Restoration of cholesterol trafficking results in decreased markers of neuronal damage in individuals with Niemann-Pick disease type C1

Poster 96

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Background

Disease Overview

Niemann-Pick disease type C (NPC) is a rare genetic disorder that impairs intracellular cholesterol trafficking, leading to progressive neurological decline and premature death.[1-3]

CNS markers related to NPC neuropathology include:[3-7]
- 24(S)-hydroxycholesterol (24[S]-OHC): neuron-derived oxysterol that is the main route for eliminating excess brain cholesterol; reduced in CSF and plasma in NPC, reflecting impaired cholesterol trafficking
- Calbindin D: calcium-binding protein especially enriched in Purkinje neurons; increased in CSF in NPC, reflecting cerebellar neuronal damage and loss
- Fatty acid–binding protein 3 (FABP3): cytosolic protein involved in membrane dynamics and synapse formation; increased in CSF in NPC, reflecting 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 re-establishing cholesterol trafficking.[6,8-10] In a Phase 1/2a study, adrabetadex restored cholesterol trafficking, reduced markers of neuronal damage and death, and improved neurological outcomes.[6] Preclinical data showed 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 100).

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 for 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.

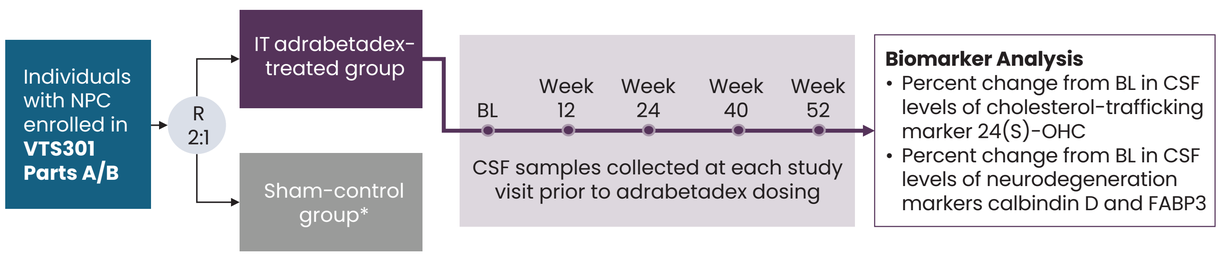
CGIC, Clinical Global Impression of Change; CNS, central nervous system; CSF, cerebrospinal fluid; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale.

Methods

Study Design and Participant Population

VTS301 was a Phase 2b/3, randomized, double-blind, sham-controlled trial evaluating the effect of intrathecal (IT) adrabetadex in participants with onset of neurologic manifestations of NPC before age 15. The trial was composed 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). IT adrabetadex 900 mg was administered Q2W; dose reduction was allowed for tolerability.

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). Nominal statistical significance was defined as $P<0.05$ without adjustment for multiplicity.

Safety

Results are reported from the Part A/B safety population, defined as all randomized subjects who received ≥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 (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.

Participants treated with adrabetadex had a nominally statistically significant increase in CSF levels of 24(S)-OHC from baseline to Week 52 (Figure 1). Participants treated with adrabetadex showed nominally statistically significant decreases in CSF levels of calbindin D (Figure 2) and FABP3 (Figure 3) from baseline to Week 52.

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

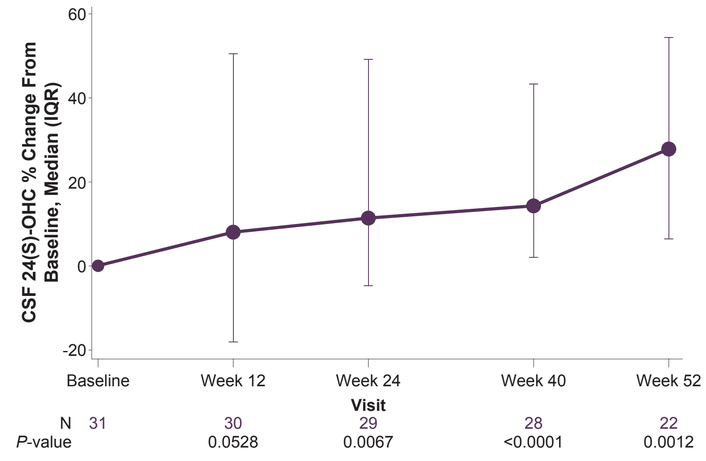


Figure 2. Percent Change in Calbindin D Levels Over 52 Weeks of Adrabetadex Treatment

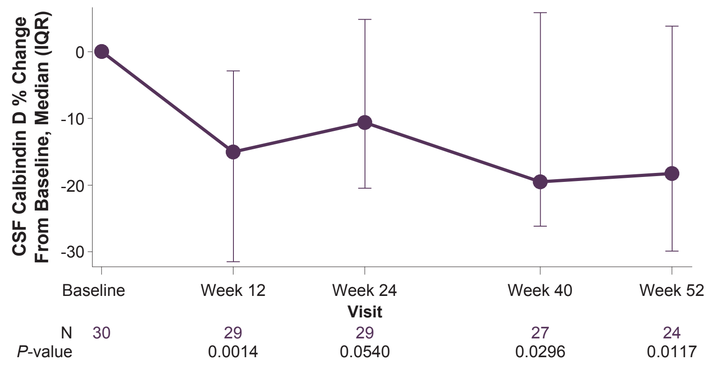
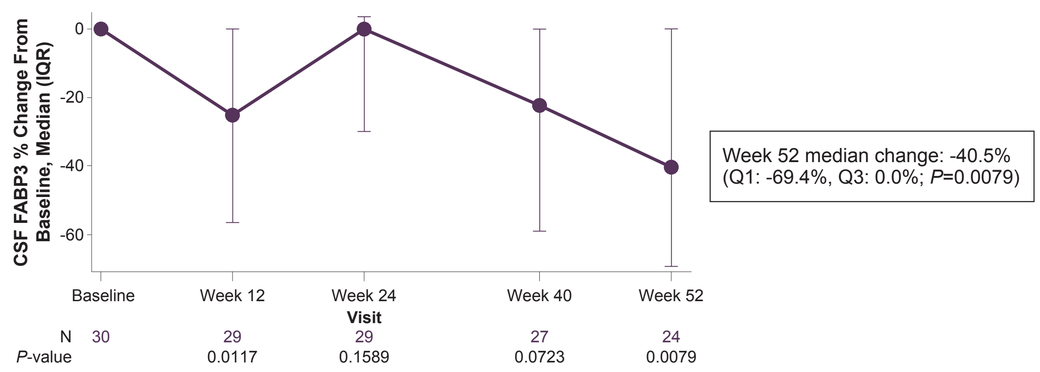


Figure 3. Percent Change in FABP3 Levels Over 52 Weeks of Adrabetadex Treatment



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

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). No participants discontinued the study due to treatment-emergent adverse events (TEAEs) in Part A/B.

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

	Adrabetadex (n=38)	Sham Control (n=18)
Any TEAE, n (%)	38 (100)	17 (94)
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 trial of adrabetadex vs sham control in 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 24(S)-OHC indicates restoration of intracellular cholesterol trafficking in neurons, while decreased calbindin D and FABP3 suggest reduced neuronal damage and cell death
- Biomarker changes were observed 14 days after dosing, demonstrating a prolonged CNS effect despite adrabetadex's short CSF half-life (~6.6 hours)[16]
- Taken together with the survival analysis (Poster 100), these data support the disease-modifying potential of adrabetadex as an investigational drug in individuals with NPC

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References:
1. Berry-Kravis E. *Semin Pediatr Neurol.* 2021;37:100879. 2. Vanier MT. *Orphanet J Rare Dis.* 2010;5:16. 3. Campbell K, Cawley NX, Luke R, et al. *Biomark Res.* 2023;11(1):14. 4. Bradbury A, Bagel J, Sampson M, et al. *J Pharmacol Exp Ther.* 2016;358(2):254-261. 5. Sun M-Y, Linsenbardt AJ, Emnett CM, et al. *Neuroscientist.* 2016;22(2):132-144. 6. Ory DS, Ottinger EA, Farhat NY, et al. *Lancet.* 2017;390(10104):1758-1768. 7. Owada Y. *Tohoku J Exp Med.* 2008;214(3):213-220. 8. Rosenbaum AI, Zhang G, Warren JD, et al. *Proc Natl Acad Sci U S A.* 2010;107(12):5477-5482. 9. Abi-Mosleh L, Infante RE, Radhakrishnan A, et al. *Proc Natl Acad Sci.* 2009;106(46):19316-19321. 10. Feltes M, Gale SE, Moores S, et al. *J Lipid Res.* 2020;61(3):403-412. 11. Peake KB, Vance JE. *J Biol Chem.* 2012;287(12):9290-9298. 12. Fukaura M, Ishitsuka Y, Shirakawa S, et al. *Int J Mol Sci.* 2021;22(1):452. 13. Tortelli B, Fujiwara H, Bagel JH, et al. *Hum Mol Genet.* 2014;23(22):6022-6033. 14. Vite CH, Bagel JH, Swain GP, et al. *Sci Transl Med.* 2015;7(276):276ra26. 15. Gurda BL, Bagel JH, Fisher SJ, et al. *J Neuropathol Exp Neurol.* 2018;77(3):229-245. 16. Schött H-F, Lütjohann D. V. *Steroids.* 2015;99(Pt B):139-150.

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