Substantial survival benefit in individuals with infantile-onset Niemann-Pick Disease Type C treated with adrabetadex

Poster S249

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Background

Disease Overview

Niemann-Pick Disease Type C (NPC) is a rare, autosomal-recessive, neurodegenerative disorder caused by pathogenic variants in *NPC1* (~95% of cases) or *NPC2*, which encode proteins essential for intracellular cholesterol transport.[1-3] Impaired cholesterol trafficking results in toxic accumulation of unesterified cholesterol in lysosomes and a relative deficiency of cytoplasmic cholesterol needed for normal cellular function. This imbalance leads to dysfunction across multiple organs—particularly the brain—ultimately causing progressive neurological decline and premature mortality.[1-3] NPC has a global incidence of ~1:89,000 live births, with ~940 individuals currently diagnosed in the United States.[4,5]

Clinical Heterogeneity

NPC is clinically heterogeneous, with age of neurological symptom onset being the most reliable clinical predictor of disease severity and survival.[1] Classification into four subtypes is determined by age of neurological onset: early infantile (2 mo to <2 y), late infantile (2 to <6 y), juvenile (6–15 y), and adolescent/adult-onset (>15 y). Earlier onset is associated with more rapid progression and poorer prognosis, with death often occurring by 5 years of age in early infantile-onset and between 7 and 12 years in late infantile onset.[1,2]

Current Treatment Landscape

Usual care for NPC has historically managed symptoms, with no cure and limited impact on survival. Miglustat, though only EMA-approved, is commonly used off-label in the United States and considered part of routine management.[1,2] Recently, the FDA approved arimoclomol (for patients ≥2 y, in combination with miglustat) and levacetylleucine (for patients ≥15 kg) for neurological manifestations of NPC; however, no FDA-approved therapies have been shown to improve survival.[6-8]

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 replacing the function of NPC1/NPC2 and re-establishing cholesterol trafficking.[9-12] The safety profile from the Phase 2b/3 trial of IT adrabetadex is described in a companion poster (Poster S250).

Here 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.

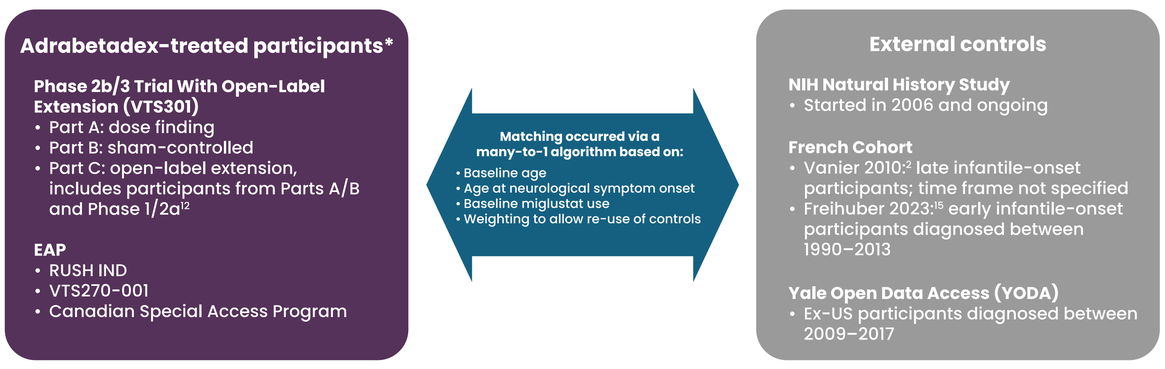
FDA, US Food and Drug Administration; EMA, European Medicines Agency.

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: NIH Natural History Study,[13] Yale Open Data Access (YODA) NPC Registry,[14] and natural history studies in France.[2,15] External controls were matched to adrabetadex-treated participants using a many-to-one algorithm based on baseline age, age at neurological symptom onset, and miglustat use, with weighting to allow reuse of controls.

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".[16]

Treatment Exposure

Adrabetadex was administered intrathecally (IT) via lumbar puncture at doses of 50–1200 mg Q4W in Phase 1/2a and 900–1800 mg 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 overall survival 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.

NIH, National Institutes of Health; Q2W, every 2 weeks; Q4W, every 4 weeks.

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). 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-Treated (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 seen for early (Figure 3a) and late infantile-onset subgroups (Figure 3b). The greater overall survival in infantile-onset NPC participants treated with adrabetadex compared with matched external controls was maintained and consistent regardless of miglustat use at baseline (Figure 4a, 4b). Overall survival showed directional consistency for the adrabetadex-treated group across all external control cohorts (Figure 5).

Figure 2. Overall Survival in Participants With Infantile-Onset NPC (Neurologic Onset <6 Years)

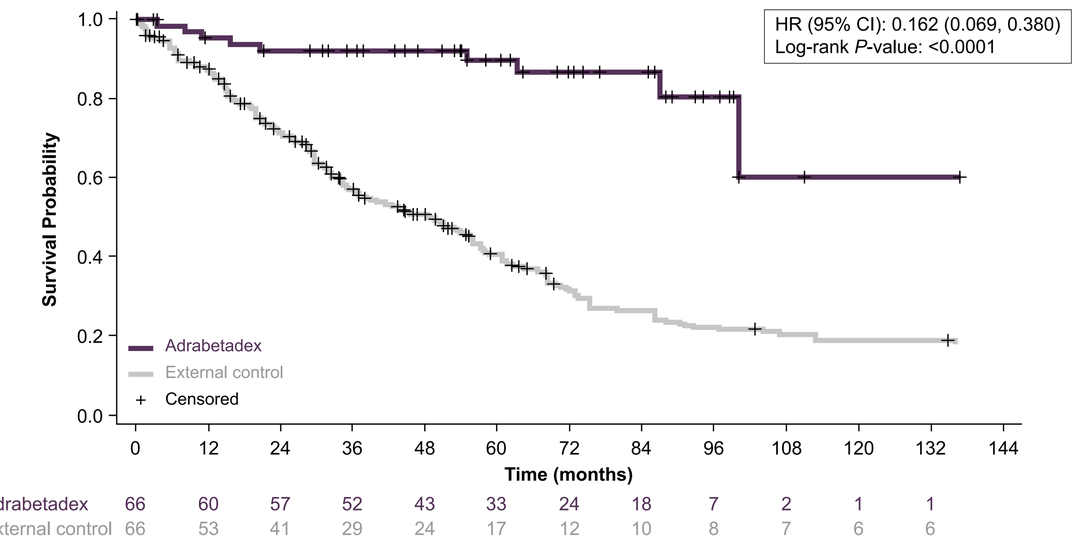
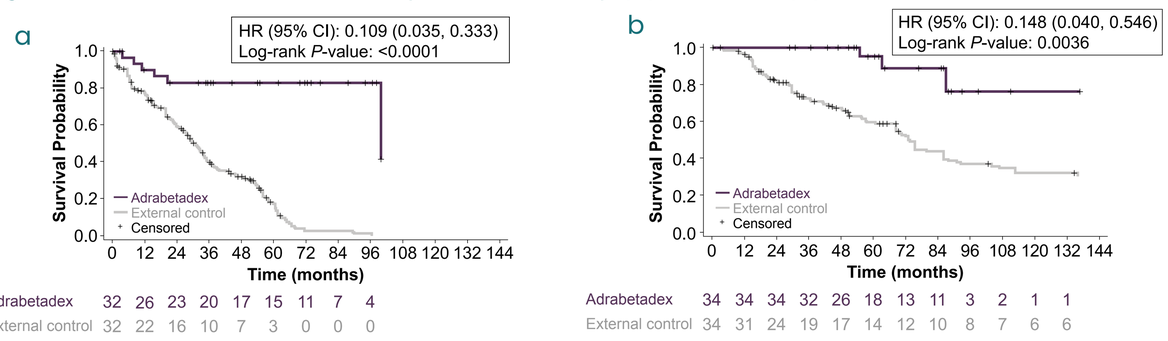


Table 2. Overall Survival Estimates and Hazard Ratio in Participants With Infantile-Onset NPC (Neurologic Onset <6 Years)

	Adrabetadex-Treated (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 control participants.
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.

Figure 4. Overall Survival in Infantile-Onset NPC Participants Treated With Adrabetadex, With (a) or Without (b) Miglustat

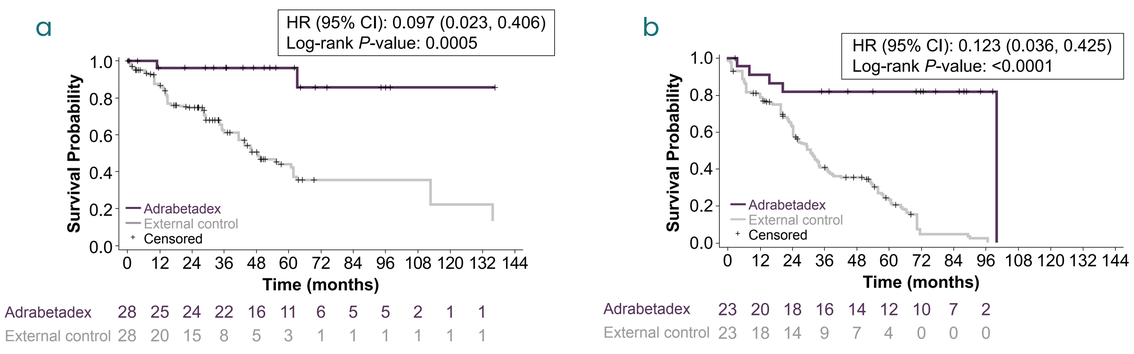


Figure 5. Overall Survival According to Treatment Effects and External Control Cohorts

Population and comparator source	No. of Deaths (%)		Hazard Ratio	*P*-Value
	Treated	Control		
Overall infantile, pooled comparator	9 (13.6%)	42 (63.3%)	0.162 (0.069, 0.380)	<0.0001
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
Early infantile, pooled comparator	6 (18.8%)	23 (72.8%)	0.109 (0.035, 0.333)	<0.0001
Late infantile, pooled comparator	3 (8.8%)	18 (54.3%)	0.148 (0.040, 0.546)	0.0036

Treated Better – Control Better
0 0.5 1 2

Conclusions

- Intrathecal adrabetadex was associated with significant and clinically meaningful improved overall survival in individuals with infantile-onset NPC compared to untreated matched external controls
- A consistent OS treatment effect was observed for the most severe disease phenotypes (early and late infantile-onset) 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
- These data are reinforced by previous clinical and nonclinical studies demonstrating that IT adrabetadex addresses the core pathology of NPC, re-establishing cholesterol trafficking, reducing lysosomal cholesterol accumulation, and decreasing neuronal cell damage and death[9-12,17,18]
- Taken together with existing mechanistic and clinical data, 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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