

Efficacy of Intrathecal Adrabetadex in Infantile-Onset Niemann-Pick Disease Type C is Supported by Survival, Clinical, and Biomarker Data

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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 death¹⁻³
- NPC subtype is classified based on age of neurological symptom onset, with infantile onset (<6 years of age) (I-NPC) being associated with the most severe phenotype and rapid rate of disease progression^{1,2,4}

NPC SOC and Measuring Disease Progression

- Usual care for NPC has historically involved management of symptoms, with no cure and limited impact on survival. Miglustat, although only approved by the European Medicines Agency (EMA), is commonly used off label in the United States and considered part of routine management⁵
- Disease progression can be assessed using a short-form NPC Clinical Severity Scale (Rescored 4-Domain NPC Clinical Severity Scale [R4DNPCCSS]), which evaluates ambulation, speech, fine-motor function, and swallowing⁶

Biomarkers related to NPC1 neuropathology are linked to:

- Underlying disease pathology
 - 24(S)-OHC: primary route for excess brain cholesterol⁶
- Neurodegeneration
 - Calbindin D: calcium-binding protein enriched in Purkinje neurons⁷
 - FABP3: cytosolic protein involved in membrane dynamics and synapse formation⁸

Adrabetadex Investigational Therapy

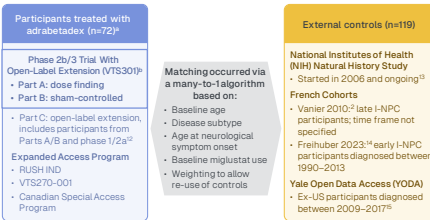
- Adrabetadex is a well-characterized 2-hydroxypropyl- β -cyclodextrin (HP β CD) mixture suitable for intrathecal (IT) administration that targets the underlying pathology of NPC by re-establishing cholesterol trafficking^{9,12}
- We report overall survival (OS) among individuals with I-NPC treated with investigational drug adrabetadex compared with external controls, and evaluate long-term disease progression in treated individuals

METHODS

Survival and NPC-CSS Outcomes and Analysis (Figure 1)

- The primary objective was to compare OS (baseline to death or last known alive) in patients with early and late I-NPC treated with adrabetadex vs external controls receiving usual care
- Match-eligible adrabetadex-treated participants had early or late I-NPC and received ≥ 1 dose of adrabetadex. Adrabetadex was administered intrathecally via lumbar puncture at doses of 50–1200 mg every 4 weeks (Q4W) in phase 1/2a and 900–1800 mg every 2 weeks (Q2W) in VTS301 Part A; 900 mg Q2W was selected as the recommended regimen for VTS301 Parts B and C. Dose reduction was allowed to manage tolerability. In the EAPs, participants started at 200 or 400 mg (depending on age) Q2W with titration up to 1200 mg (initially) or 900 mg (later revision)
- OS was compared with matched external controls from 4 major disease databases or publications.^{2,13–18} OS analysis cutoff was January 10, 2025
- Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using a weight-adjusted Cox regression model including treatment (adrabetadex-treated versus matched control) as fixed effect, and history of miglustat as a covariate
- Log-rank P-values were calculated using a weight-adjusted Kaplan-Meier (KM) analysis. Subgroup OS analyses included baseline miglustat use and participants with early and late I-NPC
- The annual rate of clinical disease progression assessed by R4DNPCCSS during adrabetadex treatment was compared with pretreatment periods. A longitudinal mixed effects model estimated mean annual rates of change pre- and post-adrabetadex treatment, with R4DNPCCSS scores imputed as 0 at birth to anchor trajectories

Figure 1. Data Sources for Survival Analysis



¹Study VTS301 Part A/B included adrabetadex and sham treatment groups. Part A/B participants were allowed to enter Part C (open-label adrabetadex) and/or the EAP. Two Study VTS301 Part C participants received open-label adrabetadex in Study VTS301-302 (2-participant study in Case Report). Continued mgustat use was allowed for the purpose of Study VTS301-302. Study VTS301 participants who continued into the EAP are identified as "Study VTS301 participants" and not as "EAP participants." The Phase 2b/3 trial (VTS301 Part A/B) was used for the biomarker and safety analyses.

Biomarker Analysis

- CSF levels of 24(S)-OHC, calbindin D, and FABP3 were measured in participants from the Phase 2b/3 trial (VTS301 Part A/B) (Supplemental Figure 1). 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. See Supplemental methods for more details

Safety

- Results are reported from the Phase 2b/3 trial (VTS301 Part A/B) safety population, defined as all randomized subjects who received ≥ 1 procedure (IT adrabetadex or sham). As reported in Supplemental results

References

1. Berry-Kravis E. *Semin Pediatr Neurol*. 2021;37:100679. 2. Vanier MT, Oryshak J. *Neuro Dis*. 2010;5:16. 3. Campbell K, et al. *Biomark Res*. 2023;11(1):14. 4. Imms J, et al. *BMC Neurol*. 2015;15:27. 5. Menges E, et al. *Med Genet Metab Res*. 2023;43:101233. 6. Lütjohann D. *Acta Neurol Scand Suppl*. 2006;185:35–42. 7. Kraybill A, et al. *J Pharmacol Exp Ther*. 2006;358(2):254–261. 8. Owyda Y. *J Exp Med*. 2008;214(3):213–220. 9. Peake KB, Vance JE. *J Biol Chem*. 2012;287(12):9290–9298. 10. Ash-Mosler L, et al. *Proc Natl Acad Sci U S A*. 2009;106(46):19316–19321. 11. Torreal B, et al. *Hum Mol Genet*. 2014;23(22):4622–4633. 12. Ory DS, et al. *Lancet*. 2017;390(10246):1168–1178. 13. NHL. *National Cancer Institute*. 2025. <https://clinicaltrials.gov/ct2/show/study/NCT02066444>. 14. Freilhuber C, et al. *Cerebrum*. 2018;18:13. 15. NHL. *National Cancer Institute*. 2023. <https://clinicaltrials.gov/ct2/show/study/NCT02066444>. 16. Schott H-F, Lütjohann D. *Steroids*. 2015;99(1):139–150.

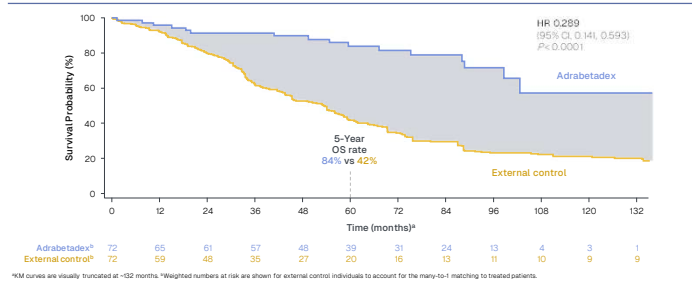
We thank the patients, caregivers, adrabetadex EAP, and VTS301 investigators involved in this program.

RESULTS

Overall Survival

- Of 80 total participants treated with adrabetadex eligible for matching, 72 (32 early infantile; 40 late infantile) were successfully matched, with a median treatment duration of 3.8 years (range 0.1–11.1 years). Of the pooled 255 I-NPC external controls eligible for matching, 119 (57 early infantile; 62 late infantile) were successfully matched
- Baseline demographic and clinical characteristics were generally comparable between the 2 groups (Table 1)
- Participants treated with adrabetadex had a significantly reduced risk of death compared with external control individuals (Figure 2)
- The OS benefit was seen in participants treated with miglustat and not treated with miglustat at baseline (Figure 3; Supplemental Figure 2)
- Survival benefit was consistent for early and late I-NPC, as well as for comparisons to each individual external control cohort (Figure 3; Supplemental Figure 3)

Figure 2. OS in Matched Participants With I-NPC



¹KM curves are visually truncated at ≈ 132 months. ²Weighted numbers at risk are shown for external control individuals to account for the many-to-1 matching to treated patients.

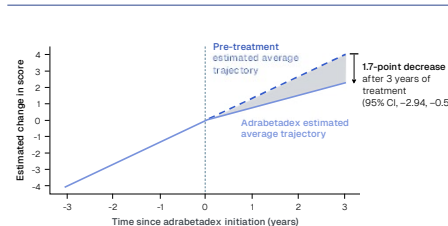
Figure 3. OS by Subgroups and Individual External Control Cohorts

Population and comparator source	Adrabetadex	External Control	HR (95% CI)	P-Value
Overall infantile	17 (23.6%)	44 (61.2%)	0.289 (0.141, 0.593)	<0.0001
Early infantile	9 (28.1%)	24 (76.1%)	0.148 (0.064, 0.343)	<0.0001
Late infantile	8 (20.0%)	20 (49.2%)	0.344 (0.146, 0.812)	0.0457
With miglustat	8 (22.9%)	10 (37.9%)	0.361 (0.173, 0.752)	0.0205
Without miglustat	7 (33.3%)	19 (91.2%)	0.139 (0.049, 0.398)	<0.0001
French comparator	9 (16.4%)	44 (80.7%)	0.113 (0.042, 0.301)	<0.0001
NIH comparator	12 (33.3%)	30 (84.2%)	0.449 (0.214, 0.946)	0.0322
YODA comparator	8 (21.6%)	6 (16.4%)	0.381 (0.128, 1.137)	0.1426

Disease Progression by NPC Clinical Severity Scores

- 79 treated participants contributed R4DNPCCSS scores. Adrabetadex treatment significantly reduced the annual rate of disease progression from 1.34 units/year before treatment to 0.76 units per year after treatment (difference 0.58 units/year; 95% CI, -0.98 to -0.18; $P < 0.005$; Supplemental Table 1), reflecting a 43% reduction in the annual rate of progression
- The mean estimated difference between treated and untreated trajectories of R4DNPCCSS scores after 3 years of adrabetadex treatment was -1.7 (95% CI, -2.94 to -0.53), illustrating a meaningful decrease in R4DNPCCSS scores in participants treated with adrabetadex (Figure 4)

Figure 4. Longitudinal Disease Progression Analysis Using Short Form NPC-CSS in Participants With I-NPC



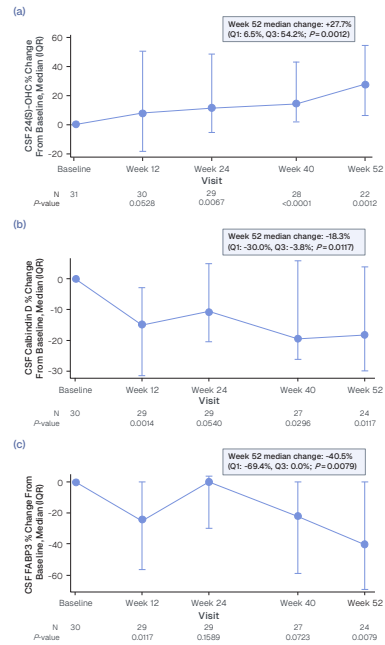
Acknowledgements

- This study was sponsored by Mandos, a subsidiary of Beren Therapeutics P.B.C.
- Medical writing support was provided by The Lockwood Group (Stamford, CT, USA) and Helios Global Group (Gulfport, CT, USA) and funded by Beren Therapeutics P.B.C.

Biomarker Analysis

- Baseline demographics and clinical characteristics were generally comparable between the 2 groups (Supplemental Table 2)
- CSF 24(S)-OHC levels increased by 27.7% after 52 weeks of intrathecal adrabetadex treatment ($n=22$; $P = 0.012$; Figure 5a)
- Adrabetadex treatment was associated with decreases in CSF calbindin D levels (18.3%; $n=24$; $P = 0.0017$; Figure 5b), and FABP3 (40.5%; $n=24$; $P = 0.0079$; Figure 5c)

Figure 5. Percent Change in CSF 24(S)-OHC (a), Calbindin D (b), and FABP3 (c) Levels Over 52 Weeks of Adrabetadex Treatment¹⁹



¹⁹Biomarker analysis was conducted in the phase 2b/3 trial (VTS301 Part A/B) population only. ²⁰Observed in samples collected 14 days after dosing prior to next dose (Q2), interquartile range (IQR), first quartile (Q1), third quartile (Q3).

CONCLUSIONS

- Adrabetadex treatment substantially improves survival in individuals with I-NPC compared with matched external controls
- Survival benefit was consistent for early and late I-NPC and regardless of miglustat use at baseline
- Treatment is associated with a 43% reduction in the annual rate of neurologic disease progression
- Biomarker findings are consistent with and build on preclinical research and early clinical studies of adrabetadex
- Biomarker changes were observed 14 days after dosing, demonstrating a prolonged CNS effect despite adrabetadex's short CSF half-life (~6.6 hours)¹⁶
- Statistically significant CSF increases of 24(S)-OHC indicate that adrabetadex targets the underlying pathology of NPC1 by re-establishing neuronal intracellular cholesterol trafficking
- Decreased CSF levels of calbindin D and FABP3 suggest that adrabetadex decreases neuronal damage and cell death
- These findings support that adrabetadex is an important investigational drug with potential as a disease modifying therapy to improve clinical outcomes in individuals with I-NPC



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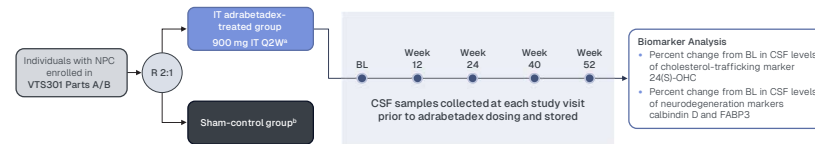
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SUPPLEMENTAL METHODS

Biomarker Analysis

- Analyses included participants from the Phase 2b/3 trial (VTS301) Part A/B (Supplemental Figure 1).
- VTS301 was a Phase 2b/3, randomized, double-blind, sham-controlled trial evaluating the effect of intrathecal (IT) adrabetadex in NPC1 participants with onset of neurologic manifestations 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.
- 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).¹ CSF levels of calbindin D and FABP3 were measured with Quantex[®] 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.

Supplemental Figure 1. Phase 2b/3 Trial (VTS301) Study Design



*Dose reduction permitted for tolerability. *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.

SUPPLEMENTAL RESULTS

Supplemental Table 1. Annual Rate of Change in Short Form NPC-CSS Score During the Untreated and Treatment Periods in Participants With I-NPC

	Infantile-Onset
Participants, n	79
Pre-treatment visits, n	337
Treatment visits, n	689
Annual change in score (units/year), estimate (95% CI)	
Pre-treatment periods	1.34 (0.98, 1.71)
Treatment periods	0.76 (0.52, 1.01)
Treatment - pre-treatment	-0.58 (-0.98, -0.18)
P-value for difference	0.0055

Supplemental Table 2. Baseline Demographics and Disease Characteristics from Phase 2b/3 trial (VTS301) Part A/B

	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, ^a 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 NPC-CSS total score (minus hearing/ABR), mean (SD)	17.8 (6.48)	16.9 (8.16)

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

Safety

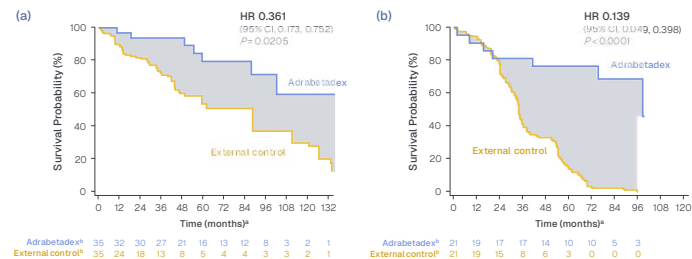
- Adverse events with $\geq 30\%$ higher incidence in the adrabetadex-treated vs sham group included vomiting, hypoacusis, back pain, diarrhea, gait disturbance, and fatigue; treatment-related events with $\geq 30\%$ higher incidence were vomiting, hypoacusis, back pain, and fatigue (Supplemental Table 3).
- No participants discontinued the study due to treatment-emergent adverse events (TEAEs) in Part A/B of VTS301.

Supplemental Table 3. Summary of Safety (Phase 2b/3 trial [VTS301] 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 (0)
Seizure	3 (8)	1 (6)
Dysphagia	2 (5)	1 (6)
Aspiration	2 (5)	1 (6)

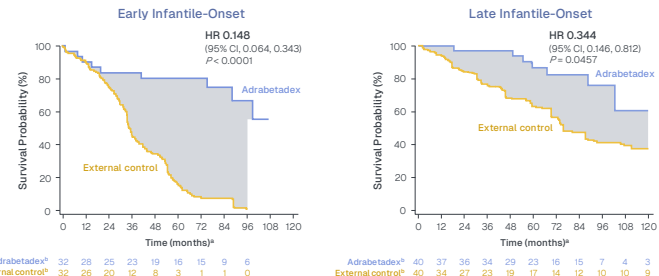
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Supplemental Figure 2. Overall Survival in I-NPC Participants With Miglustat (a) and Without Miglustat (b) Use at Baseline



*KM curves are visually truncated at -132 months in panel a and -96 months in panel b. *Weighted numbers at risk are shown for external control individuals to account for the many-to-1 matching to treated patients.

Supplemental Figure 3. Overall Survival in Participants With Early (a) and Late (b) I-NPC



*KM curves are visually truncated at -120 months. *Weighted numbers at risk are shown for external control individuals to account for the many-to-1 matching to treated patients.

References

- Beren Therapeutics P.B.C. Data on file.

Acknowledgements

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