

Early evidence of an emerging NPC treatment paradigm: adrabetadex use alongside arimoclomol and/or levacetylleucine

Poster 275

Elizabeth Berry-Kravis,¹ Laurence H Keller,² Lixia Jiao,² Jason Camm,² Natasa Rajcic,² David Huang,² Brian Tumminello,² Cary O Harding,³ Jasmine L Knoll,⁴ Sookyong Koh,⁵ Nicola Longo,⁶ Randal Richardson,⁷ Ian Rossman,⁸ Natasha E Shur,⁹ Joseph L Lasky,¹⁰ Forbes D Porter¹¹

¹Rush University, Chicago, IL, USA; ²Beren Therapeutics P.B.C., Thousand Oaks, CA, USA; ³Oregon Health and Science University, Portland, OR, USA; ⁴Phoenix Children's Hospital, Phoenix, AZ, USA; ⁵Children's Nebraska, Omaha, NE, USA; ⁶University of California Los Angeles, Los Angeles, CA, USA; ⁷Gillette Children's, St Paul, MN, USA; ⁸Akron Children's, Akron, OH, USA; ⁹Children's National Hospital, Washington, DC, USA; ¹⁰Cure 4 The Kids Foundation, Las Vegas, Nevada, USA; ¹¹National Institutes of Health, Bethesda, MD, USA

BACKGROUND

- Niemann-Pick disease type C (NPC) is a rare, progressive, neurodegenerative disorder caused by impaired cholesterol trafficking, resulting in cholesterol accumulation and downstream cellular dysfunction.¹
- FDA-approved therapies for the neurological manifestations of NPC have distinct mechanisms of action, including arimoclomol (heat shock protein co-induction; approved in combination with miglustat [substrate reduction] for patients ≥2 years of age), and levacetylleucine (modified amino acid therapy, approved for patients with NPC weighing ≥15 kg).²⁻⁴
- Adrabetadex is an investigational intrathecal therapy for NPC and the only therapy designed to directly target accumulated intracellular cholesterol in the CNS, the central pathogenic driver of NPC, by restoring cholesterol trafficking.
- Adrabetadex remains the only therapy studied and shown to improve survival in both early (neurological onset <2 years) and late infantile-onset NPC (neurological onset 2 to <6 years) compared with matched external controls.⁵
- Because adrabetadex targets the central pathogenic driver of disease, complementary therapies with distinct mechanisms may be layered on top to address downstream manifestations or provide additive benefit.
- In a recent consensus publication, most experts completely or partially agreed that combination therapy should be considered for patients with confirmed NPC; however, limited data are available regarding initiation and use of combination therapy outside of miglustat.⁴
- This analysis represents the first systematic evaluation of treatment sequencing and combination therapy in NPC, characterizing the use of adrabetadex alongside arimoclomol and/or levacetylleucine in clinical practice.

OBJECTIVES

To describe baseline characteristics, treatment sequencing, safety outcomes, and combination therapy patterns in a cohort of participants treated with adrabetadex plus arimoclomol and/or levacetylleucine in an adrabetadex expanded access program (EAP), and to evaluate evidence of an emerging combination treatment paradigm in NPC.

METHODS

- Individuals with NPC were eligible to participate in an EAP for intrathecal adrabetadex.
- Enrollment in the EAP was initiated in 2013 and required that participants be ineligible for all currently enrolling clinical trials.
- The program permitted concomitant use of other NPC therapies, arimoclomol or levacetylleucine, after their approval, allowing evaluation of adrabetadex administered concomitantly with arimoclomol, levacetylleucine, or both.
- Safety data were not available for patients receiving other NPC therapies prior to study enrollment.

RESULTS

Baseline Demographics and Disease Characteristics (Supplementary Table 1)

- At the data cutoff of March 27, 2026, 33 participants had received adrabetadex with arimoclomol and/or levacetylleucine. Six participants received adrabetadex with arimoclomol, 12 received adrabetadex with levacetylleucine, and 15 received adrabetadex, arimoclomol, and levacetylleucine.
- All 33 participants received adrabetadex, while 27 (81.8%) received levacetylleucine, 21 (63.6%) arimoclomol, and 20 (60.6%) miglustat; 10 participants were exposed to all four therapies.
- Of these, 28 participants received adrabetadex through the EAP and then began treatment with arimoclomol and/or levacetylleucine following U.S. approval.

Treatment Sequencing

- Participants receiving adrabetadex + arimoclomol + levacetylleucine:

12/15 initiated adrabetadex first, and subsequently added the other therapies

- Participants receiving adrabetadex + arimoclomol:

4/6 initiated adrabetadex first

- Participants receiving adrabetadex + levacetylleucine:

12/12 initiated adrabetadex first

- Miglustat-treated participants:

15/20 initiated miglustat before adrabetadex

Safety (Table 1)

- Of participants treated with adrabetadex ± miglustat only (n=53), 90.6% experienced at least one TEAE compared to 100% of those who started adrabetadex first, followed by levacetylleucine and/or arimoclomol (n=28) and 69.7% for those who were exposed to combination therapy at any point (n=33).
 - Those participants who were exposed to combination therapy at any point had a shorter time since first treatment dose in this analysis as most participants initiated these therapies when they became commercially available at the end of 2024.
- TEAEs of interest and grade ≥3 TEAEs were similar across the groups and the overall EAP population, except for the group who were exposed to combination therapy at any point (lowest duration of adrabetadex exposure).

Treatment sequencing suggests newer therapies are being added to, rather than substituted for, adrabetadex:

Figure 1. Timeline of Adrabetadex, Miglustat, Arimoclomol, and Levacetylleucine Therapy for Individual Participants

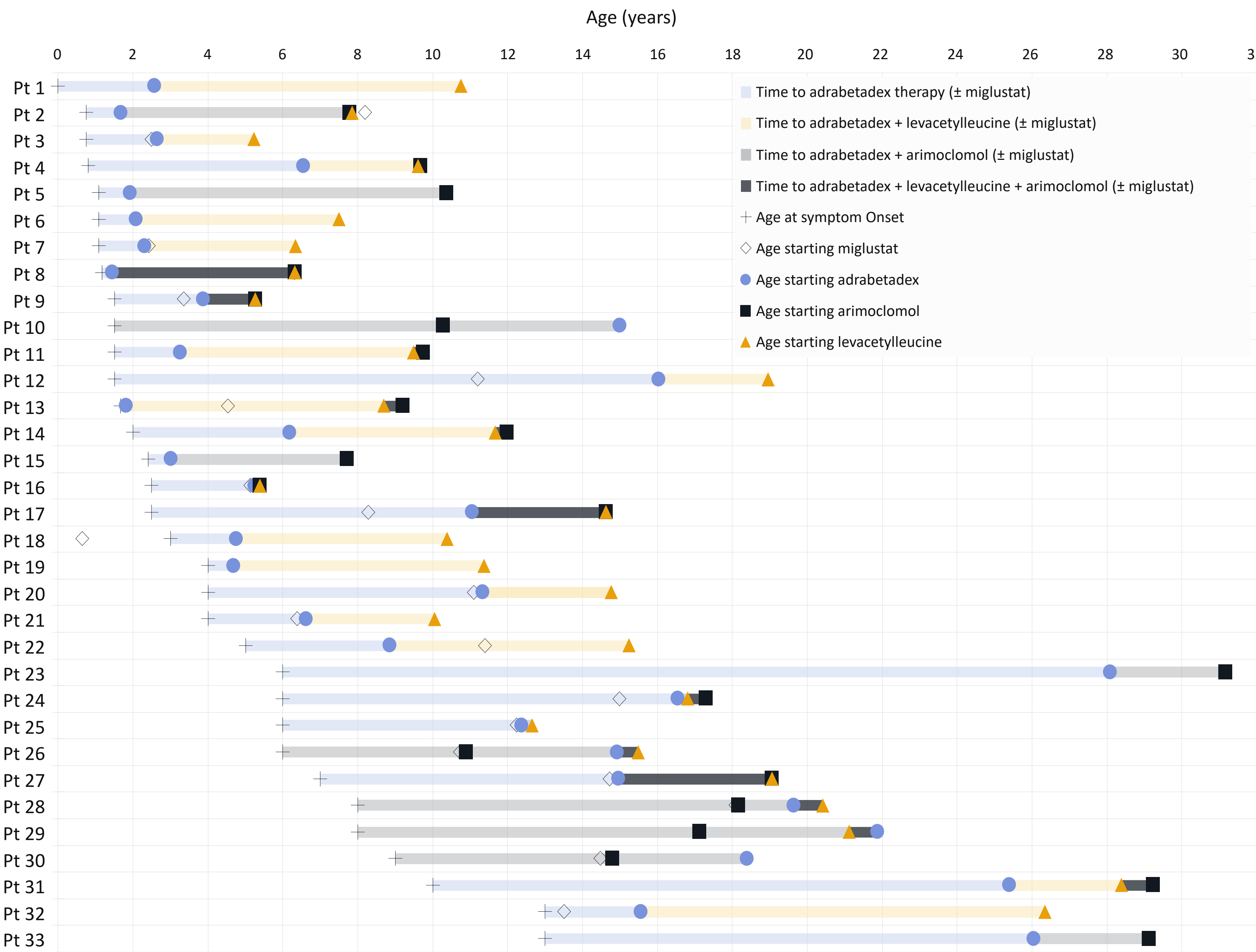


Table 1. Summary of TEAEs in Participants with NPC Receiving Combination Therapy with Adrabetadex

	Participants who started adrabetadex prior to adding levacetylleucine and/or arimoclomol (n=28)	Participants who had exposure to levacetylleucine and/or arimoclomol at any point (n=33 ^a)	Participants with no record of starting arimoclomol and/or levacetylleucine after starting adrabetadex (n=53)	All EAP (n=86)
Months between start of adrabetadex to combo, median [IQR]	48.8 [36.4, 74.0]	41.2 [16.7, 67.6]	NA	NA
Period when TEAEs reported	Adrabetadex only	After start of combination therapy only	At any time	At any time
Time since first treatment dose (months) ^b , median [IQR]	48.8 [36.4, 74.0]	16.8 [15.8, 17.8]	38.1 [12.0, 58.2]	52.8 [15.4, 74.2]
With ≥1 TEAE (any grade), n (%)	28 (100)	23 (69.7)	48 (90.6)	81 (94.2)
Leading to Death, n (%)	0	1 (3.0)	5 (9.4)	6 (7.0)
Serious AEs, n (%)	13 (46.4)	8 (24.2)	24 (45.3)	41 (47.7)
Leading to Discontinuation, n (%)	0	0	3 (5.7)	3 (3.5)
Grade ≥3, n (%)	9 (32.1)	6 (18.2)	21 (39.6)	33 (38.4)
TEAEs of Interest, n (%)	22 (78.6)	9 (27.3)	35 (66.0)	62 (72.1)
Ataxia	10 (35.7)	5 (15.2)	23 (43.4)	37 (43.0)
Fatigue	17 (60.7)	7 (21.2)	25 (47.2)	47 (54.7)
Hearing Impairment	10 (35.7)	2 (6.1)	15 (28.3)	26 (30.2)

^aThere were 5 participants who initiated treatment with arimoclomol prior to adding adrabetadex and/or levacetylleucine. ^bTime since first treatment dose is time from the first dose of adrabetadex administration to date of discontinuation from EAP or EAP cutoff date, whichever occurred earlier. Safety data were only collected while participants were in the study and receiving adrabetadex. Data analysis cut-off date is March 27, 2026. AE, adverse event; EAP, Expanded Access Program; IQR, interquartile range; NA, not applicable; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- This analysis represents the first systematic evaluation of combination therapy use in NPC, characterizing treatment sequencing and use of adrabetadex alongside arimoclomol and/or levacetylleucine.
- Most participants initiated adrabetadex prior to complementary therapies, with arimoclomol and/or levacetylleucine frequently added after adrabetadex (when they became commercially available) rather than used instead of adrabetadex.
- Importantly, >50% of participants evaluated had infantile-onset NPC, including >30% with early infantile disease, representing the youngest and most rapidly progressive patients, for whom approved treatment options remain limited or unavailable.
- Safety findings were generally consistent with the established adrabetadex safety profile, with differences in treatment exposure and observation time limiting comparisons across groups.
- These observations may help inform clinical decision-making regarding sequencing and use of therapies with complementary mechanisms of action in NPC, including infantile-onset disease.
- Observed treatment patterns may provide early evidence of an emerging treatment paradigm in which adrabetadex may serve as a foundational therapy while complementary therapies are layered based on patient need.

References

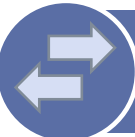
1. Vanier MT. Orphanet J Rare Dis. 2010;5:1 2. MIPLYFFA. Prescribing information. Zevra Therapeutics, Inc. Accessed April 25, 2026. <https://zevra.com/documents/MIPLYFFA-Prescribing-Information.pdf>. 3. AQNEURSA™. Prescribing information. IntraBio Inc. Accessed April 25, 2026. <https://www.aqneursahcp.com/wp-content/prescribing-information.pdf>. 4. Hiwot T et al. J Inherit Metab Dis. 2026;49:e70185. 5. Berry-Kravis E, et al. *Mol Genet Metab*. 2026;147(2):109341.

Acknowledgments

This study was funded by Beren Therapeutics P.B.C. Medical writing support was provided by Ana Mata, PhD, Carolyn M. Walsh, PhD, Mariana Dalagnol, PhD, and Tiago Silva, PharmD, PhD, CMPP, of Med Communications, Inc, and Paula Stuckart of Helios Global Group, with funding from Beren Therapeutics P.B.C.

We thank the patients and their families for their vital participation in this research, as well as the site investigators supporting this clinical study.





SUPPLEMENTARY RESULTS

Baseline Demographics and Disease Characteristics (Supplementary Table 1)

- At the data cutoff of March 27, 2026, 33 participants had received adrabetadex with arimoclomol and/or levacetylleucine. Six participants received adrabetadex with arimoclomol, 12 received adrabetadex with levacetylleucine, and 15 received adrabetadex, arimoclomol, and levacetylleucine.
- All 33 participants received adrabetadex, while 27 (81.8%) received levacetylleucine, 21 (63.6%) arimoclomol, and 20 (60.6%) miglustat; 10 participants were exposed to all four therapies.
- Of these, 28 participants received adrabetadex through the EAP and then began treatment with arimoclomol and/or levacetylleucine following U.S. approval.
- A total of 5 participants received arimoclomol before U.S. approval and later added treatment with adrabetadex. These participants received arimoclomol for an average of 3.7 years before initiating treatment with adrabetadex.

Supplementary Table 1. Baseline Demographics and Disease Characteristics

	Adrabetadex + Arimoclomol (n=6)	Adrabetadex + Levacetylleucine (n=12)	Adrabetadex + Arimoclomol + Levacetylleucine (n=15)	All EAP (N=86)
Age at neurological symptom onset category, n (%)				
<2 years old	2 (33.3)	5 (41.7)	6 (40.0)	26 (30.2)
2-6 years old	1 (16.7)	5 (41.7)	3 (20.0)	23 (26.7)
≥6 years old	3 (50.0)	2 (16.7)	6 (40.0)	29 (33.7)
Missing	0	0	0	8 (9.3)
Age at neurological symptom onset, years	n=6	n=12	n=15	n=78
Median (Q1, Q3)	4.2 (1.5, 9.0)	3.5 (1.1, 4.5)	2.5 (1.5, 7.0)	3.5 (1.5, 7.0)
Age at adrabetadex treatment start, years	n=6	n=12	n=15	n=78
Median (Q1, Q3)	16.7 (3.0, 26.0)	5.0 (2.0, 11.5)	6.0 (3.0, 16.0)	8.0 (3.0, 20.0)
Sex, n (%)				
Male	4 (66.7)	6 (50.0)	8 (53.3)	51 (59.3)
Female	2 (33.3)	6 (50.0)	7 (46.7)	34 (39.5)
Unknown	0	0	0	1 (1.2)
Race, n (%)				
Black or African American	0	0	0	1 (1.2)
White	6 (100.0)	11 (91.7)	14 (93.3)	76 (88.4)
Other	0	0	1 (6.7)	5 (5.8)
Multiple	0	1 (8.3)	0	1 (1.2)
Not Reported	0	0	0	3 (3.5)
Miglustat use at baseline, ^a n (%)				
Yes	1 (16.7)	7 (58.3)	8 (53.3)	33 (38.4)
No	5 (83.3)	5 (41.7)	7 (46.7)	46 (53.5)
Missing	0	0	0	7 (8.1)
Miglustat initiation on or before start of arimoclomol and/or levacetylleucine, ^a n (%)				NA
Yes	1 (16.7)	9 (75.0)	9 (60.0)	
No	5 (83.3)	3 (25.0)	6 (40.0)	
Time from start of adrabetadex to initiation of arimoclomol and/or levacetylleucine, months	n=6	n=12	n=15	NA
Median (Q1, Q3)	36.9 (-43.2, 56.3)	56.7 (38.1, 78.4)	36.8 (1.5, 65.8)	

^aMiglustat use is derived from concomitant medications. Miglustat use was derived as Yes if there was a record of miglustat use in the concomitant medications at or prior to the first dose of study medication. Otherwise, miglustat use is No. If miglustat was initiated at or before the start of arimoclomol and/or levacetylleucine, then ‘Yes’ otherwise ‘No’. Data analysis cutoff date is March 27, 2026. Percentages are based on the total number of participants in each treatment group (n). NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Acknowledgments

This study was funded by Beren Therapeutics P.B.C. Medical writing support was provided by Ana Mata, PhD, Carolyn M. Walsh, PhD, Mariana Dalagnol, PhD, and Tiago Silva, PharmD, PhD, CMPP, of Med Communications, Inc, and Paula Stuckart of Helios Global Group, with funding from Beren Therapeutics P.B.C.

We thank the patients and their families for their vital participation in this research, as well as the site investigators supporting this clinical study.

