Adrabetadex Treatment in Individuals With Niemann-Pick Disease Type C1 Re-establishes Cholesterol Trafficking, Resulting in Decreased Markers of Neuronal Damage and Cell Death

Poster #042

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Background

Disease Overview

- Niemann-Pick disease type C1 (NPC1) is a rare genetic disorder that impairs intracellular cholesterol trafficking, leading to progressive neurological decline and premature death[1-3]

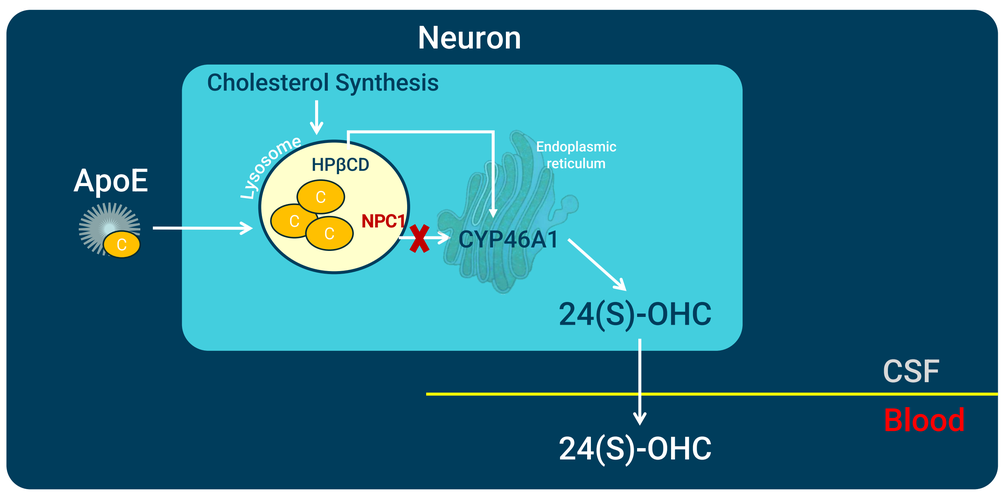
Adrabetadex Investigational Therapy

- Adrabetadex (VTS-270) is a proprietary mixture of 2-hydroxypropyl-β-cyclodextrin (HPβCD) isomers formulated for intrathecal (IT) administration that targets the underlying pathology of NPC1 by re-establishing cholesterol trafficking[4-6] (**Figure 1**)

Biomarkers related to NPC1 neuropathology are linked to[3]:

- Underlying disease pathology
  - 24(S)-OHC: primary route for excess brain cholesterol[7]
- Neurodegeneration
  - Calbindin D: calcium-binding protein enriched in Purkinje neurons[8]
  - FABP3: cytosolic protein involved in membrane dynamics and synapse formation[9]

Figure 1. 24(S)-OHC is the main route of elimination for neuronal cholesterol



24(S)-OHC, 24(S)-hydroxycholesterol; ApoE, apolipoprotein E; C, cholesterol; CSF, cerebrospinal fluid; CYP46A1, cytochrome P450 family 46 subfamily A member 1; FABP3, fatty acid binding protein 3; HPβCD, 2-hydroxypropyl-β-cyclodextrin; NPC1, Niemann-Pick disease type C1 protein.

Objective

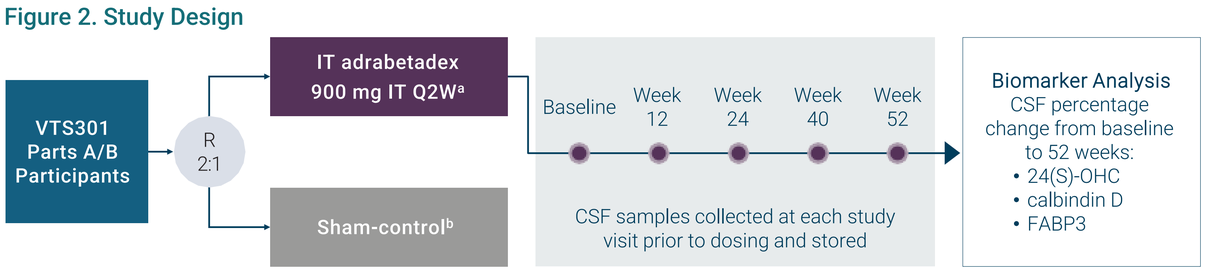
Assess treatment effects of adrabetadex in CSF levels of 24(S)-OHC, calbindin D, and FABP3 over 52 weeks.

Methods

Study Design and Participant Population

- VTS301 was a phase 2b/3, randomized, double-blind, sham-controlled trial evaluating the efficacy and safety of intrathecal (IT) adrabetadex in NPC1 participants with onset of neurologic manifestations before age 15. The trial was composed of 3 parts (**Figure 2**):
  - 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 every 2 weeks (Q2W); dose reduction was allowed for tolerability

Figure 2. Study Design



24(S)-OHC, 24(S)-hydroxycholesterol; CSF, cerebrospinal fluid; FABP3, fatty acid-binding protein 3; IT, intrathecal; Q2W, every 2 weeks; R, randomization.
[a]Dose reduction permitted for tolerability.
[b]Rescue option in study design allowed participants to transfer from sham arm to Part C at 6 months with disease progression.

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)[10]
- 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

Results

- This biomarker study included 34 participants (**Table 1**), with a mean age of 12.8 years and mean age at neurological onset of 5.7 years
  - About two-thirds were also receiving miglustat

Table 1. Baseline Demographics and Disease Characteristics

Demographics	
Age, mean (SD), years	12.8 (5.6)
Age at onset of neurological symptoms, mean (SD)[a], years	5.7 (3.5)
Male, n (%)	20 (58.8%)
Miglustat use, n (%)	23 (67.6%)
Baseline NPCCSS total score (minus hearing/ABR), mean (SD)[b]	17.8 (6.48)

ABR, auditory brain response; NPCCSS, Niemann-Pick type C Clinical Severity Scale; SD, standard deviation.
[a]Age of onset available for 32 patients.
[b]Baseline NPCCSS total score from intent-to-treat population (n=38).

Results (continued)

- At 52 weeks of treatment, nominally statistically significant increases in CSF 24(S)-OHC (27.7%; **Figure 3**) were observed, indicating adrabetadex increases neuronal cholesterol trafficking
- In addition, we observed nominally significant decreases in CSF levels of calbindin D (18.3%; **Figure 4**) and FABP3 (40.5%; **Figure 5**) over the same period
  - These biomarkers are associated with neuronal damage and cell death, so their reduction suggests a neuroprotective effect of adrabetadex
  - In the case of calbindin D, this indicates a potential preservation of Purkinje neurons of the cerebellum, an area of the brain notably affected in NPC

Figure 3. CSF 24(S)-OHC Increases With Adrabetadex Treatment

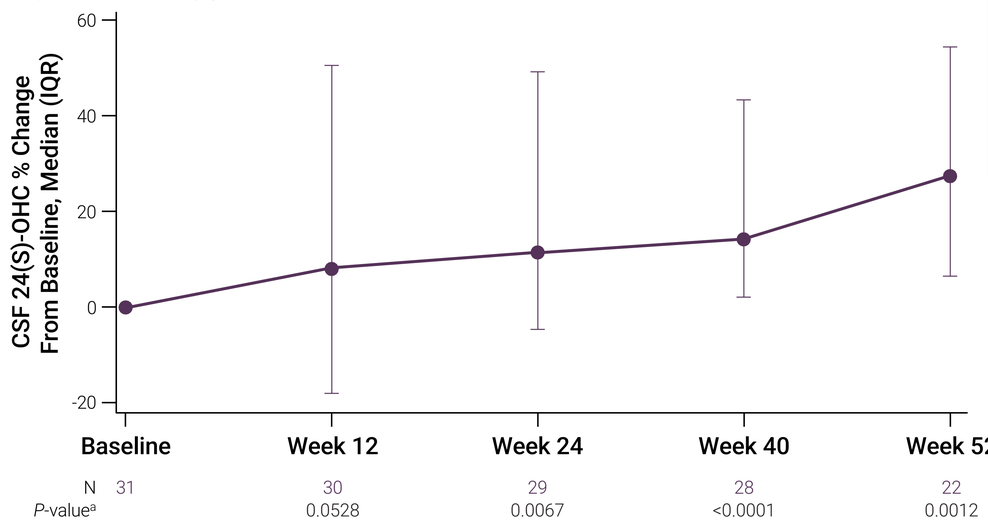


Figure 4. CSF Calbindin D Decreases With Adrabetadex Treatment

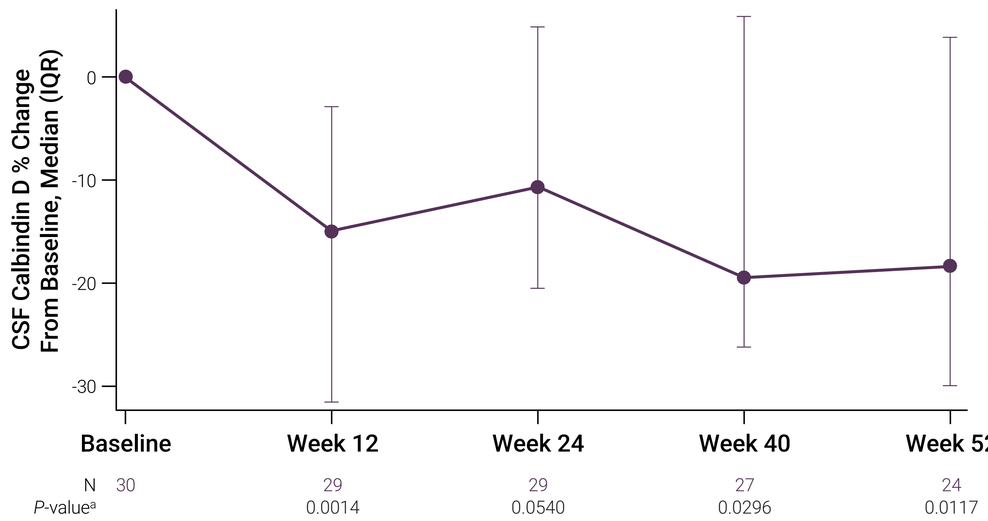
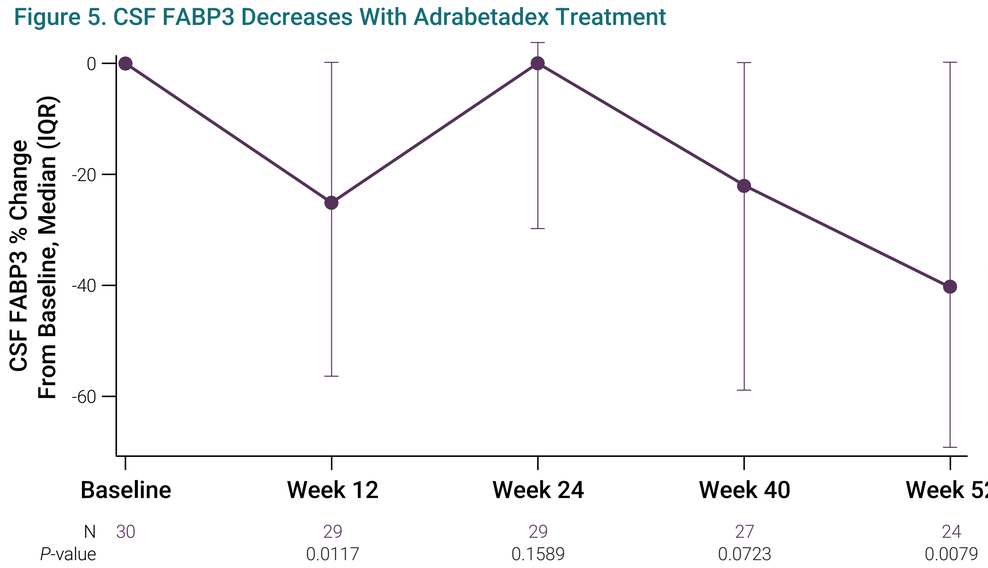


Figure 5. CSF FABP3 Decreases With Adrabetadex Treatment



[a]Within-group *P*-values are from Wilcoxon signed rank test. 24(S)-OHC, 24(S)-hydroxycholesterol; CSF, cerebrospinal fluid; FABP3, fatty acid-binding protein 3; IQR, interquartile range.

Conclusions

- **Statistically significant increases in CSF levels of 24(S)-OHC indicate adrabetadex addresses the underlying pathology of NPC1 by re-establishing intracellular cholesterol trafficking**
  - **Observed in samples collected 14 days after dosing, demonstrating a prolonged CNS effect despite short CSF half-life of adrabetadex (~6.6 hours)[11]**
- **Reduced CSF calbindin D and FABP3 suggest adrabetadex decreases neuronal damage and cell death**
- **Biomarker data, together with improved survival and slowed disease progression (Posters #043/LB-013), support the potential of adrabetadex as a disease-modifying treatment[a]**

24(S)-OHC, 24(S)-hydroxycholesterol; CNS, central nervous system; CSF, cerebrospinal fluid; FABP3, fatty acid-binding protein 3; NPC1, Niemann-Pick disease type C1.
[a]Adrabetadex is not approved by the FDA or any other health authority.

References

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Acknowledgements

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Additional Posters (Latebreaker-13, #043) at WORLDSymposium 2026