

# Substantial Survival Benefit and Slowing of Disease Progression With Adrabetadex Treatment in Individuals With Infantile-onset Niemann-pick Disease Type C (NPC)

Poster LB-13

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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<sup>1-3</sup>
- NPC subtype is classified based on age of neurological symptom onset, with infantile onset (<6 years of age) being associated with the most severe phenotype and rapid rate of disease progression<sup>1,2,4</sup>

### 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 management<sup>1,2</sup>
- Disease progression can be assessed using a short-form NPC Clinical Severity Scale (Rescored 4-Domain NPC Clinical Severity Scale [R4DNPCSS]), which evaluates ambulation, speech, fine-motor function, and swallowing<sup>5</sup>

### Adrabetadex Investigational Therapy

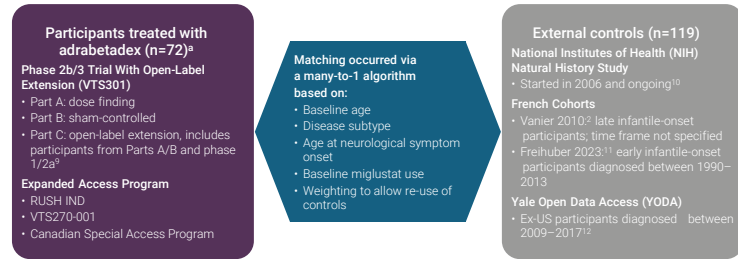
- Adrabetadex (VTS-270) is a proprietary mixture of 2-hydroxypropyl-β-cyclodextrin isomers suitable for intrathecal (IT) administration that targets the underlying pathology of NPC by re-establishing cholesterol trafficking<sup>6,9</sup>
- We report overall survival (OS) among individuals with infantile-onset NPC treated with investigational drug adrabetadex compared with external controls, and evaluate long-term disease progression in treated individuals.

## Methods

### Study Design (Figure 1)

- Match-eligible adrabetadex-treated participants had early or late infantile-onset NPC and received >1 dose of adrabetadex
  - Participants were pooled from the phase 2b/3 trial with open-label extension (VTS301, Parts A/B [NCT02534844] and Part C [NCT04958642], which included participants from Parts A/B and the phase 1/2a study; NCT01747135) and from Expanded Access Program (EAPs; RUSH IND 119856, VTS-270-001, and Canadian Special Access Program)
- OS was compared with matched external controls from 4 major disease databases or publications<sup>2,10-12</sup>

### Figure 1. Data Sources



<sup>a</sup>Study 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 VTS-270-302 (a 2-participant study in Costa Rica). 1 continued into the EAP. For the purposes of Study MIND-270-00-303, Study VTS301 participants who continued into the EAP are nevertheless identified as "Study VTS301 participants" and not as "EAP participants."<sup>11</sup>

### Treatment Exposure

- 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)
- Miglustat use was permitted; other recently approved therapies were not prohibited in the EAP, but exposure was minimal before the OS analysis cutoff (January 10, 2025)

### Outcomes and Analysis

- The primary objective was to compare OS (baseline to death or last known alive) in patients with early and late infantile-onset NPC treated with adrabetadex vs external controls receiving usual care; those lost to follow-up or still alive at the last available follow-up were censored. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using a weight-adjusted Cox regression model including treatment (adrabetadex-treated versus matched controls) 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
- The annual rate of clinical disease progression assessed by R4DNPCSS during adrabetadex treatment was compared with pre-treatment periods. A longitudinal mixed effects model estimated mean annual rates of change pre- and post-adrabetadex treatment, with R4DNPCSS scores imputed as 0 at birth to anchor trajectories

## Results

- 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 infantile-onset 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)

Table 1. Baseline Demographics and Disease Characteristics

	Adrabetadex (N=72)	External Control (N=119)
<b>Age at onset category, n/N (%)</b>		
<2 Years	32/72 (44)	57/119 (48)
2–6 Years	40/72 (56)	62/119 (52)
<b>Median age at neurological onset, months (Q1, Q3)</b>	25 (0, 68)	24 (0, 68)
<b>Overall miglustat use, n/N (%)</b>	52/72 (72)	72/119 (61)
<b>G-tube, n/N (%)<sup>a</sup></b>	11/50 (22)	6/26 (23)
<b>Respiratory therapy, n/N (%)</b>	9/50 (18)	2/26 (8)
<b>Race, n/N (%)<sup>a</sup></b>		
White	65/72 (90)	22/26 (85)
Other	7/72 (10)	4/26 (15)
<b>Region, n/N (%)<sup>a</sup></b>		
Europe	11/72 (15)	90/119 (76)
North America	61/72 (85)	27/119 (23)
South America	0 (0)	2/119 (2)

<sup>a</sup>Comparability factors were not available from all sources. G-tube, gastrostomy tube; Q, quartile.

### References

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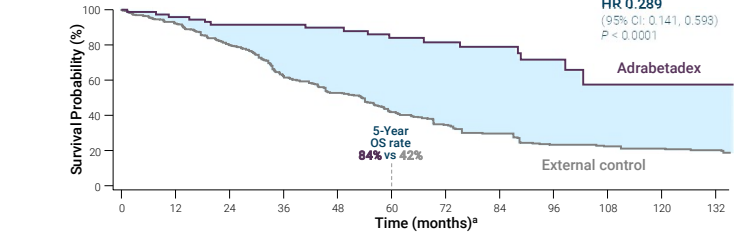
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## Results (continued)

### Overall Survival

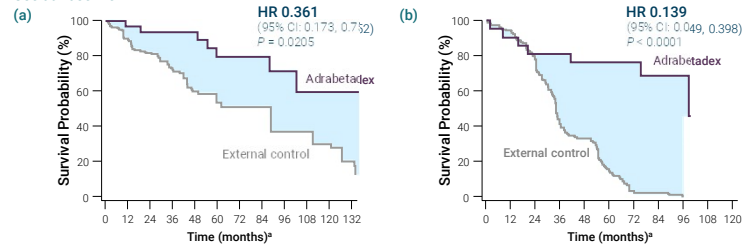
- Participants treated with adrabetadex had a significantly reduced risk of death compared with external control individuals (Figure 2)
- The OS benefit was seen in participants treated with miglustat and not treated with miglustat at baseline (Figure 3a, 3b)
- Survival benefit was consistent for early and late infantile-onset, as well as for comparisons to each individual external control cohort (Figure 4)

### Figure 2. OS in Matched Participants With Infantile-Onset NPC



<sup>a</sup>KM curves are visually truncated at ~132 months.  
<sup>b</sup>Weighted numbers at risk are shown for external control individuals to account for the many-to-1 matching to treated patients.

### Figure 3. Overall Survival in Infantile-Onset NPC Participants With Miglustat (a) and Without Miglustat (b) Use at Baseline



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

### Figure 4. 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%)	13 (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

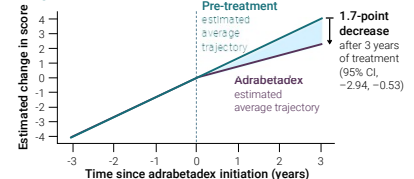
### Disease Progression by NPC Clinical Severity Scores

- 79 treated participants contributed R4DNPCSS scores. Adrabetadex treatment significantly reduced the annual rate of disease progression from 1.34 units/year before treatment to 0.76 units/year after treatment (difference 0.58 units/year, 95% CI, -0.98 to -0.18, P=0.0055; Table 2), reflecting a 43% reduction in the annual rate of progression
- The mean estimated difference between treated and untreated trajectories of R4DNPCSS scores after 3 years of adrabetadex treatment was -1.7 (95% CI, -2.94 to -0.53), illustrating a meaningful decrease in R4DNPCSS scores in participants treated with adrabetadex (Figure 5)

Table 2. Annual Rate of Change in Short Form NPCSS Score During the Untreated and Treatment Periods in Participants With Infantile-Onset NPC

	Infantile
Participants, n	79
Pre-treatment visits, n	337
Treatment visits, n	689
<b>Annual change in score (units/year), estimate (95% CI)</b>	
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

Figure 5. Longitudinal Disease Progression Analysis Using Short Form NPCSS in Participants With Infantile-Onset NPC



## Conclusions

- Adrabetadex substantially improved overall survival in a large cohort of patients with infantile-onset NPC compared with untreated matched external controls
  - Survival benefit is consistent for early and late infantile-onset NPC, and independent of miglustat use at baseline
- Treatment with adrabetadex resulted in a 43% reduction in the annual rate of neurologic disease progression
- Together with biomarker data in Poster #042 demonstrating improved neuronal cholesterol trafficking and decreased neuronal damage and 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 infantile-onset NPC