NPCCSS, Clinician CGIC), and there was no disease progression in the adrabetadex-treated or control groups in either primary endpoint. Limitations of the study include the short study duration (52 weeks), a high degree of variability associated with each of the co-primary endpoint assessments, small sample size, and imputation methodology.[16] The present analysis evaluates CSF biomarkers from the Phase 2b/3 trial to explore CNS-targeted effects of adrabetadex in participants with NPC.

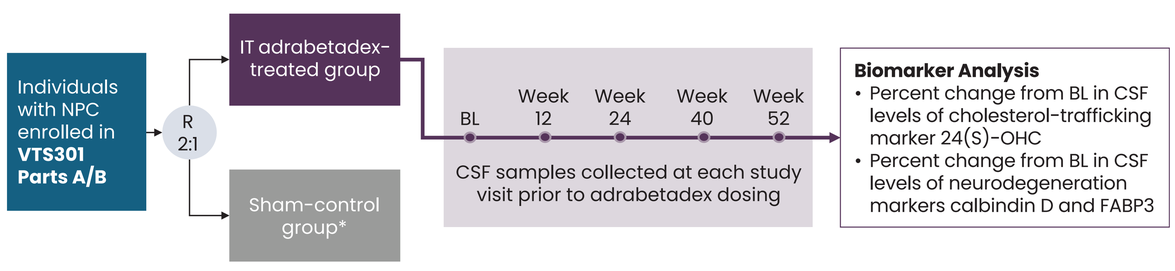
CGIC, Clinical Global Impression of Change; CNS, central nervous system; CSF, cerebrospinal fluid; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale.

## Methods

### Study Design and Participant Population

VTS301 was a Phase 2b/3, randomized, double-blind, sham-controlled trial that evaluated the effect of intrathecal (IT) adrabetadex in participants with onset of neurologic manifestations of NPC before age 15. The trial was comprised of 3 parts: Part A (dose finding) and Part B (sham-controlled): NCT02534844; Part C (open-label extension): NCT04958642, which included participants from Parts A/B and from the Phase 1/2a study (NCT01747135). Adrabetadex 900 mg was administered intrathecally Q2W; dose reduction was allowed for tolerability. CSF biomarker changes were assessed at baseline (Day 0) and predose at Weeks 12, 24, 40, and 52 in all randomized participants from Parts A/B who received ≥1 dose of adrabetadex and had ≥1 postbaseline measurement.

Figure 1. Study Design




*Rescue option in study design allowed participants to transfer from sham arm to Part C at 6 months with disease progression.
BL, baseline; Q2W, once every 2 weeks; R, randomization.

### Biological Assays and Statistical Analyses

Biomarker assays were validated for sensitivity, precision, and reproducibility according to FDA guidelines. CSF levels of 24(S)-OHC were quantified using an oxysterol assay gas chromatography–mass spectrometry selected ion monitoring protocol developed at the laboratory of Dr Dieter Lütjohann (University of Bonn, Germany).[16] CSF levels of calbindin D and FABP3 were measured with Quanterix® immunoassays at Rules-Based Medicine (IQVIA, Austin, TX). Wilcoxon signed-rank test was used to assess within-group changes in CSF biomarkers from baseline to Week 52 (SAS v9.4).

### Safety

Results are reported from the Part A/B safety population, defined as all randomized subjects who received at least 1 procedure (IT adrabetadex or sham).

## Results

At the end of Part B, 56 participants were enrolled in Parts A/B; of these, 38 were randomized to adrabetadex and received ≥1 dose of study drug, while 18 were randomized to the sham procedure (Table 1). CSF collection and biomarker testing were conducted only in the adrabetadex-treated group, prior to each adrabetadex dose.

Table 1. Baseline Demographics and Disease Characteristics

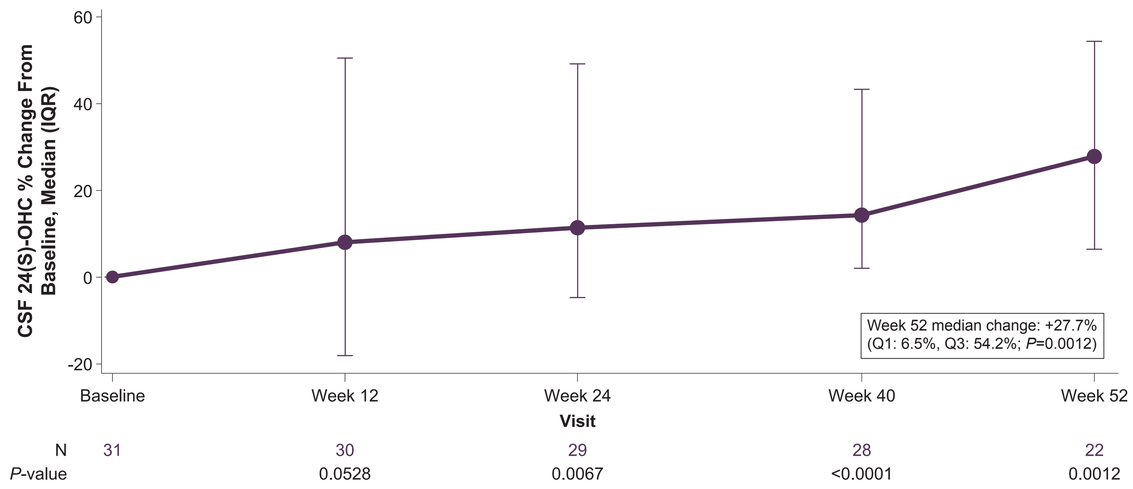
| | Adrabetadex-Treated (n=38) | Sham Control (n=18) |
|---|---|---|
| Age (years), mean (SD) | 12.7 (5.64) | 11.7 (5.10) |
| Male, n (%) | 22 (58) | 8 (44) |
| Weight (kg), mean (SD) | 48.1 (25.27) | 40.2 (18.98) |
| Miglustat use,* n (%) | 25 (66) | 9 (50) |
| Seizures, n (%) | 15 (39) | 5 (28) |
| Duration of neurologic symptoms (years), mean (SD) | 7.1 (4.15) | 5.9 (5.16) |
| Baseline NPCCSS total score (minus hearing/ABR), mean (SD) | 17.8 (6.48) | 16.9 (8.16) |

*Participants with record of miglustat use prior to receiving the first dose of study drug.
ABR, auditory brain response; NPCCSS, Niemann-Pick type C Clinical Severity Scale; SD, standard deviation.

**CNS Cholesterol Trafficking: 24(S)-OHC**

Participants treated with adrabetadex had a nominally statistically significant increase in CSF levels of 24(S)-OHC from baseline to Week 52 (Figure 1).

Figure 1. Percent Change in CSF 24(S)-OHC Levels Over 52 Weeks of Adrabetadex Treatment




IQR, interquartile range; Q1, first quartile; Q3, third quartile.

**Neuronal Damage and Death: Calbindin D and FABP3**

Participants treated with adrabetadex showed nominally statistically significant decreases in CSF levels of calbindin D (Figure 2a) and FABP3 (Figure 2b) from baseline to Week 52.

Figure 2a. Percent Change in Calbindin D Levels Over 52 Weeks of Adrabetadex Treatment

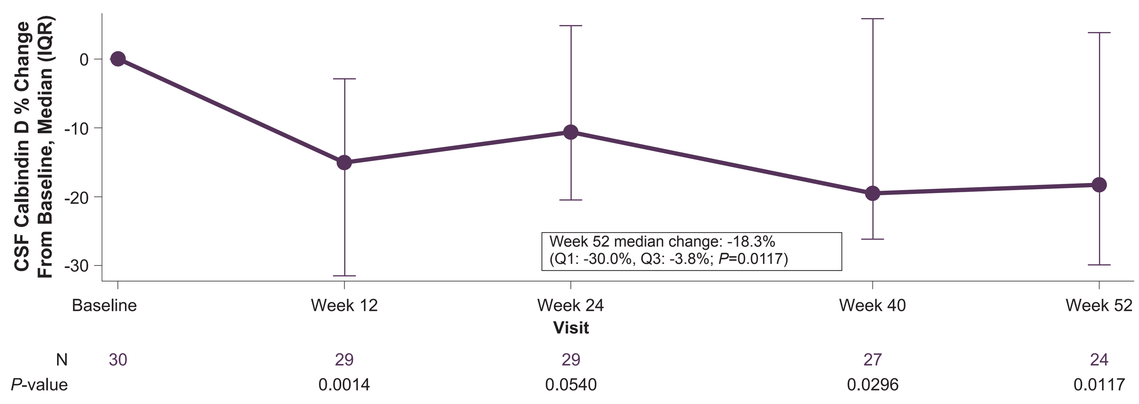
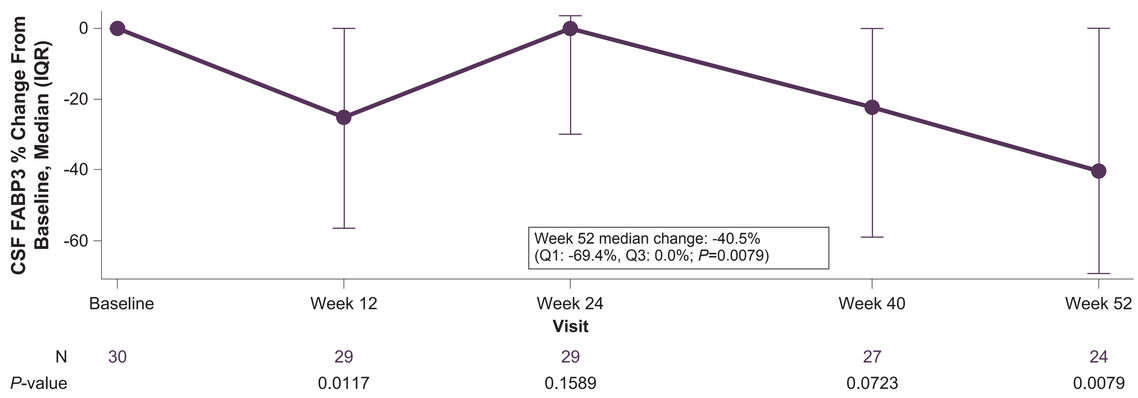



Figure 2b. Percent Change in FABP3 Levels Over 52 Weeks of Adrabetadex Treatment




## Safety

Adverse events with ≥30% higher incidence in the adrabetadex-treated vs sham group included vomiting, hypoacusis, back pain, diarrhea, gait disturbance, and fatigue; treatment-related events with ≥30% higher incidence were vomiting, hypoacusis, back pain, and fatigue (Table 2).

Table 2. Summary of Safety (Part A/B, Safety Population)

| | Adrabetadex-Treated (n=38) | Sham Control (n=18) |
|---|---|---|
| Any TEAE, n (%) | 38 (100) | 17 (94) |
| Dose interruption, n (%) | 15 (39) | 2 (11) |
| Most common TEAEs, n (%) | | |
| Vomiting | 21 (55) | 2 (11) |
| Back pain | 19 (50) | 3 (17) |
| Fatigue | 18 (47) | 3 (17) |
| Gait disturbance | 16 (42) | 2 (11) |
| Hearing impaired | 15 (39) | 6 (33) |
| Hypoacusis | 14 (37) | 0 |
| Diarrhea | 14 (37) | 1 (6) |
| Pyrexia | 14 (37) | 3 (17) |
| Non-fatal treatment-emergent SAE, n (%) | 20 (53) | 4 (22) |
| SAE occurring in >1 participant receiving adrabetadex, n (%) | | |
| Hearing impaired | 4 (11) | 1 (6) |
| Pneumonia, aspiration | 4 (11) | 1 (6) |
| Deafness | 3 (8) | 0 |
| Seizure | 3 (8) | 1 (6) |
| Dysphagia | 2 (5) | 1 (6) |
| Aspiration | 2 (5) | 1 (6) |

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

## Conclusions

- In a post hoc analysis of a prior Phase 2b/3 clinical trial of adrabetadex vs sham control in participants with NPC1, IT adrabetadex treatment resulted in statistically significant increases in 24(S)-OHC and decreases in calbindin D and FABP3 at 52 weeks
  - Increased CSF levels of 24(S)-OHC indicate that adrabetadex addresses the core pathology of NPC by restoring intracellular cholesterol trafficking in neurons
  - Decreased CSF levels of calbindin D and FABP3 suggest that adrabetadex decreases neuronal damage and death
- Biomarker changes were observed in samples collected 14 days after dosing, demonstrating a prolonged CNS effect despite the short CSF half-life of adrabetadex (~6.6 hours)[16]
- Taken together, these data show that adrabetadex addresses the core pathology in NPC and decreases neuronal damage and death, providing support for the disease-modifying potential of this investigational drug in individuals with NPC

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**Acknowledgments**
Medical writing support was provided by BGB Group (Manhattan, USA) and funded by Beren Therapeutics.

We thank the patients and their families for their vital participation in this research, as well as the site investigators supporting this clinical study.