Survival, Clinical, and Biomarker Data Support the Efficacy of Intrathecal Adrabetadex in Niemann-Pick Disease Type C

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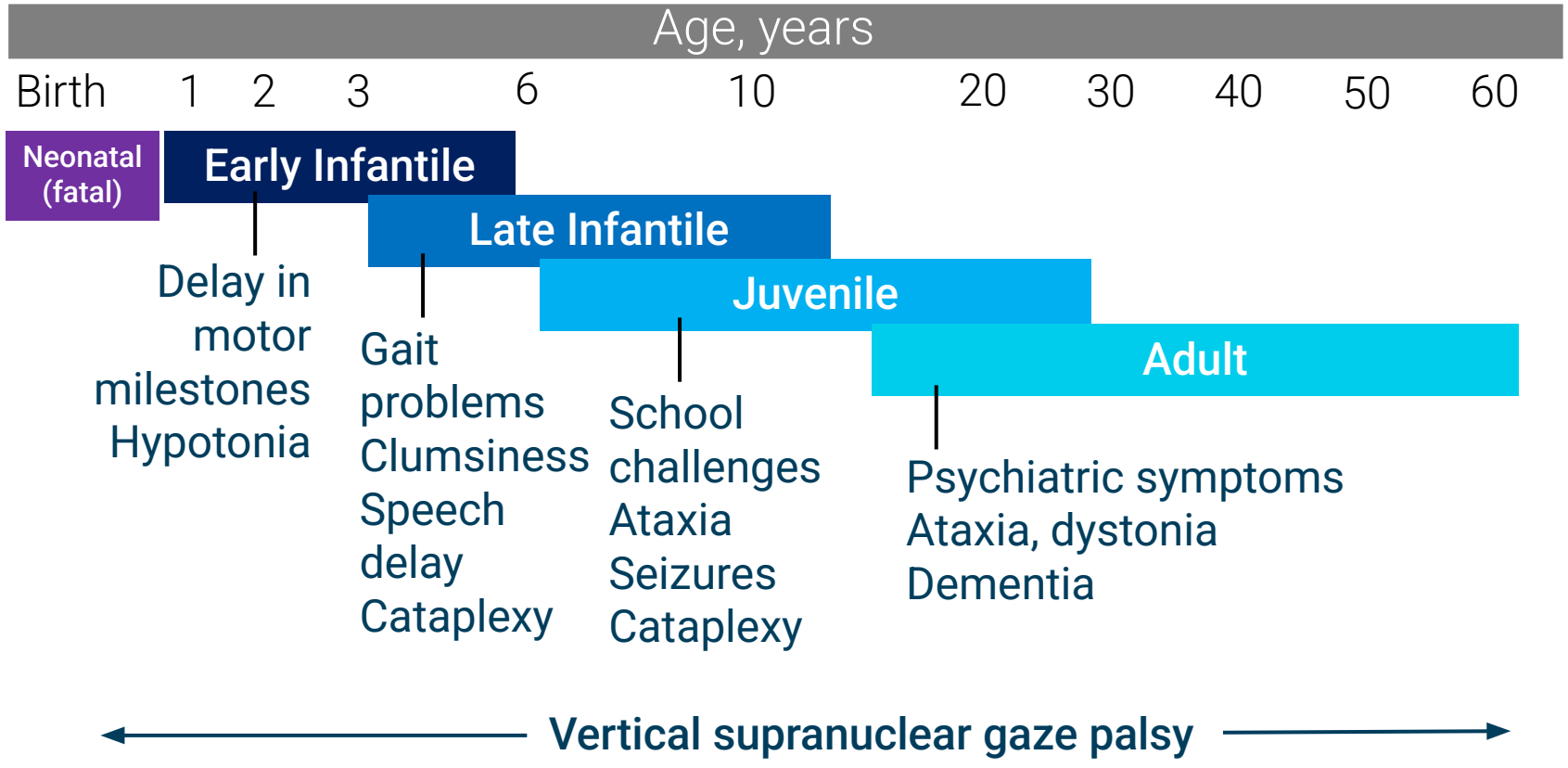
Niemann-Pick Disease Type C (NPC)

- Inherited lysosomal disease due to **impaired NPC proteins**[1]
- **Neuronal dysfunction and cell death result from** cholesterol accumulation, lysosomal dysfunction, and decreased cellular cholesterol bioavailability[2]
- **Earlier neurological symptom onset correlates with more severe impairment**, rapid progression, and earlier **mortality in childhood** or adolescence[2]

Neurological Phenotype



Adapted from Vanier 2010

NPC, Niemann-Pick disease type C.

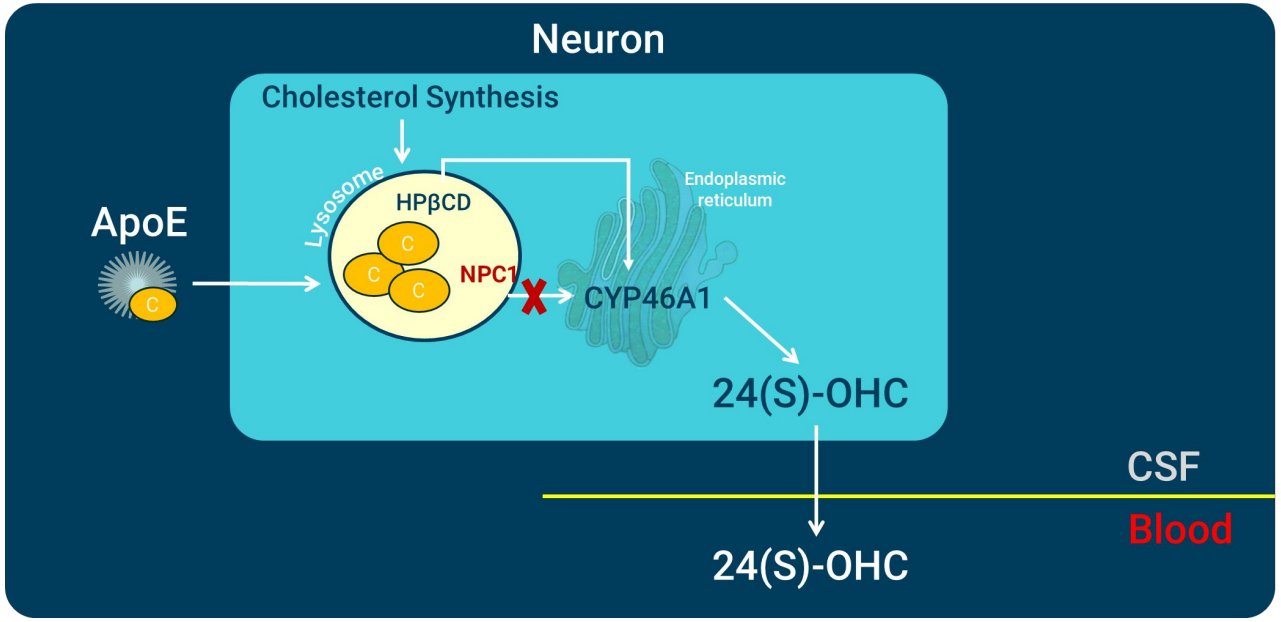
1. Berry-Kravis E. *Semin Pediatr Neurol.* 2021;37:100879. 2. Vanier MT. *Orphanet J Rare Dis.* 2010;5:16

Biomarkers Related to NPC1 Neuropathology

Pharmacodynamic biomarker of underlying disease pathology

24(S)-hydroxycholesterol (24[S]-OHC)

- Neuron-derived oxysterol[1]
- Main route for eliminating excess neuronal cholesterol[1]
- Reduced levels in NPC1, consistent with impaired cholesterol trafficking[2]



Biomarkers of Neuronal Degeneration

Calbindin D

- Calcium-binding protein
- Enriched in Purkinje neurons
- Increased in CSF of individuals with NPC1, reflecting cerebellar neuronal damage and cell loss[3-5]

Fatty Acid-Binding Protein 3 (FABP3)

- Cytosolic protein involved in membrane dynamics and synapse formation[6]
- Elevated expression and increased CSF levels in individuals with NPC1, reflecting neuronal damage and cell death[5,7]

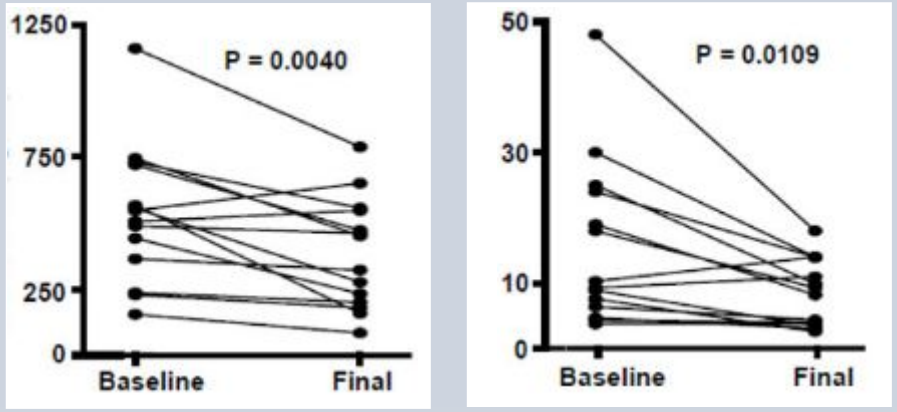
ApoE, apolipoprotein E; CSF, cerebrospinal fluid; CYP46, cholesterol 24-hydroxylase; HPβCD, 2-hydroxypropyl-β-cyclodextrin, NPC, Niemann–Pick disease type C.

1. Lütjohann D, et al. *Proc Natl Acad Sci U S A.* 1996;93(18):9799-804. 2. Porter, FD, et al., *Sci Transl Med*, 2010. 2(56): p. 56ra81. 3. Campbell K, et al. *Biomark Res.* 2023;11(1):14. 4. Bradbury A, et al. *J Pharmacol Exp Ther.* 2016;358(2):254-261. 5. Ory DS, et al. *Lancet*. 2017;390(10104):1758-1768. 6. Owada Y, et al. *Exp Med.* 2008;214(3):213-220. 7. Cologna SM, et al *PLoS One*. 2012;7(10):e47845.

Adrabetadex: An Investigational Treatment for NPC

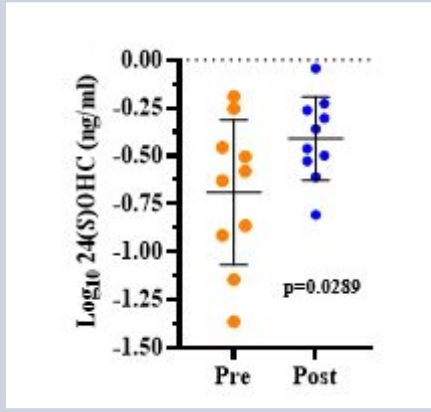
- A well characterized HPβCD mixture with a specific compositional fingerprint and limits for impurities, formulated for intrathecal (IT) administration to achieve therapeutic CNS concentrations[1,2]
- Replaces the function of deficient NPC proteins and increases intracellular cholesterol trafficking[1-6]
- NPC animal models show reduction in cerebellar Purkinje neuron loss and improved survival with HPβCDs[9]
- Phase 1/2a study demonstrated re-established cholesterol trafficking, reduced markers of neuronal damage and death, and improved neurological outcomes[3]
- Post-dose increases after up to 4 years of treatment suggest 24(S)-OHC as potential long-term pharmacodynamic marker[10]

CSF Calbindin-D (left) and **FABP3** (right) decrease after 18 months of treatment (Study Phase 1/2a)



Ory 2017

CSF levels of 24(S)-OHC increased ~48 hours after administration in patients receiving treatment for up to 4 yrs



Porter 2025

24[S]-OHC, 24(S)-hydroxycholesterol; CSF, cerebrospinal fluid; CNS, central nervous system; FABP3, fatty acid-binding protein 3; NPC, Niemann–Pick disease type C.

1. Vite CH, et al. *Sci Transl Med*. 2015;7(276):276ra26 2. Ramirez CM, et al. *Pediatr Res*. 2010;68(4):309-15. 3. Ory DS, et al. *Lancet*. 2017;390(10104):1758-1768. 4. Rosenbaum AI, et al. *Proc Natl Acad Sci USA*. 2010;107(12):5477-5482. 5. Abi-Mosleh L, et al. *Proc Natl Acad Sci*. 2009;106(46):19316-19321. 6. Feltes M, et al. J Lipid Res. 2020;61(3):403-412. 7. Peake KB, et al. *J Biol Chem*. 2012;287(12):9290-9298. 8. Tortelli B, et al. *Hum Mol Genet*. 2014;23(22):6022-6033. 9. Fukaura M, et al. *Int J Mol Sci*. 2021;22(1):452. 10. Porter FD, et al. *Mol Genet Metab*. 2025;146(4):109254.

Study Objectives and Survival Analysis Framework

- Compare survival among individuals with infantile-onset NPC treated with adrabetadex to matched external controls
- Evaluate long-term disease progression in adrabetadex-treated individuals

Matching Algorithm Addresses the Most Important Prognostic Factors

Adrabetadex-treated (n=72)

- **Phase 2b/3 Trial + Open-Label Extension (VTS301)**
  - Part A: dose finding
  - Part B: sham-controlled
  - Part C: open-label extension, includes participants from Parts A/B and phase 1/2a[5a]
- **Expanded Access Program (EAP)**

Matched based on

- Baseline age
- Disease subtype
- Age at neurological symptom onset
- Baseline miglustat use

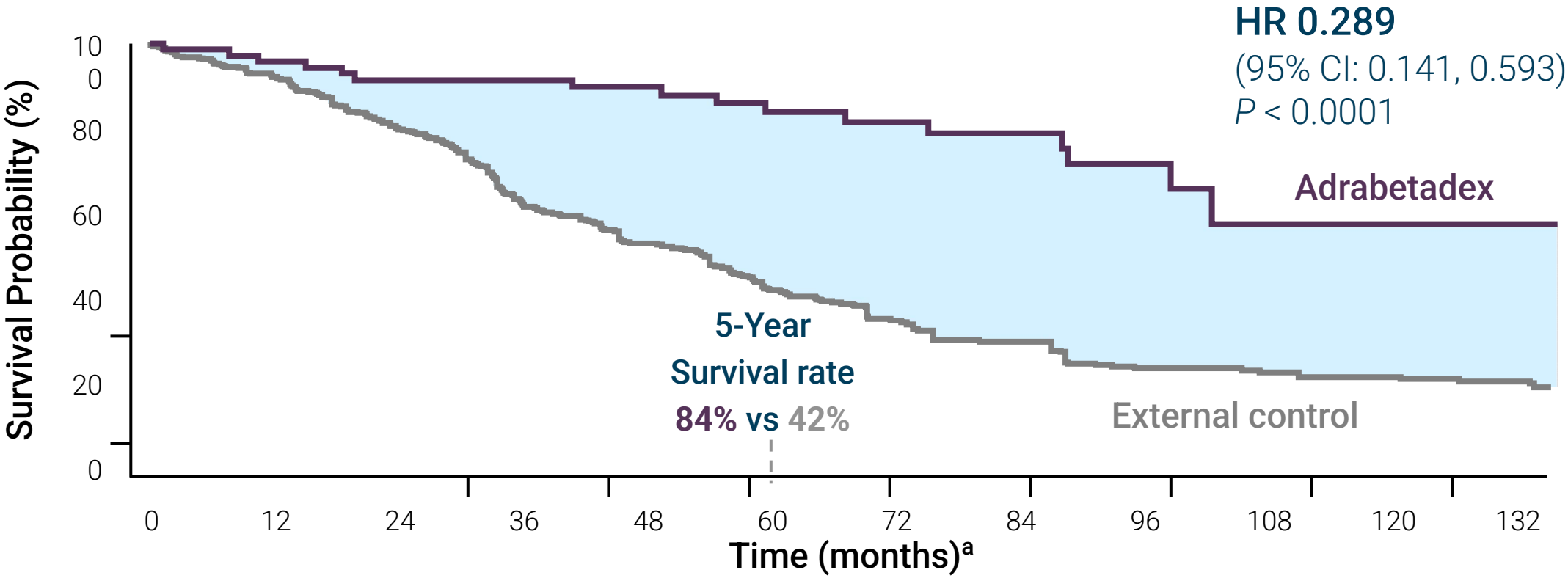
External controls (n=119)

- **NIH Natural History Study**[1]
- **French Cohorts**
  - Vanier 2010[2]
  - Freihuber 2023[3]
- **Yale Open Data Access (YODA)**[4]

1. NIH. Available from: https://clinicalstudies.info.nih.gov/protocoldetails.aspx?id=06-CH-0186&&query. Accessed January 2026. 2. Vanier MT. *Orphanet J Rare Dis.* 2010;5:16. 3. Freihuber C, et al. *Orphanet J Rare Dis.* 2023;18(1):204. 4. Yale Open Data Access. Available from: https://yoda.yale.edu. Accessed January 2026. 5. Ory DS, et al. Lancet. 2017;390(10104):1758-1768

a. One Phase 1/2a patient was not in the VTS301 Part C

Results: Adrabetadex Substantially Improves Overall Survival in Infantile-Onset NPC



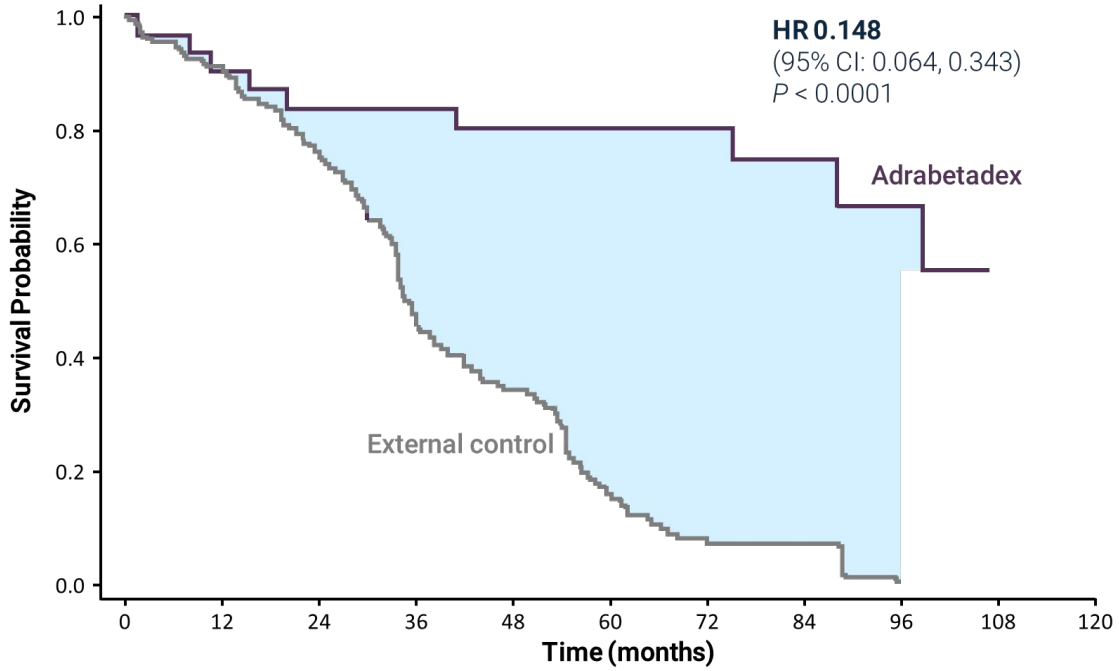
Adrabetadex[b]	72	65	61	57	48	39	31	24	13	4	3	1
External control[b]	72	59	48	35	27	20	16	13	11	10	9	9

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

Log-rank p-value was generated from a weighted KM HR (95% CI) was generated from a weighted Cox regression model including treatment (adrabetadex-treated versus matched controls) as fixed effect, and history of miglustat as a covariate.

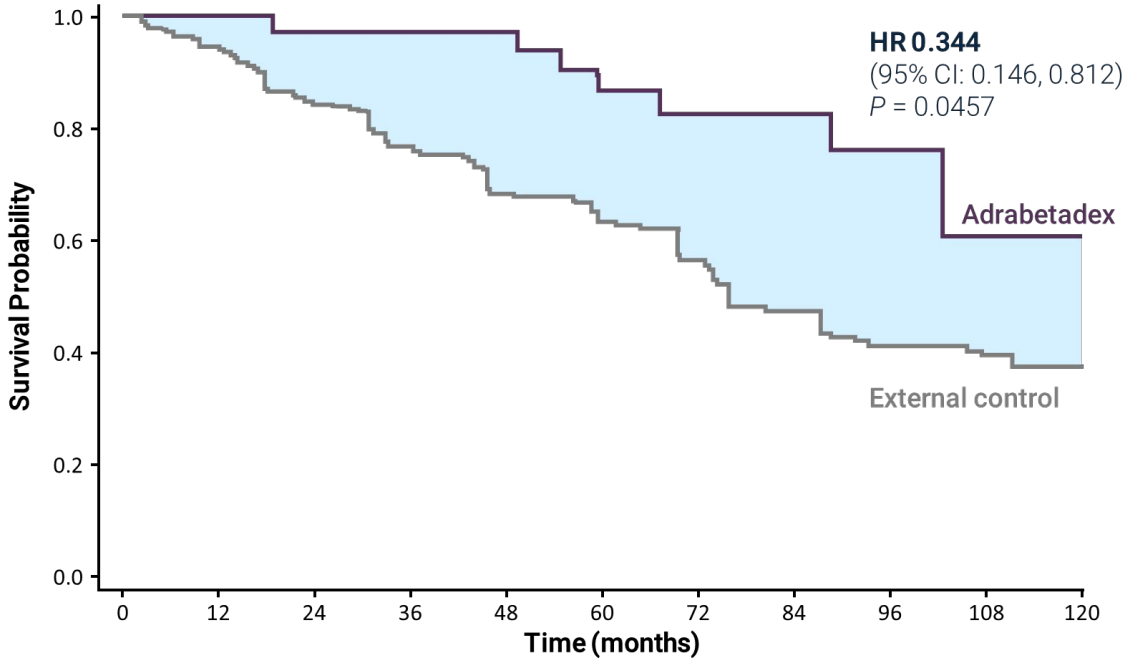
Results: Overall Survival in Participants With Early and Late Infantile-Onset NPC

Early Infantile-Onset



Adrabetadex	32	28	25	23	19	16	15	9	6
External control	32	26	20	12	8	3	1	1	0

Late Infantile-Onset

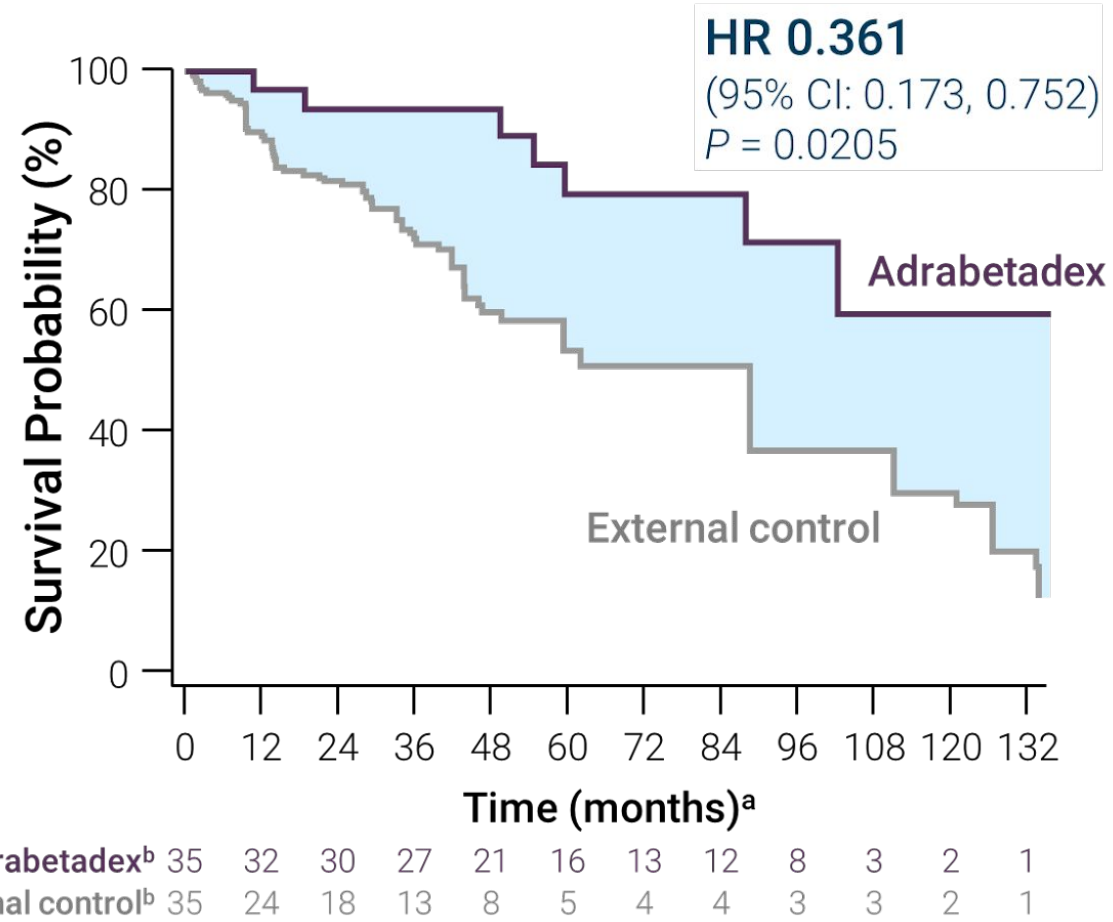


Adrabetadex	40	37	36	34	29	23	16	15	7	4	3
External control	40	34	27	23	19	17	14	12	10	10	9

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
CI = confidence interval; HR = hazard ratio

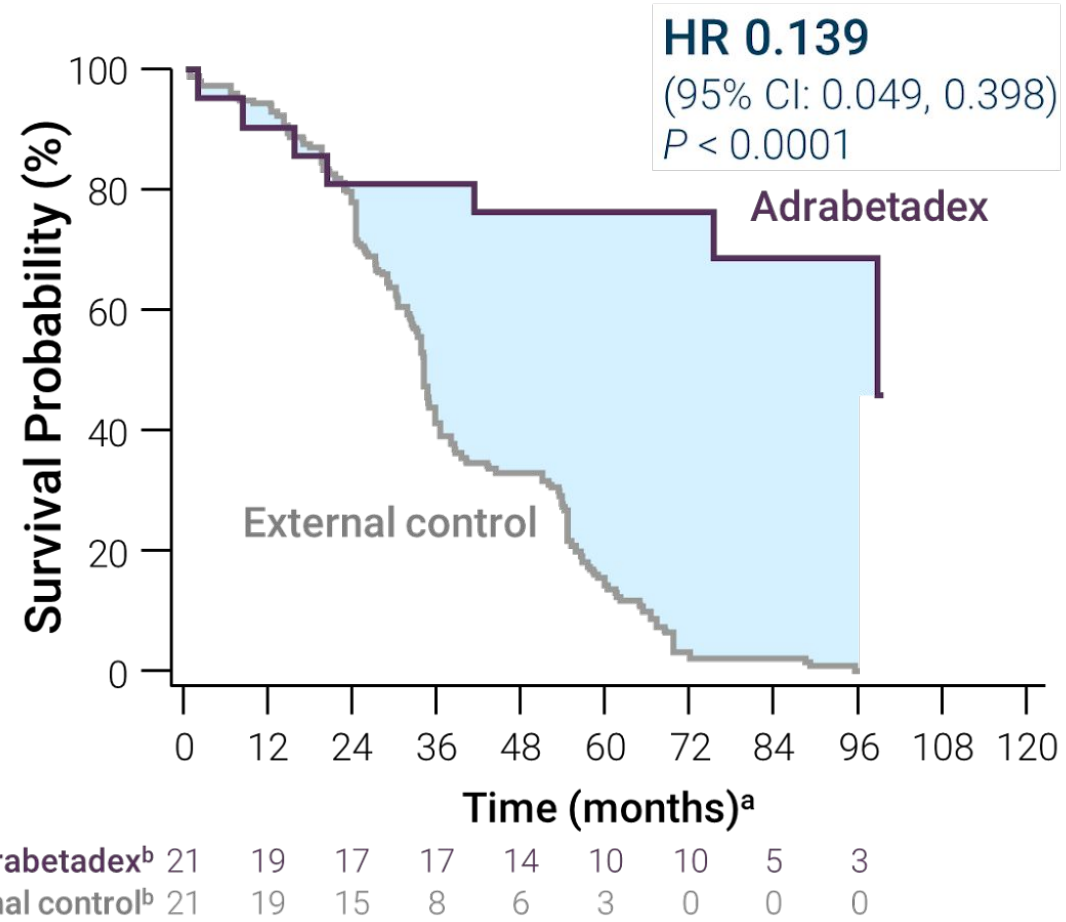
Results: Consistent Survival Benefit in Infantile-onset NPC Regardless of Miglustat Use at Baseline

With Miglustat



Adrabetadex[b]	35	32	30	27	21	16	13	12	8	3	2	1
External control[b]	35	24	18	13	8	5	4	4	3	3	2	1

Without Miglustat



Adrabetadex[b]	21	19	17	17	14	10	10	5	3
External control[b]	21	19	15	8	6	3	0	0	0

[a]KM curves are visually truncated at ~132 months.
[b]Weighted numbers at risk are shown for external control individuals to account for the many-to-1 matching to treated patients
CI = confidence interval; HR = hazard ratio

Results: Consistent Survival Benefit Across Subgroups

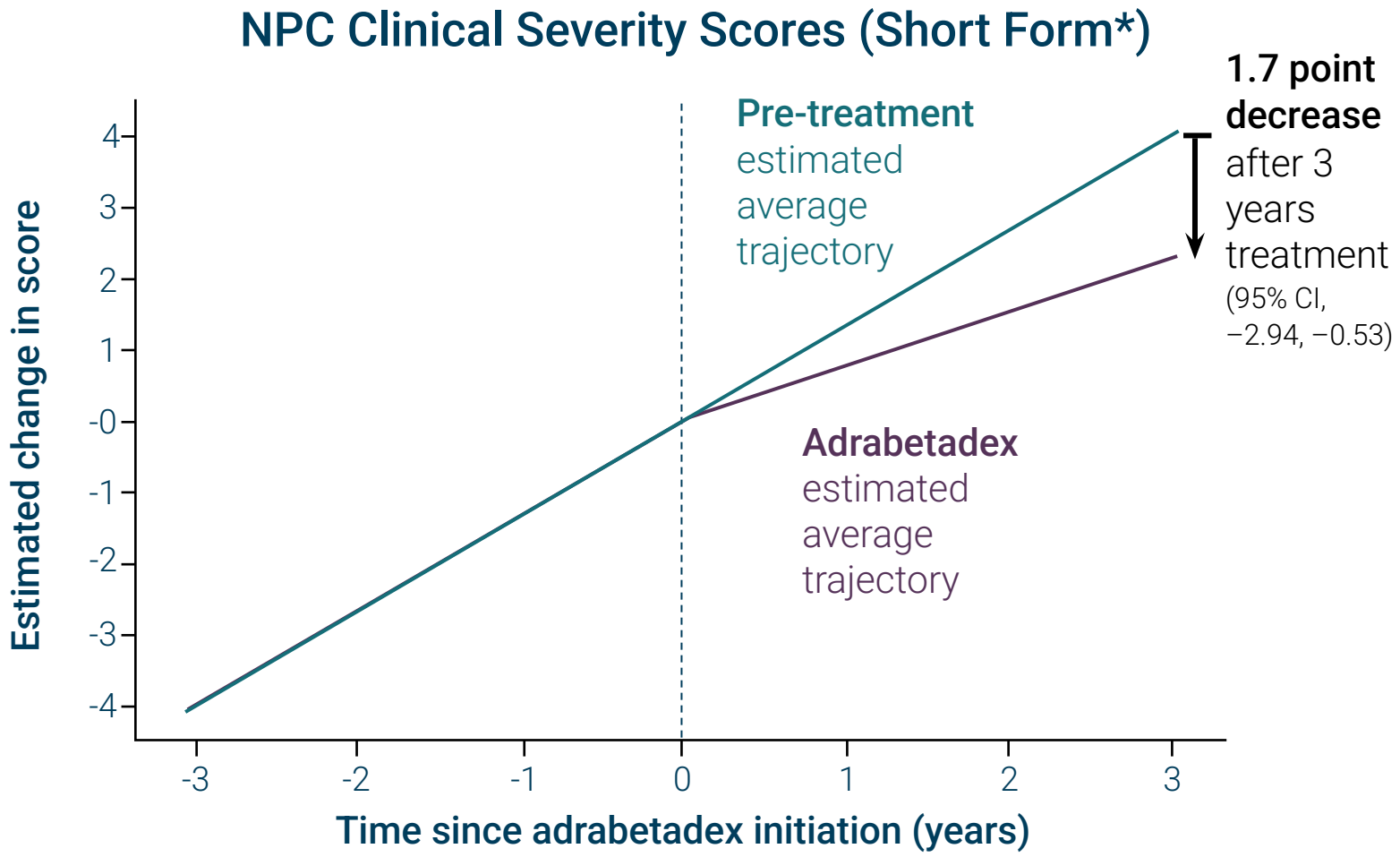
Population and comparator source	No. of Deaths (%)		HR (95% CI)	*P*-Value
	Adrabetadex	External Control		
Overall infantile	17 (23.6%)	44 (61.2%)	0.289 (0.141, 0.593)	<0.0001
Early infantile (<2y)	9 (28.1%)	24 (76.1%)	0.148 (0.064, 0.343)	<0.0001
Late infantile (2 to <6y)	8 (20.0%)	20 (49.2%)	0.344 (0.146, 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

Results: Adrabetadex Treatment Associated With 43% Reduction in Annual Rate of Disease Progression in Infantile-Onset NPC

- Disease progression was assessed in 79 infantile-onset individuals from clinical trials and EAP
- Longitudinal mixed-effects models estimate mean annual rates of change pre- vs post-treatment

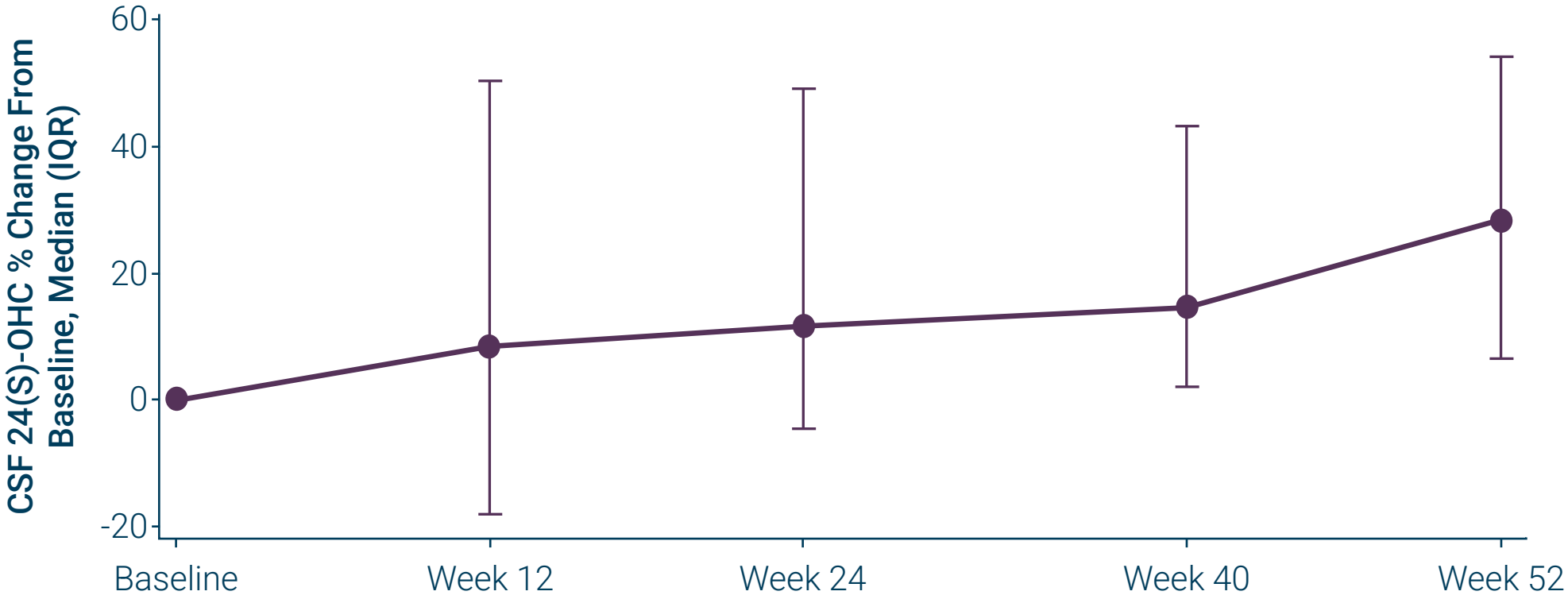
Annual Rate of Change*

	Infantile
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



* 4-Domain Composite NPC Clinical Severity Scale (R4DNPCCSS): ambulation, speech, fine-motor function, rescored swallowing

Results: CSF 24(S)-OHC Increases with Adrabetadex Treatment



	Baseline	Week 12	Week 24	Week 40	Week 52
N	31	30	29	28	22
P-value[a]		0.0528	0.0067	<0.0001	0.0012

27.7% increase from baseline at 52 weeks

n=22
IQR (6.5%, 54.2%)
p=0.0012

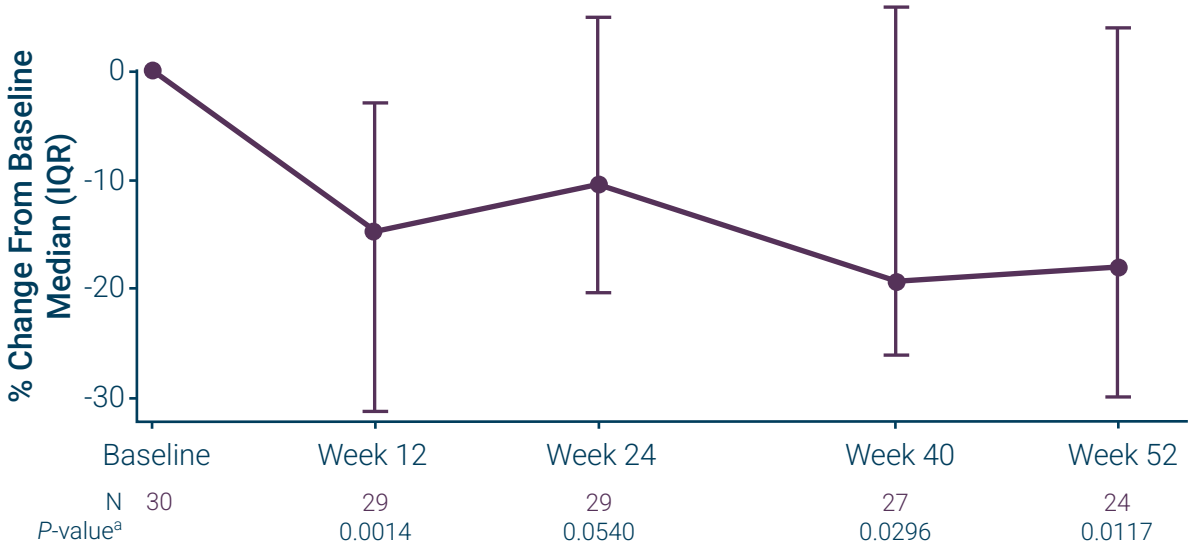
An increase in 24(S)-OHC indicates increased neuronal cholesterol trafficking

Observed in samples collected 14 days after dosing

[a]Within-group p-values are from Wilcoxon signed rank test. 24[S]-OHC, 24(S)-hydroxycholesterol; CSF, cerebrospinal fluid; IQR, interquartile range.

Results: CSF Calbindin D and FABP3 Decreases with Adrabetadex Treatment

Calbindin D

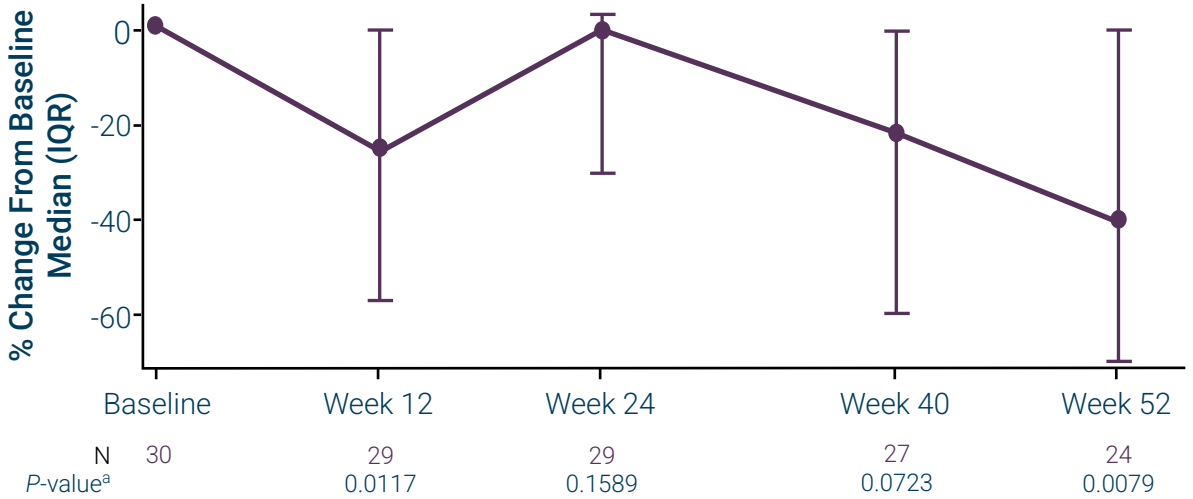


18.3% decrease from baseline at 52 weeks

n=24
IQR, −30.0%, 3.8%
p=0.0117[a]

Decreased calbindin D levels suggest increased Purkinje neuron survival

FABP3



40.5% decrease from baseline at 52 weeks

n=24
IQR, −69.4%, 0.0%
p=0.0079[a]

Decreased levels of FABP3 suggest reduced neuronal damage and cell death

[a]Within-group p-values are from Wilcoxon signed rank test. CSF, cerebrospinal fluid; FABP3, fatty acid-binding protein 3; IQR, interquartile range.

Conclusions

- Adrabetadex treatment **substantially improves survival** in individuals with infantile-onset NPC compared with matched external controls
- Survival benefit was **consistent for early and late infantile-onset 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
    - 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 infantile onset NPC

* Adrabetadex is not approved by the Food and Drug Administration or any other health authority

24[S]-OHC, 24(S)-hydroxycholesterol; CNS, central nervous system; CSF, cerebrospinal fluid; FABP3, fatty acid-binding protein 3; IQR, interquartile range; NPC1, Niemann-Pick disease type C1.
1. Internal data from Study 13-CH-0001 (Phase 1/2a)

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