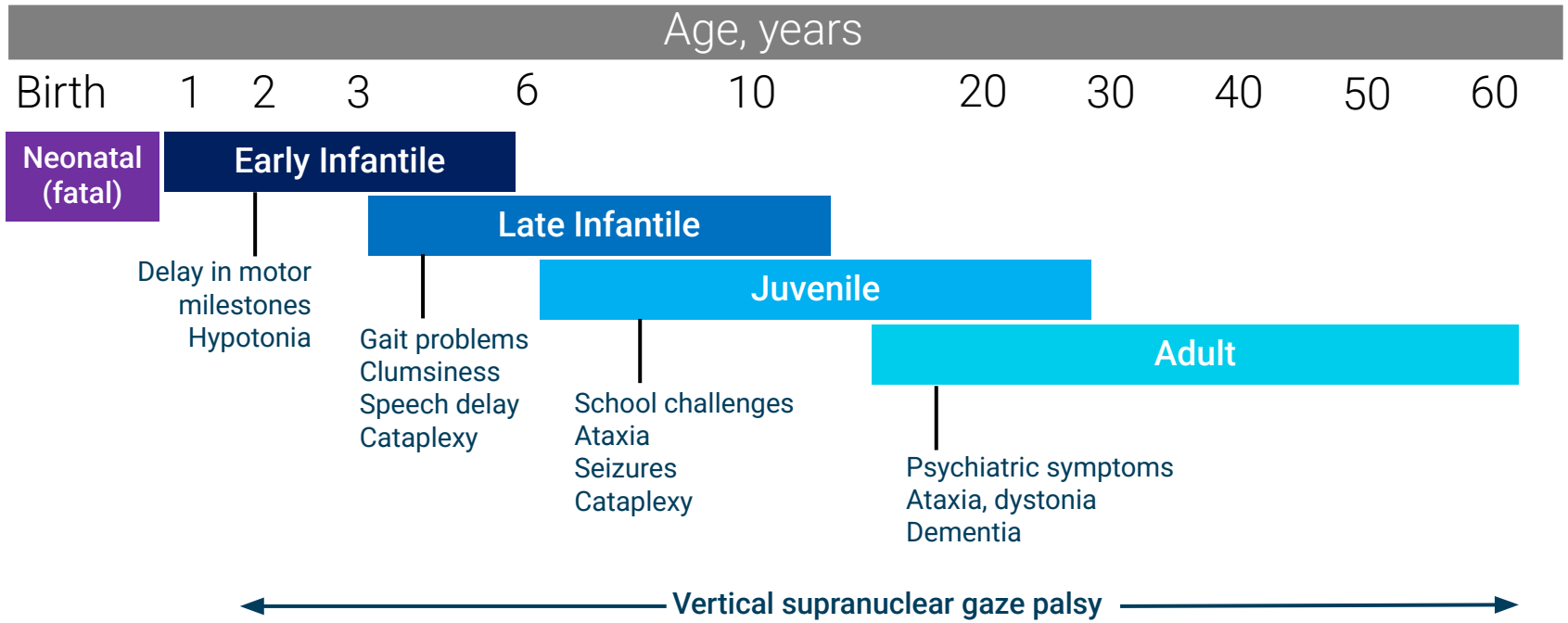
Adrabetadex Treatment in Individuals With Niemann-Pick Disease Type C1 Re-establishes Cholesterol Trafficking, Resulting in Decreased Markers of Neuronal Damage and Cell Death

Elizabeth Berry-Kravis, MD, PhD
Rush University Medical Center, Chicago, IL

Niemann-Pick Disease Type C (NPC)

- 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 onset correlates with more severe impairment**, rapid progression and **mortality in childhood** or adolescence[2]

Neurological Phenotype



Adapted from Vanier 2010

NPC, Niemann-Pick disease type C.

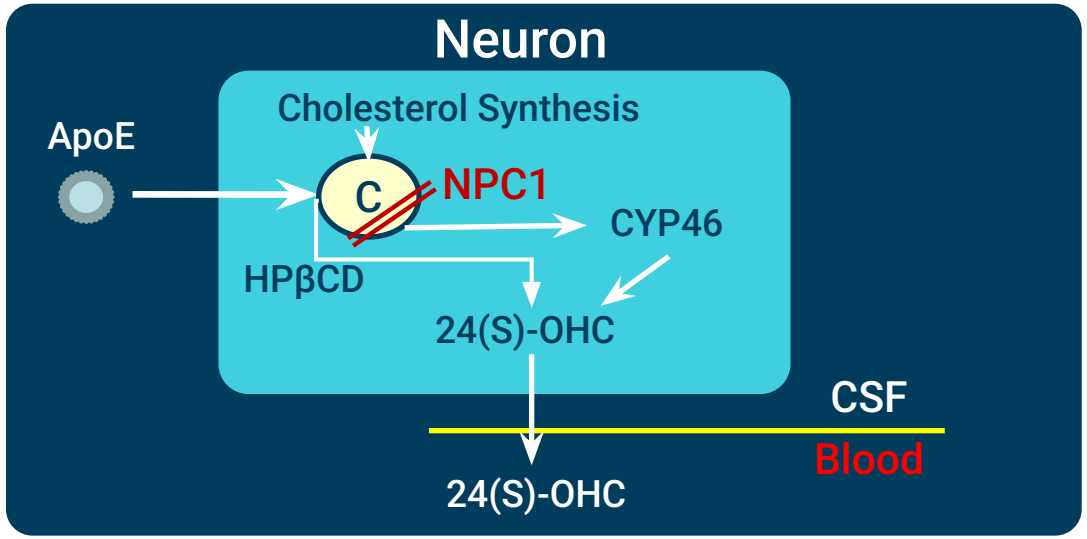
1. Berry-Kravis E. *Semin Pediatr Neurol.* 2021;37:100879. 2. Vanier MT. *Orphanet J Rare Dis.* 2010;5:16

Biomarkers Related to NPC Neuropathology

Underlying Disease Pathology

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

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



Neurodegeneration

Calbindin D

- Calcium-binding protein
- Enriched in Purkinje neurons
- Increased in CSF of patients with NPC, 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 patients with NPC, reflecting neuronal damage and cell death[5,7]

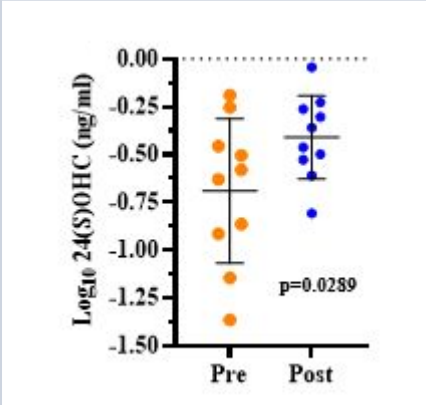
ApoE, apolipoprotein E; CSF, cerebrospinal fluid; CYP46, cholesterol 24-hydroxylase; HPβCD, 2-hydroxypropyl-β-cyclodextrin, NPC, Niemann–Pick disease type C.

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

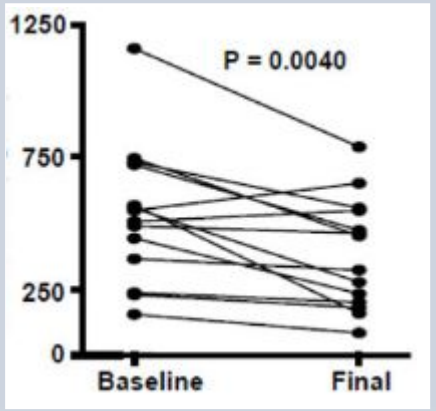
- Proprietary mixture of 2-hydroxypropyl-β-cyclodextrin (HPβCD) isomers formulated for intrathecal (IT) administration to achieve therapeutic CNS concentrations[1,2]
- Replaces the function of deficient NPC proteins and increases intracellular cholesterol trafficking[1-6]
- NPC animal models show reduction in Purkinje cell 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]

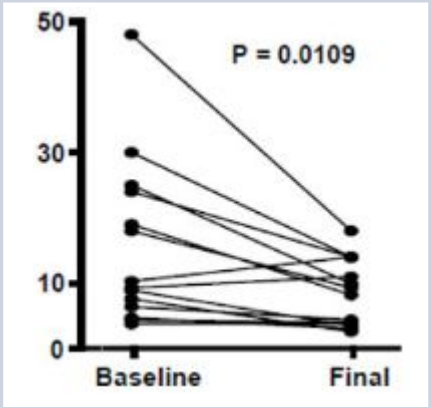
CSF levels of 24(S)-OHC increased ~48 hours after administration in patients receiving treatment for up to 4 yrs



Porter 2025

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





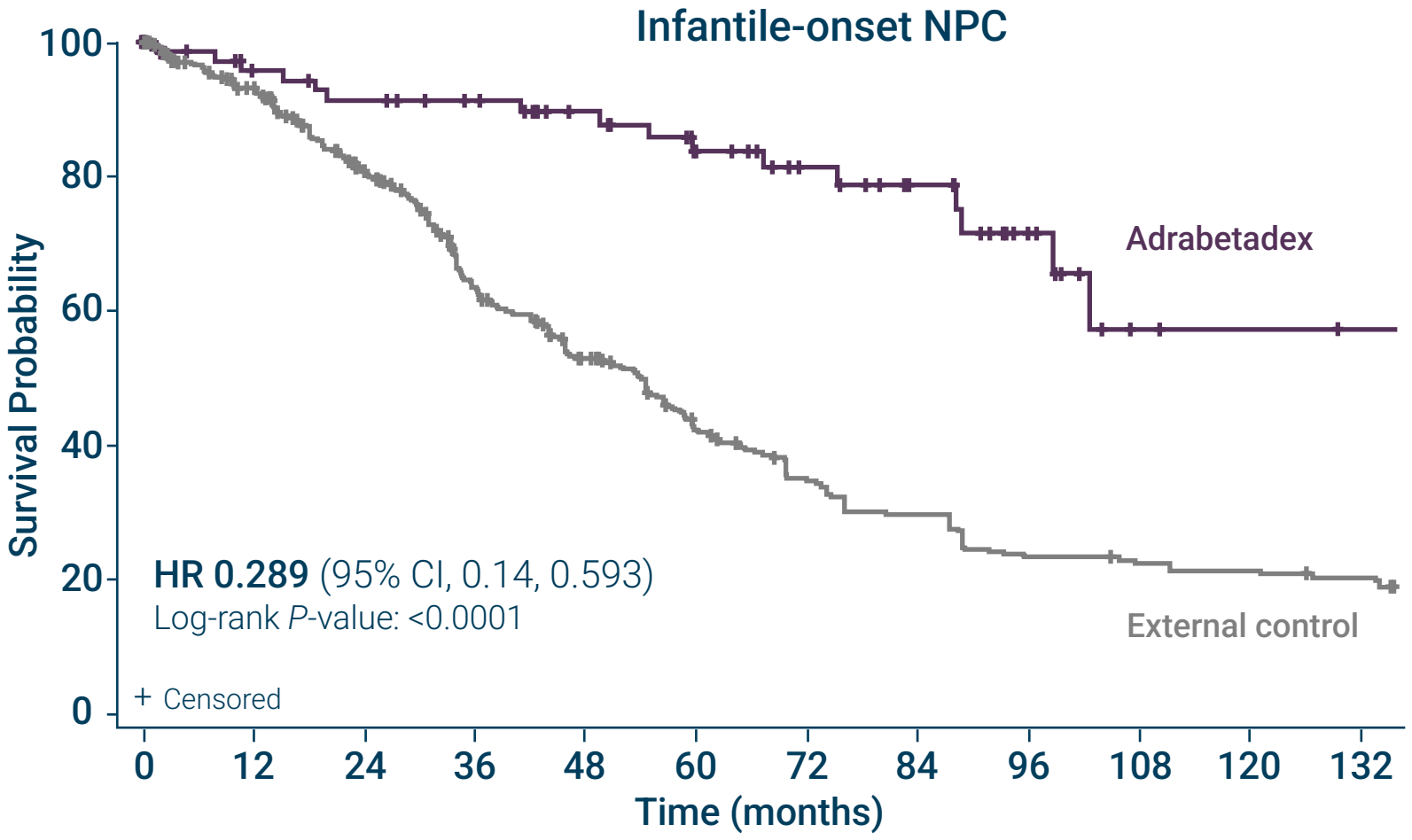
Ory 2017

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.

Prolonged Survival with Adrabetadex Treatment[1]

Substantial overall survival benefit in infantile-onset NPC compared to untreated matched external controls*



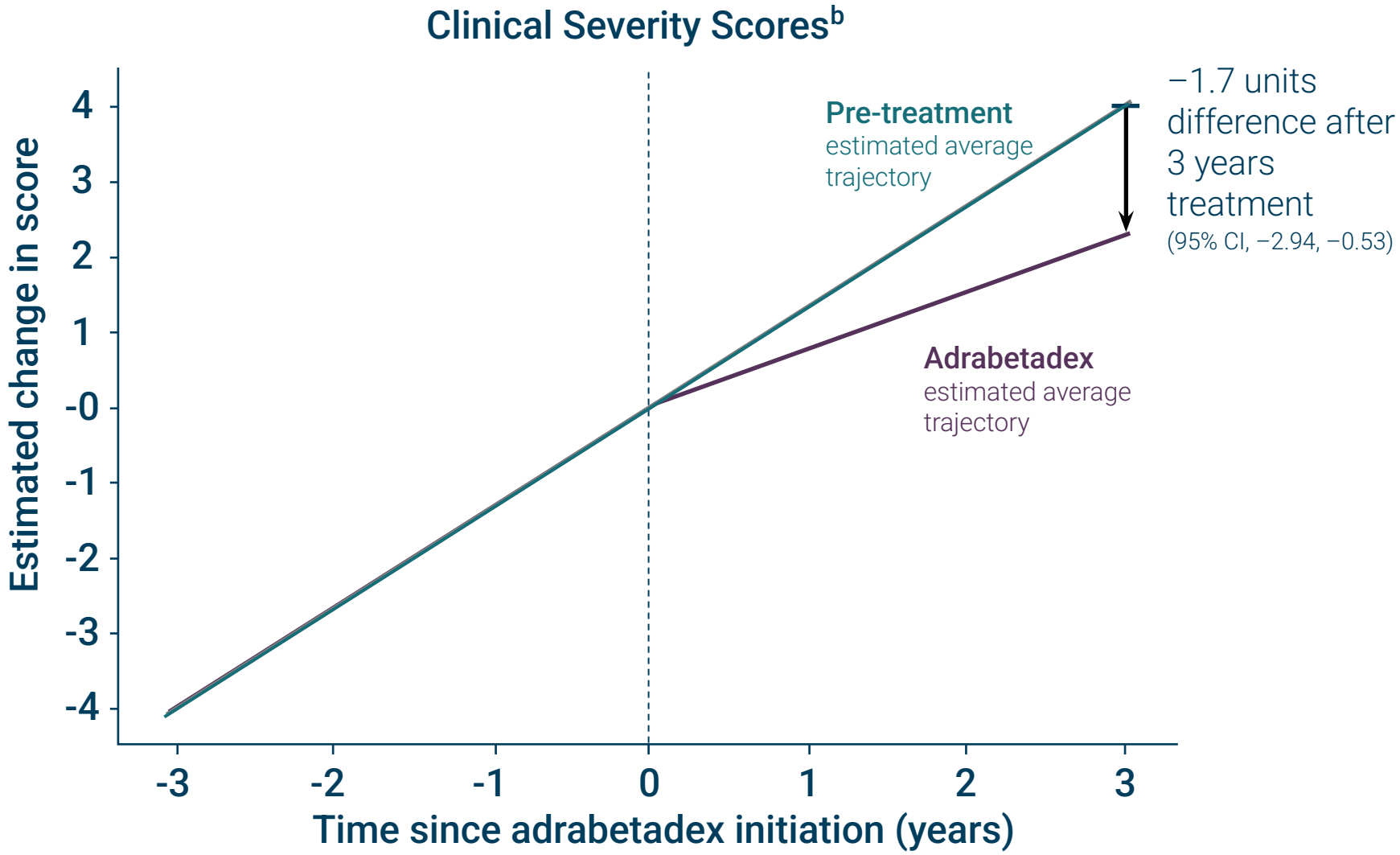
Adrabetadex	72	65	61	57	48	39	31	24	13	4	3	1
External control	72	59	48	35	27	20	16	13	11	10	9	9

CI, confidence interval; HR, hazard ratio; NPC, Niemann–Pick disease type C.
* Adrabetadex data from clinical trials and an ongoing expanded access program (EAP), matched to external controls from four major NPC sources.

1. Berry-Kravis E et al. *Molec Gen Metab*. In Press 2026

Adrabetadex Treatment Significantly Slowed Disease Progression[1]

Adrabetadex treatment[a] **decreases annual progression rate by 0.58 units/year** compared to pre-treatment in infantile-onset NPC (n=79; 95% CI, −0.98, −0.18; p=0.006)

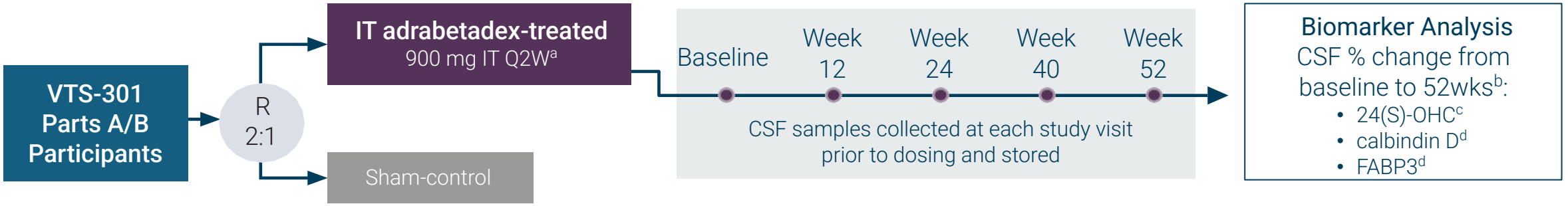


CI, confidence interval; NPC, Niemann–Pick disease type C.
[a] Data from clinical trials and an ongoing EAP
[b] NPCCSS short form (4 domains of ambulation, speech, fine-motor, swallowing)

1. Berry-Kravis E et al. *Molec Gen Metab*. In Press 2026

VTS-301: Phase 2b/3 Study Design and Participant Population

Safety and efficacy of IT adrabetadex was evaluated in a randomized, double-blind, sham-controlled trial in NPC1 participants with neurological manifestations before age 15 years[1-3]



Part A: dose finding[2]

Part B: sham-controlled[2]

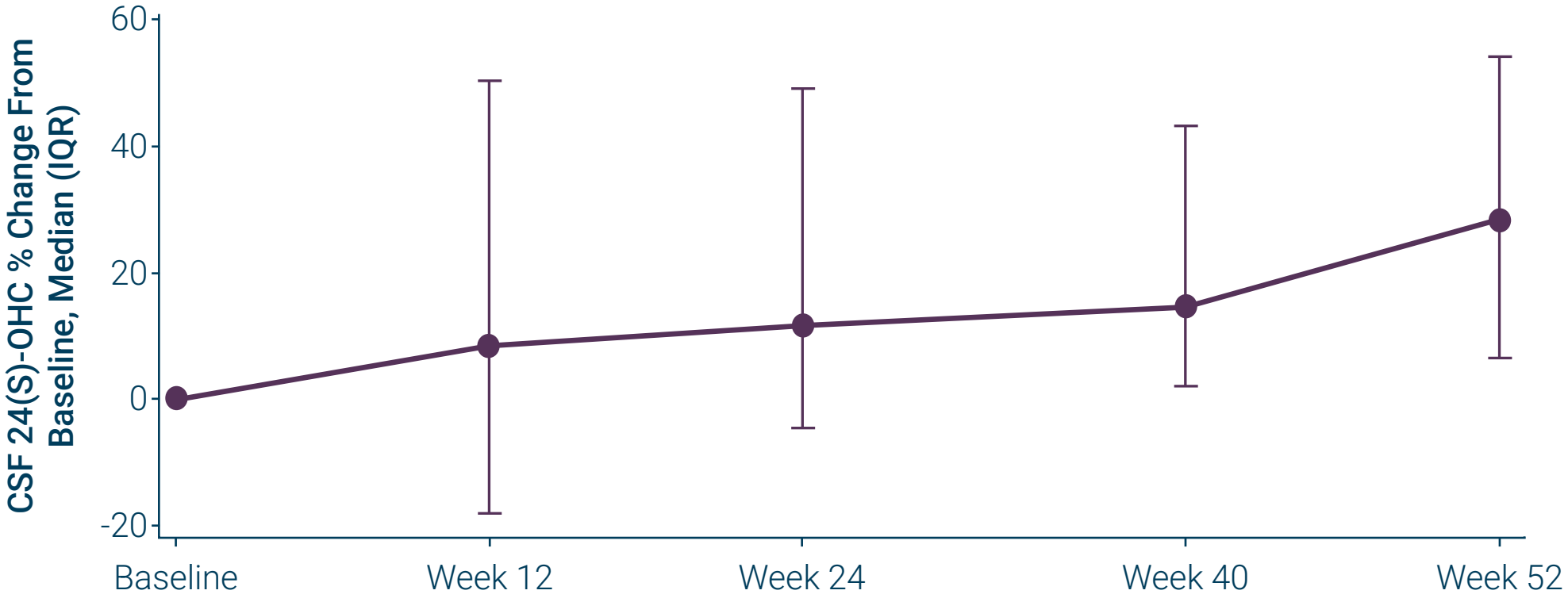
Part C: open-label extension[3]

Baseline Demographics (N=34)	
Age, mean (SD)	12.8 (5.6) years
Age at onset of neurological symptoms, mean (SD)[e]	5.7 (3.5) years
Male, n (%)	20 (58.8%)
Miglustat use, n (%)	23 (67.6%)
Baseline NPCCSS total score (minus hearing/ABR), mean (SD)[f]	17.8 (6.48)

24[S]-OHC, 24(S)-hydroxycholesterol; CSF, cerebrospinal fluid; FABP3, fatty acid-binding protein 3; IT, intrathecal; NPC, Niemann–Pick disease type C; Q2W, every 2 weeks; R, randomization; SD, standard deviation.
[a]Dose reduction permitted for tolerability; [b]Wilcoxon signed-rank test was used to assess within-group changes in CSF biomarkers from baseline to Week 52 (SAS v9.4); [c]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); [d]Measured with Quanterix® immunoassays at Rules-Based Medicine (IQVIA, Austin, TX); [e]Age of onset available for 32 patients; [f]Baseline NPCCSS total score from intent to treat population (n=38)

1. Porter FD et al . 150th Annual Meeting ANA 2025. *Ann Neurol,* 98(suppl 34): S250: page S135. https://doi.org/10.1002/ana.78015 2. VTS-270 to Treat Niemann-Pick Type C1 (NPC1) Disease. ClinicalTrials.gov identifier: NCT02534844 Updated Feb 22, 2023. Accessed Jan 13, 2026. 3. Hydroxypropyl Beta Cyclodextrin for Niemann-Pick Type C1 Disease. ClinicalTrials.gov identifier: NCT01747135. Updated Feb 22, 2023. Accessed Jan 13, 2026.

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



N	31	30	29	28	22
P-value[a]		0.0528	0.0067	<0.0001	0.0012

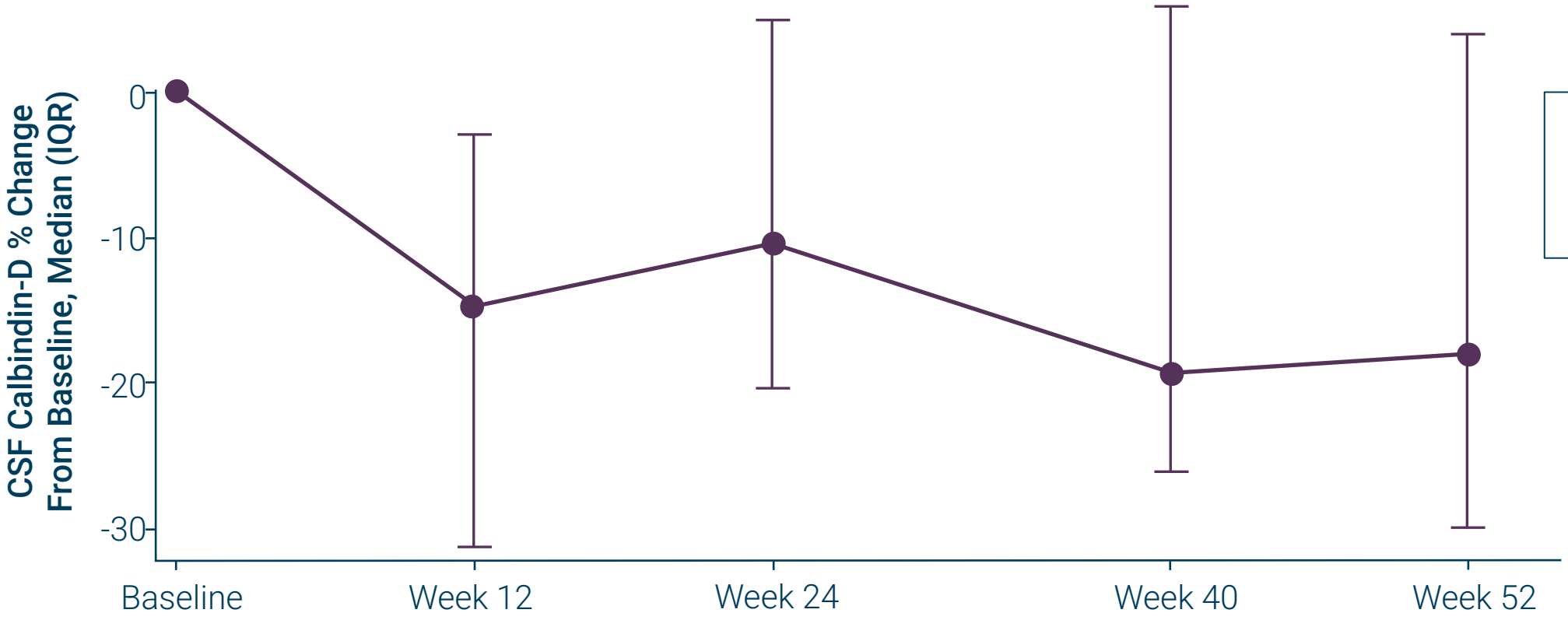
27.7% increase from baseline at 52 weeks

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

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

[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 Decreases with Adrabetadex Treatment



N	30	29	29	27	24
P-value[a]		0.0014	0.0540	0.0296	0.0117

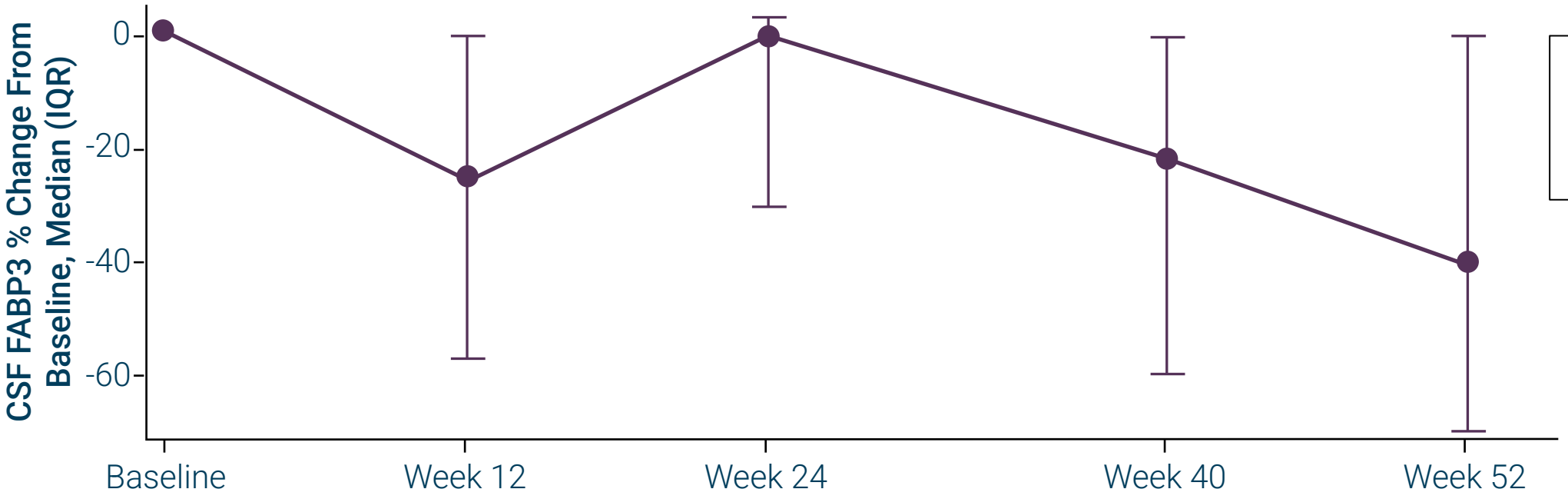
18.3% decrease from baseline at 52 weeks

n=24
IQR (−30.0%, 3.8%)
p=0.0117

Decreased calbindin-D levels suggest increased survival of Purkinje neurons

[a]Within-group p-values are from Wilcoxon signed rank test. CSF, cerebrospinal fluid, IQR, interquartile range.

Results: CSF FABP3 Decreases with Adrabetadex Treatment



N	30	29	29	27	24
P-value[a]		0.0117	0.1589	0.0723	0.0079

40.5% decrease from baseline at 52 weeks

n=24
IQR (−69.4%, 0.0%)
p=0.0079

Decreased levels of FABP3 suggest decreased 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

- 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**
  - Observed in samples collected 14 days after dosing, demonstrating a prolonged CNS effect despite the short CSF half-life of adrabetadex (~6.6 hours[1])
- Decreased CSF levels of calbindin D and FABP3 suggest that adrabetadex **decreases neuronal damage and cell death**
- **Biomarker evidence suggests adrabetadex targets the underlying pathology of NPC and, together with observed improved survival and slowing of disease progression, is consistent with its potential as a disease-modifying treatment***

* 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)

Acknowledgments

- **Authors**
  - **Elizabeth Berry-Kravis, MD, PhD**, *Rush University Medical Center, Chicago, IL*
  - **Laurence H. Keller, MD**, *Mandos by Beren Therapeutics P.B.C., Thousand Oaks, CA*
  - **Lixia Jiao, PhD**, *Mandos by Beren Therapeutics P.B.C., Thousand Oaks, CA*
  - **Julja Burchard, MS**, *Mandos by Beren Therapeutics P.B.C., Thousand Oaks, CA*
  - **Christina Copland, PhD, MPH**, *Mandos by Beren Therapeutics P.B.C., Thousand Oaks, CA*
  - **Forbes D. Porter, MD, PhD**, *Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD*
- **Funding/Support**
  - This study was sponsored by Mandos, a subsidiary of Beren Therapeutics P.B.C.
- **Latebreaker-13, Posters 042 & 043**

THANK YOU to patients, caregivers, adrabetadex EAP, & VTS-301 investigators involved in this program