Substantial survival benefit in individuals with infantile-onset Niemann-Pick disease type C treated with adrabetadex

Poster 100

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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] NPC subtype is classified based on age of neurological symptom onset, with infantile onset (<6 y) being associated with rapid progression and prognosis.[1,2,4]

Current Treatment Landscape

Usual care for NPC has historically managed 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.[1,2] Recently, the US Food and Drug Administration (FDA) approved arimoclomol (for patients ≥2 y, with miglustat) and levacetylleucine (for patients ≥15 kg) for neurological manifestations of NPC; however, no FDA-approved therapies improve survival.[5-7]

Adrabetadex Investigational Therapy

Adrabetadex (VTS270) is a proprietary mixture of 2-hydroxypropyl-β-cyclodextrin isomers suitable for intrathecal (IT) administration that addresses the core pathology of NPC by re-establishing cholesterol trafficking.[8-11] The safety profile from the Phase 2b/3 trial of IT adrabetadex is described in a companion poster (Poster 96).

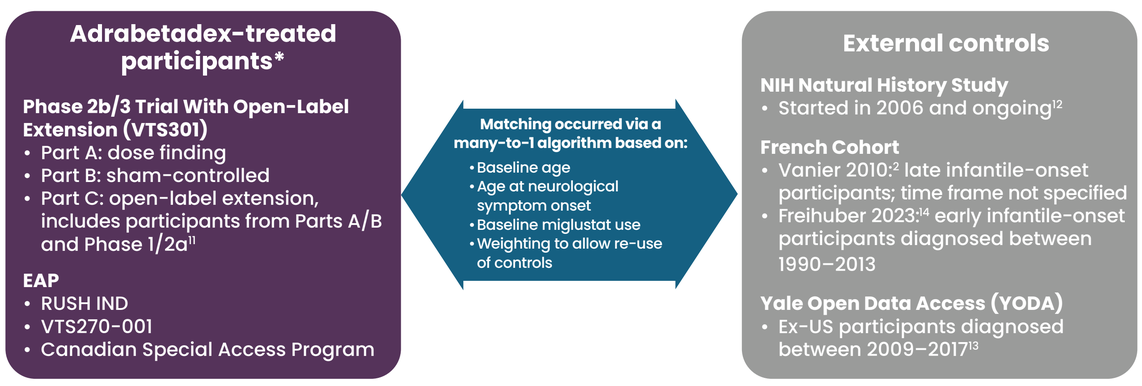
We report overall survival (OS) in individuals with infantile-onset NPC treated with adrabetadex across Phase 1/2b and 2b/3 trials and Expanded Access Programs (EAPs) compared with matched external controls.

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 EAPs (RUSH IND 119856, VTS270-001, and Canadian Special Access Program). OS was compared with matched external controls obtained from 4 major disease databases or publications.[2,12-14]

Figure 1. Data Sources



*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 VTS270-302 (a 2-participant study in Costa Rica): 1 continued into the EAP. For the purposes of Study MND-270-00-303, Study VTS301 participants who continued into the EAP are nevertheless identified as "Study VTS301 participants" and not as "EAP participants."[15]

Treatment Exposure

IT adrabetadex was administered 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 (June 24, 2024).

Outcomes and Analysis

The primary objective was to compare OS (baseline to death or last known alive) among individuals with early and late infantile-onset NPC who were treated with adrabetadex vs external controls receiving usual care; participants lost to follow-up or still alive at the last available follow-up were censored. Log-rank *P*-values were calculated using a weight-adjusted Kaplan-Meier (KM) analysis; hazard ratios (HR) with 95% confidence intervals (CI) were calculated using a weight-adjusted Cox regression model. Subgroup analyses evaluated early vs late infantile-onset and baseline miglustat use.

Results

Of 78 total adrabetadex-treated participants eligible for matching, 66 (32 early; 34 late) were successfully matched, with a median treatment duration of 3.0 years (range 0.2–9.8 y). Of the pooled 246 infantile-onset external controls eligible for matching, 110 (53 early; 57 late) were successfully matched. Baseline demographic and clinical characteristics were generally comparable between the 2 groups (Table 1).

Table 1. Baseline Demographics and Disease Characteristics

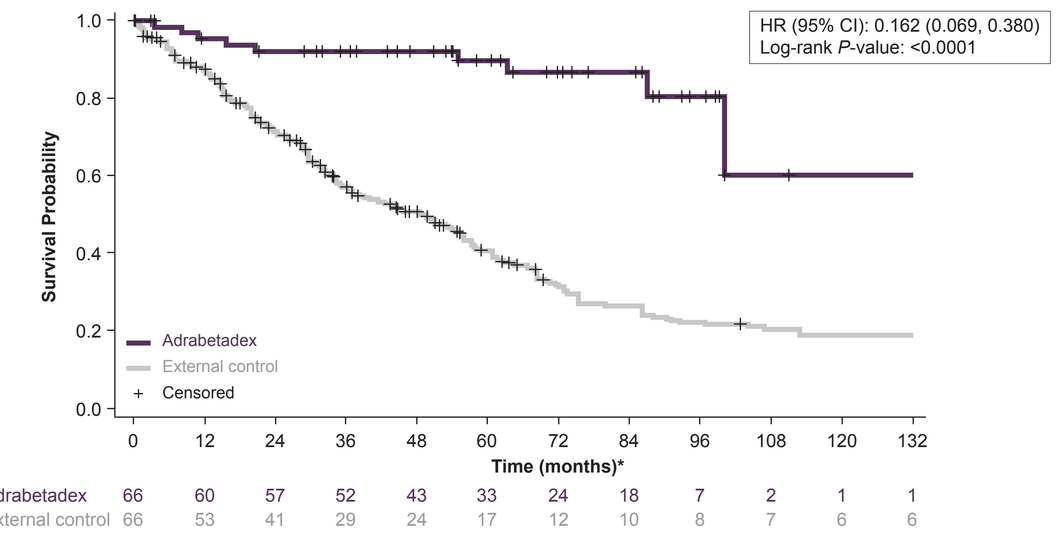
	Adrabetadex (N=66)	External Control (N=110)
Age at onset category, n/N (%)		
<2 Years	32/66 (49)	53/110 (48)
2-<6 Years	34/66 (52)	57/110 (52)
Median age at neurological onset, months (Q1, Q3)	24 (14, 48)	24 (13, 38)
Overall miglustat use, n/N (%)	41/66 (62)	63/91 (69)
G-tube, n/N (%)*	17/66 (26)	5/18 (28)
Respiratory therapy, n/N (%)	12/40 (30)	5/18 (28)
Race, n/N (%)*		
White	54/63 (86)	15/18 (83)
Other	9/63 (14)	3/18 (17)
Region, n/N (%)*		
Europe	12/63 (19)	2/18 (11)
North America	50/63 (79)	16/18 (89)
Oceania	1/63 (2)	0

*Comparability factors were not available from all sources.
G-tube=gastrostomy tube; Q=quartile.

Overall Survival

Adrabetadex was associated with a significantly reduced risk of death (Figure 2; Table 2). Increased OS for participants treated with adrabetadex was observed for early (neurological onset <2 y) and late (2 to <6 y) infantile-onset subgroups (Figure 3a, 3b). The greater OS in infantile-onset NPC participants treated with adrabetadex compared with matched external controls was maintained and consistent regardless of miglustat use at baseline (Figure 4). OS showed directional consistency for the adrabetadex-treated group across all external control cohorts (Figure 4).

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



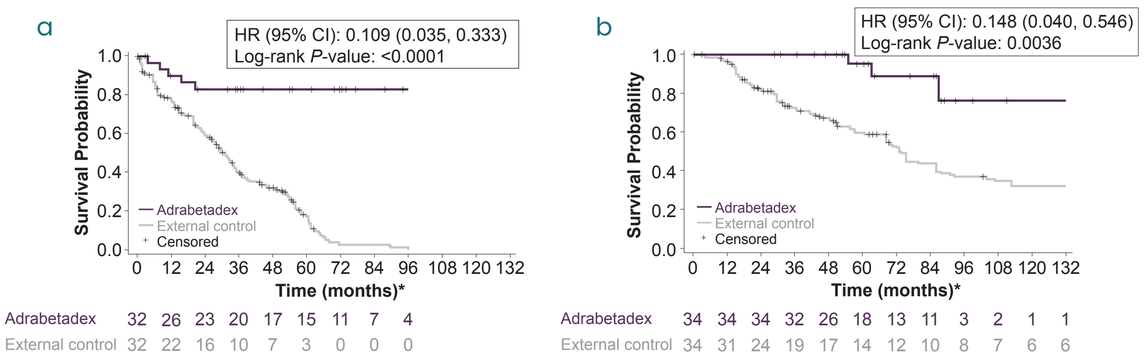
*KM curves are visually truncated at 132 months.

Table 2. OS Estimates and HRs in Participants With Infantile-Onset NPC

	Adrabetadex (N=66)		External Control* (N=66)	
Number of Deaths (%)	9 (13.6)		42 (63.3)	
50th Percentile (Median) Survival Time, Months (95% CI)	NE (100, NE)		48 (34, 60)	
KM Survival Probability	% (95% CI)	n at risk	% (95% CI)	n at risk
1 Year	95 (86, 98)	60	87 (81, 92)	53
3 Years	92 (82, 97)	52	57 (48, 65)	29
5 Years	90 (78, 95)	33	40 (31, 50)	17
7 Years	87 (73, 94)	18	26 (17, 37)	10
10 Years	60 (19, 86)	1	19 (10, 30)	6
HR (95% CI)	0.162 (0.069, 0.380)			
Log-Rank *P*-Value	<0.0001			

*110 uniquely matched external controls.
NE=not estimable.

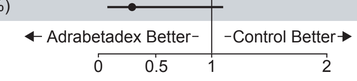
Figure 3. Overall Survival in Participants With Early (a) and Late (b) Infantile-Onset NPC



53 uniquely matched early infantile-onset external control participants; 57 uniquely matched late infantile-onset external control participants.
*KM curves are visually truncated at 132 months in panel a and 96 months in panel b.

Figure 4. OS by Subgroups and Individual External Control Cohorts

Population and comparator source	No. of Deaths (%)		HR (95% CI)	*P*-Value
	Adrabetadex	External Control		
Overall infantile	9 (13.6%)	42 (63.3%)	0.162 (0.069, 0.380)	<0.0001
Early infantile	6 (18.8%)	23 (72.8%)	0.109 (0.035, 0.333)	<0.0001
Late infantile	3 (8.8%)	18 (54.3%)	0.148 (0.040, 0.546)	0.0036
With miglustat	2 (7.1%)	12 (41.8%)	0.097 (0.023, 0.406)	0.0005
Without miglustat	5 (21.7%)	18 (79.9%)	0.123 (0.036, 0.425)	<0.0001
French comparator	5 (9.8%)	42 (82.1%)	0.073 (0.023, 0.236)	<0.0001
NIH comparator	5 (15.2%)	24 (71.2%)	0.176 (0.060, 0.517)	<0.0001
YODA comparator	4 (11.4%)	6 (17.9%)	0.298 (0.082, 1.086)	0.1168



Conclusions

- IT adrabetadex was associated with significant and clinically meaningful improved OS in individuals with infantile-onset NPC vs matched external controls
- A consistent OS treatment effect was observed for each of the most severe disease phenotypes (early and late infantile-onset NPC) and regardless of miglustat use at baseline
- This study is the first to demonstrate a survival benefit associated with an investigational drug administered to individuals with early infantile-onset NPC, a population with historically poor prognosis and limited treatment options
- Taken together with biomarker data (Poster 96) demonstrating restoration of cholesterol trafficking in neurons and suggesting decreased neuronal damage and death, these findings strengthen the evidence base for adrabetadex and support that it is an important investigational drug for treatment of individuals with infantile-onset NPC

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15. Mandos Health by Beren Therapeutics P.B.C. Data on file.

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