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Research Paper

Long-term real-world safety and effectiveness of arimoclomol in individuals with NPC: Outcomes from the US early access program over a 4-year period

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ABSTRACT

Background: The United States-based Early Access Program (US EAP) provided access to arimoclomol for individuals with Niemann-Pick disease Type C (NPC) ineligible or unable to enroll in clinical trials, generating 4 years of real-world safety and effectiveness data.

Methods: Participants were enrolled at 14 US sites. Investigators collected adverse events (AEs) and assessed disease severity using the 5-domain NPC Clinical Severity Scale (5DNPCCSS) at Baseline and follow-up visits as part of routine clinical care.

Results: Among 109 participants, 53 (48.6%) were adults (≥18 years) and 71 (65.1%) received miglustat alongside arimoclomol. Mean (SD) arimoclomol exposure was 820 (539) days. Of 248 reported AEs, 17 events in 13 participants (12.8%) were treatment related. 5DNPCCSS scores remained relatively stable throughout the program, with mean (SD) total scores of 11.0 (6.15) at Baseline (n = 100) and 12.0 (7.32) at Year 4 (n = 22). Among participants with Baseline and Year 1 assessments, mean (SD) scores were 11.2 (6.33) at Baseline and 11.1 (6.63) at Year 1 ($n = 78$). Similar patterns were observed for those with Baseline and Year 2, Year 3, or Year 4 assessments. Rescored 4-domain NPCCSS (R4DNPCCSS) scores (calculated based on 5DNPCCSS data) showed comparable longitudinal trends.

Conclusion: The US EAP provides robust real-world evidence data up to 4 years, supporting the tolerability and effectiveness of arimoclomol in a broad NPC population, including adults and those not treated with miglustat. These findings complement and extend clinical trials results, reinforcing the role of arimoclomol, especially in combination with miglustat, as an important therapeutic option in routine clinical practice.

Abbreviations: 5D-NPCCSS, 5-domain Niemann-Pick disease type C Clinical Severity Scale; AE, adverse event; CLEAR, Coordinated Lysosomal Expression And Regulation; EAP, Early Access Program; FDA, Food and Drug Administration; NPC, Niemann-Pick disease type C; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; OLE, open-label extension; PT, Preferred Term; R4DNPCCSS, rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale; RWD, real-world data; SAE, serious adverse event; SD, standard deviation; SOC, System Organ Class; TEAs, treatment-emergent adverse events; US, United States.

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1. Introduction

Niemann-Pick disease type C (NPC) is an ultra-rare and heterogenous disease characterized by progressive neurological decline, with an estimated incidence of ~1:100,000 live births [1]. The disease arises from biallelic pathogenic variants in either the *NPC1* or *NPC2* gene, encoding lysosomal proteins that are essential in intracellular transport and metabolism of lipids [2,3]. As a result, NPC proteins are often misfolded and degraded prematurely, leading to impaired lysosomal function and accumulation of multiple lipid species. Natural history studies have demonstrated that NPC leads to neurodegeneration, including cognitive impairment, dysarthria, ataxia, vertical supranuclear gaze palsy, and dysphagia [4], and may impact the liver, spleen, and lungs over time. The age of onset for NPC disease can vary greatly, from a neonatal rapidly progressive fatal disorder to a more slowly progressing adult-onset neurodegenerative disease [1]. If left untreated, the progressive neurological symptoms of NPC lead to disability and premature death [1,5–7].

In 2024, arimoclomol (MIPLYFFA®) became the first treatment to receive US Food and Drug Administration (FDA) approval to treat the neurological manifestations of NPC in adult and pediatric patients ≥2 years of age when given alongside miglustat (a glucosylceramide synthase inhibitor). Arimoclomol, an orally available small molecule that crosses the blood-brain barrier, impacts NPC by enhancing transcription of CLEAR (Coordinated Lysosomal Expression and Regulation) network genes including *NPC1* and *NPC2*. In NPC patient fibroblasts, arimoclomol increased both *NPC1* gene expression and NPC1 protein levels and reduced lysosomal cholesterol accumulation through NPC1-dependent and -independent pathways, supporting its therapeutic potential in NPC [8].

FDA approval of arimoclomol was supported by positive results of the 12-month phase 2/3, double-blind, placebo-controlled NPC-002 trial ($N = 50$) and its subsequent open-label extension (OLE) study ($N = 41$) (clinicaltrials.gov #NCT02612129) [9,10]. The pre-defined primary endpoint of the study was disease progression, which was assessed using the validated 5-Domain NPC Clinical Severity Scale (5DNPCCSS), an abbreviated version of the 17-domain NPCCSS, including the ambulation, swallow, cognition, speech, and fine motor domains [9,11]. In the primary analysis, arimoclomol (combined with miglustat as part of routine care in most participants), resulted in a significant and clinically meaningful slowing of disease progression through 12 months of treatment [9]. The 5DNPCCS score increased by a mean of 0.76 during the first year after initiating arimoclomol, which is notably below the progression rate of 2.15 seen in the placebo group or the 1.5 annual progression rate reported in the NPC-001 natural history study, in which 30 of 36 participants received miglustat [9,12]. These findings were confirmed by a *post-hoc* analysis using the rescored 4-Domain NPC Clinical Severity Scale (R4DNPCCSS), which excludes the cognition domain to address regulatory concerns that differences in patient environment may impact the cognition scoring, and incorporates a refined swallowing score analysis to allow for a more linear interpretation of the scoring categories [13]. The OLE study further demonstrated sustained treatment benefits for at least five years using both the 5DNPCCSS and R4DNPCCSS [10]. Interpretation of arimoclomol monotherapy effects was limited by the small number of participants not taking miglustat and imbalances in Baseline characteristics between those taking and not taking miglustat [9,10]. Across both the placebo-controlled trial and the OLE, arimoclomol was well tolerated for up to 5 years of treatment [10].

After completion of the phase 2/3 trial, an Early Access Program (EAP) was launched in the US to provide arimoclomol to a broader group of individuals with NPC, including those who were not eligible for or able to participate in other clinical trials or had completed treatment in the OLE part of the phase 2/3 study. The EAP remained active until arimoclomol became commercially available, generating up to 4 years of real-world safety and effectiveness data for arimoclomol with and without miglustat for individuals with wider ranges of age and disease severity at treatment initiation than those represented in the clinical trial.

2. Methods

2.1. EAP design

The objective of the EAP was to provide early access to arimoclomol due to the unmet medical need prior to regulatory approval. Enrollment was initiated in July 2020 and was closed at the time of commercial approval in September 2024. Participants were enrolled on a rolling basis over the 4-year duration of the program. As a real-world study conducted under standard-of-care conditions, the EAP did not include a defined end-of-study visit or a mandated visit schedule beyond Baseline. Combined with rolling enrollment, this resulted in variable follow-up durations across participants. Arimoclomol was provided by the Sponsor on an individual basis with dose based on the participant's weight and consistent with the dosing regimen in the phase 2/3 study [9]. Treating physicians were responsible for determining therapeutic strategies for participants from their center. Participants received arimoclomol orally in addition to their routine clinical care.

Safety reporting, including adverse events (AEs), and special situations, such as arimoclomol use during pregnancy, breastfeeding, or any misuse, was mandatory. All other disease-specific and real-world data assessments were performed as part of routine clinical care and were neither prespecified in timing nor mandatory. Data elements of interest are outlined in Supplementary Table S1.

Participants and/or their parent or legal guardian were required to provide written informed consent to participate in the EAP. They had the option to consent for real-world data collection independently of receiving arimoclomol. The study was conducted in line with the ethical principles of the Declaration of Helsinki. All data was handled in accordance with the regulations specified in the US Health Insurance Portability and Accountability Act of 1996 and the EU General Data Protection Regulation. It was the treating physician's responsibility to obtain Institutional Review Board approval of the EAP and related documentation.

2.2. Participants

The EAP was open to US-based individuals who were ≥ 2 years of age, had a confirmed diagnosis of NPC, and at least one neurological symptom. Participants who were taking miglustat were required to be on the target dose for a minimum of 6 weeks prior to initiating treatment with arimoclomol. Participants with severe liver or renal insufficiency, uncontrolled epilepsy, a suspected allergy to arimoclomol or its constituents, or a medical condition that would interfere with the participant's ability to adhere to treatment were not eligible for inclusion. As the impact of arimoclomol during pregnancy had not been established, participants of childbearing ability were required to have a negative pregnancy test and all participants agreed to the use of highly effective contraception during the EAP.

2.3. Arimoclomol treatment

Participants received arimoclomol orally in addition to their routine clinical care. Body weight was measured at each visit and used to calculate arimoclomol dose as recommended, i.e., 8–15 kg: 47 mg three times a day (tid); >15–30 kg: 62 mg tid; >30–55 kg: 93 mg tid; >55 kg: 124 mg tid [9,14]. Therapy was discontinued in case of withdrawal of informed consent, safety concerns, investigator decision, participation in another interventional study, pregnancy, death, or loss to follow-up.

2.4. Safety evaluations

Physicians were required to report safety based on AEs, special

situations (such as arimoclomol use during pregnancy, breastfeeding, or any misuse), and a predefined laboratory panel, as outlined in Supplementary Table S1. All events were classified using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs and special situations had to be reported by the treating physician within 1 business day of becoming aware of the event. Serious AEs (SAEs) were to be reported immediately and no later than 24 h after first awareness. Physicians were required to provide information preferably with a diagnosis or with signs and symptoms, start and stop dates, severity, causal relationship to arimoclomol and outcome.

For new participants initiating arimoclomol (excluding those transitioning from phase 2/3 study), a standard laboratory panel (renal, hepatic, hematology) was performed at Baseline and Months 1, 4, and 7. Laboratory findings significantly outside the normal range required safety evaluation and Sponsor Medical Team review prior to resupply.

2.5. Outcome measures

2.5.1. 5DNPCCSS

The 5DNPCCSS is an NPC-specific and validated measure of disease progression comprising the 5 most clinically relevant domains (cognition, speech, swallow, fine motor skills and ambulation) of the 17-domain NPCCSS, as identified by treating physicians and patient/caregivers [11,15]. Each domain is rated on a 0–5 scale, with higher scores indicating more severe clinical impairment. Previous research has shown that a 1-point change in the score can be considered clinically significant [11]. The 5DNPCCSS was suggested to be performed at the investigator's discretion at clinic visits and according to local standard of care. Rater training was provided to ensure consistent and reliable scoring.

2.5.2. R4DNPCCSS

The R4DNPCCSS was introduced as a *post-hoc* primary outcome measure in the NPC-002 clinical trial to more accurately assess disease progression in a heterogeneous group of individuals with NPC and to align with regulatory guidance [13]. It includes speech, swallow, fine motor skills and ambulation domains. The cognition domain was removed to address concerns regarding the potential impact of patient environment on cognition outcomes and the complexity of assessing cognition over the broad age range of individuals included. The scoring algorithm of the swallow domain of the R4DNPCCSS was optimized to provide a more linear interpretation of swallowing dysfunction.

2.6. Statistical analysis

Descriptive statistics were performed, comprising the mean, standard deviation (SD), median, and range. Effectiveness was assessed by comparing 5DNPCCSS and R4DNPCCSS scores at Baseline and follow-up. To summarize longer-term trends, a subset of participants with a Baseline 5DNPCCSS assessment and at least 1 year of follow-up were analyzed. Because the timing of clinical assessments varied across participants, assessment windows were defined based on the time period after first dose as follows: Year 1 (Days 183–548), Year 2 (Days 549–914), Year 3 (Days 915–1280), and Year 4 (Days 1281–1646). If multiple assessments occurred within a given window, the value closest to the midpoint of that window was used for analysis. Subgroup analyses were performed according to miglustat use (defined as any recorded concomitant use overlapping an assessment window), age at treatment initiation (<18 years and ≥ 18 years), and phenotype based on neurological onset (late-infantile [≥2–<6 years], juvenile [≥6–16 years], and adult [≥16 years]). Due to the low number of participants with early-onset NPC (<2 years at neurological onset), no subgroup analysis was performed for this group. Comparisons between groups and across timepoints were descriptive and observational only, in accordance with the prespecified statistical analysis plan and the real-world, non-interventional design of the EAP.

3. Results

3.1. EAP population

A total of 111 participants from 14 sites were enrolled in the EAP. Of these, 110 (99.1%) were treated with arimoclomol and 109 (98.2%) consented to real-world data collection, allowing for inclusion in the main efficacy analysis (Fig. 1).

Enrollment began in 2020 and continued on a rolling basis until arimoclomol approval, resulting in variable follow-up durations across participants (Supplementary Table S2). Only the 23 participants enrolled in 2020 were eligible to complete 4 years of follow-up. While the 20 participants who completed Baseline and Year 4 5DNPCCSS assessments may only represent 18.3% of the overall population, they represent 87% of the participants who could have completed 4 years of follow-up.

At the time of commercialization of arimoclomol, 81 of 109 participants (74.3%) were still in the EAP; all of them transitioned to commercial treatment when it became available, which was the most common reason for discontinuation from the EAP. Other reasons for study discontinuation were death not related to treatment with arimoclomol ($n = 12$) and AEs ($n = 5$). Four participants discontinued from the EAP to initiate treatment with another investigational treatment for NPC.

Table 1 presents demographics and Baseline characteristics for the overall group and key subgroups. The overall group demographics were well balanced with 52 female (47.7%) participants, and 53 (48.6%) adult participants (≥18 years of age). The mean (SD) age at diagnosis was 16.4 (13.0) in the overall group. Information about age at neurological onset was available for 87 participants, with 6 having early-infantile (6.9%), 22 late-infantile (25.3%), 30 juvenile (34.5%), and 29 adult-onset NPC (33.3%). Genetic confirmation of NPC was available for 101 participants, all of whom were identified as having *NPC1*. The mean (SD) age at treatment initiation was 19.9 (13.1) years for the overall group, with ages ranging from 2.0 to 64.5 years. Among participants with known final dose dates, exposure to arimoclomol ranged from 15 to 1622 days (4.4 years), with a mean of 820 days (2.2 years). Overall, 71 participants (65%) received miglustat alongside arimoclomol at some point during the EAP (arimoclomol + miglustat group). Mean Baseline 5DNPCCSS and R4DNPCCSS scores were 11.0 and 8.1, respectively, with scores spanning the full range from 0 to the maximum value for both severity scales.

Adults had a slightly longer mean duration of arimoclomol exposure than pediatric participants (888 vs. 760 days) and a slightly higher mean Baseline 5DNPCCSS score (11.9 vs. 10.1), reflecting more advanced neurologic disease. The arimoclomol only group was older at diagnosis (mean age: 19.2 vs. 15.0 years) and at treatment initiation (22.1 vs. 18.7 years, respectively) and had shorter mean exposure time than the arimoclomol + miglustat group (668 days vs. 897 days).

3.2. Concomitant NPC-specific medication use during the EAP

About half of the participants ($n = 57$; 52.3%), equally distributed between the pediatric and the adult groups, received miglustat in combination with arimoclomol at treatment initiation. Mean and median exposure to miglustat at treatment initiation were 1018 days and 322 days, respectively. Six participants (2 pediatric and 4 adult) reported use of levacetylleucine (Aqneursa®) during the EAP, all after both levacetylleucine and arimoclomol had received FDA approval. In four participants with known start dates, the mean duration of combined levacetylleucine and arimoclomol treatment was 54 days (range 13–112 days). No AEs were reported for these participants during the time they were on concomitant levacetylleucine treatment.

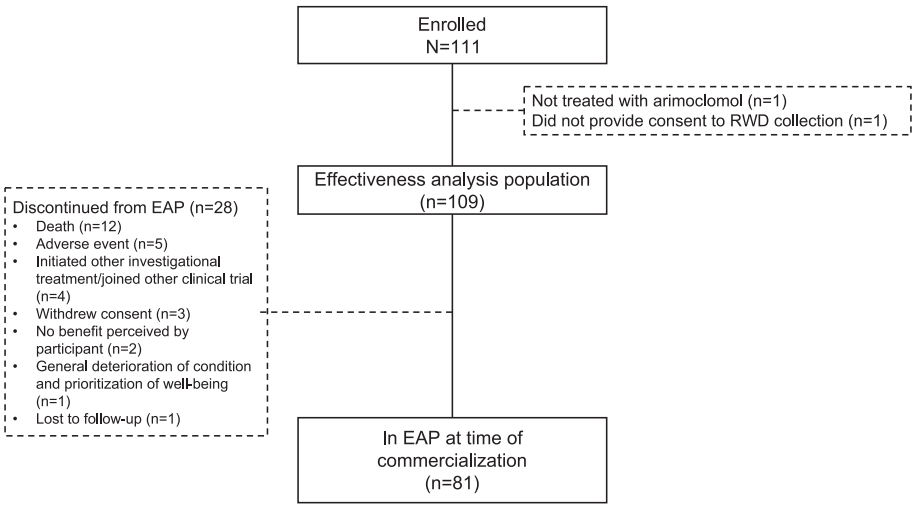

Fig. 1. Disposition of participants.
RWD: real-world data.

Table 1
Demographics and treatment characteristics of participants in the arimoclomol EAP.

Demographic variable	Overall ($N = 109$)	Treatment subgroups		Age at treatment initiation subgroups	
		Arimoclomol only ($N = 38$)	Arimoclomol + miglustat ($N = 71$)	Pediatric ($N = 56$)	Adult ($N = 53$)
Gender – n (%)					
Male	57 (52.3)	22 (57.9)	35 (49.3)	29 (51.8)	28 (52.8)
Female	52 (47.7)	16 (42.1)	36 (50.7)	27 (48.2)	25 (47.2)
Age at diagnosis (years)					
n	106	36	70	54	52
Mean (SD)	16.4 (13.0)	19.2 (15.6)	15.0 (11.2)	7.2 (4.6)	26.0 (11.9)
Median (min, max)	12.0 (0.0, 62.0)	13.2 (0.0, 62.0)	12.0 (0.1, 43.0)	8.0 (0.0, 15.0)	24.8 (1.8, 62.0)
Age at treatment initiation (years)					
n	109	38	71	56	53
Mean (SD)	19.9 (13.1)	22.1 (15.4)	18.7 (11.6)	9.4 (4.7)	31.1 (9.2)
Median (min, max)	17.3 (2.0, 64.5)	17.5 (2.0, 64.5)	17.3 (2.2, 43.0)	9.6 (2.0, 17.8)	29.8 (18.0, 64.5)
Duration of treatment with arimoclomol (days)[a]					
n	102	34	68	52	50
Mean (SD)	820 (539)	668 (566)	897 (513)	760 (536)	883 (541)
Median (min, max)	836 (15, 1622)	460 (15, 1622)	1038 (54, 1590)	735 (15, 1560)	937 (71, 1622)
5DNPCCSS score at treatment initiation					
n	100	36	64	52	48
Mean (SD)	11.0 (6.2)	11.1 (6.9)	11.0 (5.7)	10.1 (6.9)	11.9 (5.2)
Median (min, max)	10.0 (0, 25)	10.0 (0, 25)	10.0 (0, 25)	9.0 (0, 25)	11.0 (1, 25)
R4DNPCCSS score at treatment initiation					
n	100	36	64	52	48
Mean (SD)	8.1 (5.0)	8.3 (5.6)	7.9 (4.6)	7.4 (5.6)	8.8 (4.2)
Median (min, max)	7.0 (0,20)	7.5 (0, 20)	7.0 (0, 20)	6.0 (0, 20)	8.5 (0, 20)

5DNPCCSS: 5-domain NPC Clinical Severity Scale; EAP: Early Access Program; max: maximum; min: minimum; N indicates the number of participants who could be included in the overall or subgroup analyses based on availability of data; n: number of participants with available data; R4DNPCCSS: rescored 4-domain NPC Clinical Severity Scale; SD: standard deviation.

[a] Duration of exposure is defined as time on treatment from the date of treatment initiation to final dose date of arimoclomol in the EAP.

3.3. Safety

A total of 248 AEs were reported during the EAP (Table 2). Of these, 241 were classified as treatment-emergent based on known date of administration. Thirteen participants (12.8%) reported a total of 17 AEs deemed related to arimoclomol (Supplementary table S3). The most frequently reported treatment-related AEs by System Organ Class (SOC) were gastrointestinal disorders (5 events in 5 participants [4.6%]) and investigations (including abnormalities in laboratory test results, physical examination findings and imaging results; 5 events in 4 participants [3.7%]). The most frequent AEs by Preferred Term (PT) were diarrhea, increased blood creatinine, and rash (Supplementary table S3). At the conclusion of the EAP, 9 treatment-related AEs were recovered/resolved, 3 were recovering/resolving, 4 were not recovered/not resolved, and the status of 1 was unknown. None were deemed SAEs. AEs occurred with similar distribution among gender and age groups (Supplementary table S3).

Five participants (4.6%) in the arimoclomol-only group experienced

Table 2
Summary of adverse events in participants exposed to arimoclomol during the EAP ($N = 109$).

	Overall (N = 109) n (%) e
Any AE	109 (100) 248
Treatment-related AEs	13 (11.9) 17
Any SAEs	36 (33.0) 95
Treatment-related SAEs	0
AEs that led to discontinuation of arimoclomol	5 (4.6) 5
Deaths	12 (11.0)
Most frequently reported treatment-related AEs[a]	
Diarrhea	3 (2.8) 3
Increased blood creatinine	2 (1.8) 2
Rash	2 (1.8) 2

AE: adverse event; e: incidence; EAP: Early Access Program; n: number of participants; SAE: serious adverse event.
[a] Treatment-related AEs occurring in >1 participant are included.

5 AEs that led to discontinuation of arimoclomol: upper abdominal pain, diarrhea, nervous system disorder, tremor, and agitation. Of these, diarrhea, upper abdominal pain, and agitation were deemed related to arimoclomol.

A total of 95 AEs in 36 (33.0%) participants, including 12 deaths (11.0%), were classified as SAEs. None of these were classified by the investigator as related to arimoclomol. Ages at death varied from 6 to 42 years. The latest recorded 5DNPCCSS and R4DNPCCSS total scores before death ranged from 10 to 25 and from 6 to 20, respectively. The most common causes of death were acute respiratory failure ($n = 4$), pneumonia ($n = 3$), and sepsis ($n = 2$) (Supplementary table S4).

3.4. Outcome measures

3.4.1. 5DNPCCSS score

Of the 109 exposed participants, 100 (92%) had a Baseline 5DNPCCSS assessment. Mean total score fluctuated slightly from year to year but remained relatively stable throughout the duration of the program. In the overall group, mean (SD) total scores were 11.0 (6.15) at Baseline ($n = 100$), 11.2 (6.57) at Year 1 ($n = 86$), 11.3 (6.00) at Year 2 ($n = 50$), 10.9 (6.62) at Year 3 ($n = 43$), and 12.0 (7.32) at Year 4 ($n = 22$) (Fig. 2; Supplementary Table S5).

Baseline total 5DNPCCSS total scores were generally similar across age at treatment-initiation subgroups, except for lower mean (SD) Baseline scores in pediatric versus adult participants (10.1 [6.86] vs 11.9 [5.17]). At later timepoints, including Year 4, the rolling enrollment design of the EAP and subsequent transition to commercial treatment resulted in fewer participants contributing data and a greater variability. At Year 4, mean (SD; range) scores were 13.9 (9.88; 2–25) in the pediatric group (n = 8) and 10.9 (5.53; 6–22) in the adult subgroup ($n = 14$). By treatment group, mean (SD; range) scores were 11.1 (6.89; 0–25) at Baseline and 14.2 (8.98; 2–25) at Year 4 in the arimoclomol-only group, and 11.0 (5.74; 0–25) at Baseline and 11.2 (6.75; 2–25) at Year 4 in the arimoclomol + miglustat group, with variability observed year-to-year (Fig. 3; Supplementary Table S5).

Individual domain results remained relatively stable for the duration of the EAP with no single domain driving changes in the total 5DNPCCSS score (Supplementary Table S6).

To characterize longer-term trends, an analysis of participants with both Baseline and at least 1 follow-up 5DNPCCSS assessments was performed. Of these, 78 participants (71.6%) completed Baseline and Year 1 assessments. Of the 23 participants enrolled in 2020, 20 (87%) remained in the EAP throughout its duration and completed assessments at Baseline and Year 4 (Fig. 4). Baseline characteristics of participants included in the long-term analysis were comparable to those of the overall group (Supplementary table S7). This analysis demonstrated minimal changes in disease severity over time (Fig. 4; Supplementary Table S8). Among the 78 participants with Baseline and Year 1 data, mean (SD) scores were 11.2 (6.33) at Baseline and 11.1 (6.63) at Year 1. Similar patterns were observed for participants with Baseline and Year 2, Year 3, or Year 4 assessments. For the 20 participants with Baseline and Year 4 data, mean (SD) scores were unchanged at 11.6 (5.75) and 11.6 (6.98), respectively. Results of subgroup analyses by treatment and age at treatment initiation for participants with both Baseline and at least 1 follow-up 5DNPCCSS assessments are presented in Supplementary Table S9, showing similar results as the subgroup analyses considering all available data.

3.4.2. R4DNPCCSS score

Overall, R4DNPCCSS total scores followed similar longitudinal patterns as total 5DNPCCSS scores. Across all participants, mean (SD) total R4DNPCCSS score was 8.1 (4.98) at Baseline ($n = 100$), 8.2 (5.41) at Year 1 ($n = 86$), 8.2 (4.95) at Year 2 ($n = 50$), 8.2 (5.53) at Year 3 ($n = 43$), and 9.0 (6.33) at Year 4 ($n = 22$) (Fig. 2 and Supplementary table S10).

Among the 78 participants with a Baseline assessment and Year 1 data, mean (SD) R4DNPCCSS scores were 8.2 (5.17) at Baseline and 8.1 (5.52) at Year 1. Similar patterns were observed for participants with Baseline and Year 2, Year 3, or Year 4 assessments. For the 20 participants with Baseline and Year 4 data, mean (SD) scores were unchanged

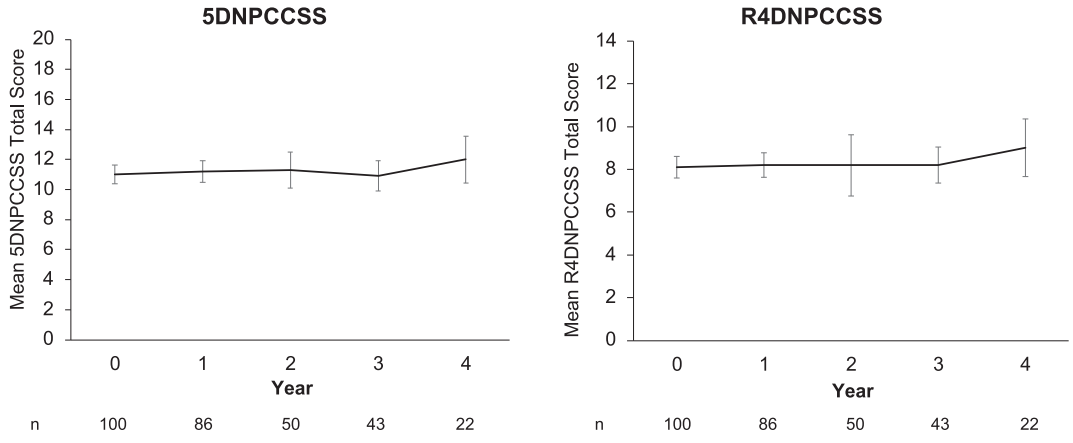

Fig. 2. Mean total (SE) 5DNPCCSS and R4DNPCCSS scores over time in the overall group.
5DNPCCSS: 5-domain NPC Clinical Severity Scale; n: number of participants with available data; R4DNPCCSS: rescored 4-domain NPC Clinical Severity Scale; SE: standard error.
Of the 109 exposed participants, 100 had a Baseline 5DNPCCSS score and are included in this analysis. Participants had different maximum possible follow-up durations depending on when they entered the EAP.

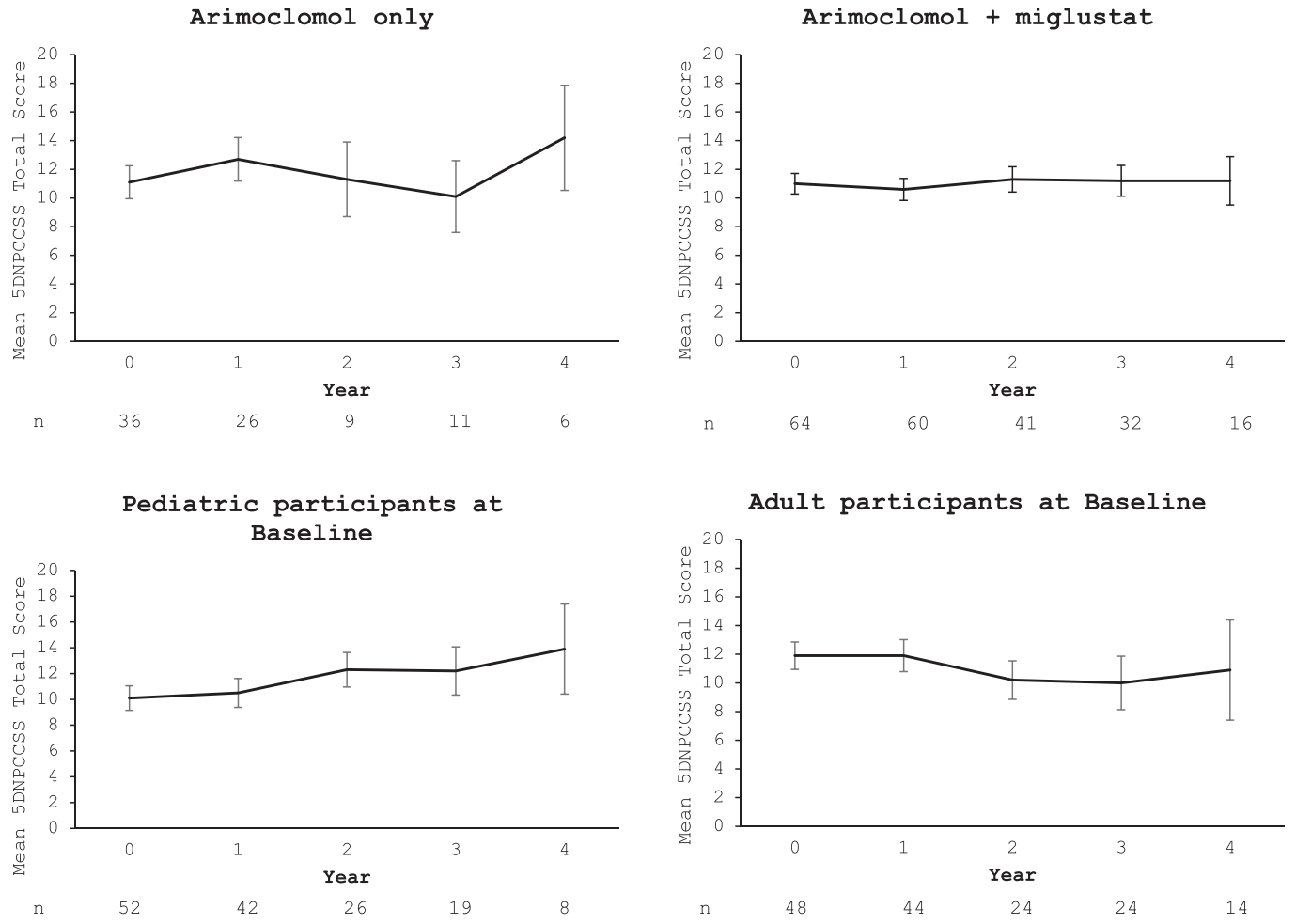

Fig. 3. Mean total (SE) 5DNPCCSS scores over time in age and treatment subgroups.
5DNPCCSS: 5-domain NPC Clinical Severity Scale; n: number of participants with available data; SE: standard error.
Of the 109 exposed participants, 100 had a Baseline 5DNPCCSS score and are included in this analysis. Participants had different maximum possible follow-up durations depending on when they entered the EAP.

at 8.7 (4.55) and 8.6 (6.13), respectively (Supplementary Table S11).

3.5. Phenotype subgroup analysis

Demographics and treatment characteristics of the phenotype subgroups, as well as total severity scores at Baseline and Year 1 are presented in Supplementary Table S12. Subgroup analyses were not performed for either early-infantile NPC or follow-up visits beyond 1 year as a result of small numbers of participants and missing data. For the late-infantile group, the mean (SD) age at onset of first neurological symptoms was 3.5 (1.2) years, mean age at diagnosis was 6.9 (5.4) years, and mean age at EAP enrollment (arimoclomol treatment initiation) was 10.5 (6.5) years, with a baseline 5DNPCCSS score of 12.5 (6.9). Mean (SD) Baseline 5DNPCCSS total scores were slightly lower in the adult- and juvenile-onset groups (11.5 [5.74] and 11.4 [5.16], respectively) than in the late-infantile group. Over the first year of treatment, mean (SD) 5DNPCCSS total scores changed from 12.5 (6.86) at Baseline to 13.9 (7.92) at Year 1 in the late-infantile group, remained stable in the juvenile group (Baseline: 11.4 [5.16], Year 1: 11.5 [4.63]), and decreased from 11.5 (5.74) to 10.9 (6.71) in the adult group (Supplementary Table S12 and Fig. S1). R4DNPCCSS total scores followed similar longitudinal patterns as total 5DNPCCSS scores (Supplementary Fig. S2).

4. Discussion

The US EAP provides first real-world evidence on the safety and effectiveness of arimoclomol in a broad and heterogeneous NPC population, with participants followed for up to 4 years. The EAP had ongoing enrollment until marketing approval by the FDA, at which point all patients enrolled in the EAP were transferred to commercial product. Prior to FDA approval in 2024, the program provided early access to arimoclomol for individuals with NPC who were unable to participate in clinical trials and, according to the clinical judgement of the treating physician, may benefit from treatment with arimoclomol. As a result, the EAP enrolled a broader and more heterogeneous population than the clinical trials, with a wider age range (including adults) and spectrum of disease severity, and more individuals not receiving miglustat, making these data more representative of the clinical diversity observed across the NPC population [1,6,7,16].

Overall, safety findings of the EAP were consistent with the pivotal NPC-002 clinical trial results, which demonstrated a favorable tolerability profile [9,10]. Arimoclomol was well tolerated for up to 4 years in the EAP, and no new safety signals were observed; importantly, none of the reported SAEs or deaths were considered related to treatment.

Effectiveness outcomes demonstrated that disease progression, as measured using the 5DNPCCSS and the R4DNPCCSS, fluctuated over time but overall remained relatively stable. In the overall EAP population, total 5DNPCCSS scores changed from 11.0 at Baseline to 12.0 at

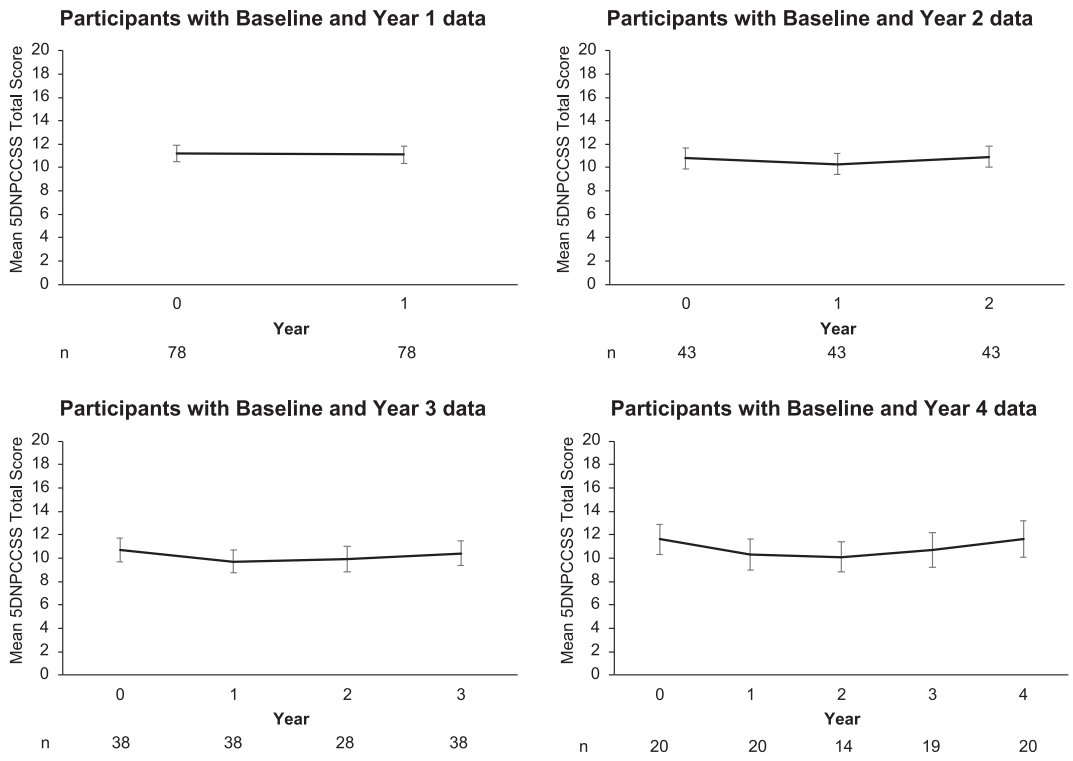

Fig. 4. 5DNPCCSS scores in participants with both Baseline and follow-up assessments at Year 1, 2, 3 and 4.
5DNPCCSS: 5-domain NPC Clinical Severity Scale; n: number of participants with available data; SE: standard error. Data of participants who contributed both Baseline and follow-up measurements at the corresponding time points are presented. Participants had different maximum possible follow-up durations depending on when they entered the EAP.

Year 4; R4DNPCCSS scores followed the same trend. Among participants with both a Baseline and at least 1 follow-up assessment, results were similarly consistent, including in those followed for 4 years.

Subgroup analyses by treatment and age at treatment initiation provided new insights into the effectiveness of arimoclomol across different patient populations. Miglustat has been reported to attenuate disease progression in patients with NPC, although evidence for efficacy in patients with early-infantile onset remains limited [17,18]. The NPC-002 clinical trial demonstrated a clear additional benefit in patients receiving both arimoclomol and miglustat compared to those on miglustat alone [9,10]. Similarly, participants receiving arimoclomol in combination with miglustat in the US EAP showed stabilization of disease progression, consistent with results from previous clinical trials [9,10]. Overall, these findings reinforce the additive benefits of a combined therapeutic approach due to a complementary mechanism of action of both therapies.

As previously reported, the subgroup of participants not on miglustat represents a highly heterogeneous group [9], likely contributing to greater variability observed compared with those on concomitant miglustat. It should be noted that participants in the arimoclomol only group were slightly older at diagnosis (19.2 vs 15.0 years) and at treatment initiation (22.1 vs 18.7 years), which may have influenced the results. The limited number of participants receiving arimoclomol monotherapy in the NPC-002 trial precluded a meaningful assessment of this population. Emerging real-world evidence from the US EAP, in which approximately one-third of participants were not receiving miglustat, provides some real-world insight into outcomes in patients in whom miglustat is not used as part of routine care. Mean 5DNPCCSS scores in this population were 11.1 at Baseline and 14.2 at Year 4, corresponding to a mean annual progression rate of 0.8, though with great variability over time and a limited number of participants with more than 1 year of follow-up. Further studies in a larger population and with longer follow-up are therefore warranted to confirm the observed results.

Among pediatric participants, 5DNPCCSS total scores aligned with results from the Phase 2/3 NPC-002 study, in which children and adolescents receiving arimoclomol demonstrated slower disease progression compared with patients in the placebo arm, and its open-label extension [9,10]. The increase in disease severity for the pediatric group is anticipated with the progressive disease severity of NPC and remains below the 1.5-point annual progression rate reported for untreated pediatric patients in the NPC-001 natural history study, in which 30 of 36 participants received miglustat [9,12]. The EAP also provides the first published real-world data on arimoclomol use in adults with NPC, a population not included in the clinical trials [9]. Adults, who represented nearly half of the EAP population, exhibited low progression rates. However, lack of published natural history data for adults with NPC limits interpretation of treatment effectiveness in this group. The differences in progression rates observed between children and adults reflect phenotypic differences between these populations. Patients aged 2–18 years present with a broad spectrum of disease manifestations, ranging from mild to aggressive and early fatal forms, while adults, likely with adult-onset neurological disease, generally demonstrate slower progression than earlier-onset cases [1,4,19].

Phenotype subgroup analyses confirmed a higher disease burden in participants with late-infantile neurological onset versus later-onset groups, as reflected by higher Baseline severity scores. It should be noted that among participants with the late-infantile phenotype, first neurological symptoms appeared at a mean age of 3.5 years, while mean age at diagnosis was 6.9 years. These findings underscore the continued unmet need to reduce diagnostic delay and accelerate treatment initiation in this highly vulnerable patient population. The progression observed in the first year of treatment in the late-infantile subgroup is consistent with expectations, as this phenotype is historically associated with more rapid disease progression [4]. The juvenile subgroup demonstrated relatively limited progression over 1 year compared to an

expected progression based on natural history data [9,12], a finding consistent with treatment-associated attenuation of disease progression relative to expected disease trajectories. Individuals with adult-onset NPC are expected to progress slowly [19]; in this cohort, progression was minimal and appeared to improve overall. Notably, age at onset of neurological symptoms was not a required EAP data field and was therefore unavailable for some participants. Incomplete phenotype data, combined with the rolling enrollment design of the EAP and the resulting variation in follow-up duration across participants (Supplementary table S2), limited the number of participants available for these analyses. Consequently, subgroup analyses for the early-infantile subgroup were not feasible, and fewer participants had the opportunity to accrue longer-term follow-up within the EAP. This resulted in an insufficient number of evaluable participants for meaningful analyses beyond 1 year for the remaining phenotype subgroups. While the initial results and data look promising, further real-world evidence is needed to confirm these findings and to characterize treatment effects across phenotypes [1,17,19].

Some limitations of the current analysis should be acknowledged. As a real-world observational program, the EAP was subject to inconsistent reporting, variability in data quality, irregular assessment timing, and missing data, all of which may have reduced the robustness of the findings. Interpretation is also complicated by the inherent clinical heterogeneity and non-linear progression of NPC and by Baseline disease progression scores spanning the full severity range, introducing potential floor and ceiling effects. The longitudinal overall and subgroup analyses were further constrained by the rolling enrollment design of the EAP and subsequent transition to commercial treatment, resulting in fewer participants having the opportunity to accrue longer follow-up within the program. A total of 23 participants were enrolled in 2020, making them eligible (based on timing of enrollment) to be included in the 4-year analysis. Of these, 20 (87%) had both Baseline and Year 4 data, providing extended safety and effectiveness evidence. Mean age and disease severity at treatment initiation in this subgroup were comparable to the overall population, suggesting minimal selection bias. Despite observed stability in outcomes over time, no formal statistical analyses were performed. This descriptive approach was pre-specified due to the absence of a control group, potential selection bias, heterogeneous clinical follow-up, and incomplete longitudinal data inherent to the observational design.

5. Conclusions

The EAP provides 4 years of real-world evidence supporting the safety and effectiveness profile of arimoclomol in a broad NPC population, spanning a wide age range and a broad spectrum of disease severity. These findings complement and extend clinical trial results, reinforcing the durable impact of arimoclomol, especially in combination with miglustat, and its role as an important therapeutic option in the management of NPC. While outcomes in the pediatric group reinforce the results of the phase 2/3 clinical trial, the adult data provides the most robust data and first published real-world insights in this understudied NPC population. Moreover, these real-world findings are consistent with the disease stabilizing effect of arimoclomol demonstrated in the phase 2/3 clinical trial. Continued research in clinical practice over longer follow-up periods especially in the adult population will be important to strengthen and refine these observations and to further characterize long-term outcomes in routine clinical practice.

CRediT authorship contribution statement

Elizabeth Berry-Kravis: Investigation, Data curation, Writing – review & editing. **Nicolas J. Abreu:** Investigation, Data curation, Writing – review & editing. **Walla Al-Hertani:** Investigation, Data curation, Writing – review & editing. **Radhika Dhamija:** Investigation, Data curation, Writing – review & editing. **Can Ficicioglu:** Investigation, Data curation, Writing – review & editing. **Kristina Julich:** Investigation, Data curation, Writing – review & editing. **Caroline Hastings:** Investigation, Data curation, Writing – review & editing. **Paul R. Hillman:** Investigation, Data curation, Writing – review & editing. **Nancy Leslie:** Investigation, Data curation, Writing – review & editing. **Damara Ortiz:** Investigation, Data curation, Writing – review & editing. **Melinda Peters:** Investigation, Data curation, Writing – review & editing. **Paula Schleifer:** Investigation, Data curation, Writing – review & editing. **Ronan O'Reilly:** Validation, Methodology, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Blair C. Ornstein:** Validation, Methodology, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Christine í Dali:** Validation, Methodology, Formal analysis, Data curation, Conceptualization, Writing – review & editing.

Ethics approval and consent to participate

The study was approved by the relevant independent ethics committees and/or institutional review boards, and written informed consent was obtained at enrollment from either the patient or their legal guardian.

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Declaration of competing interest

Elizabeth Berry-Kravis has received funding from Acadia, Arbor, Biogen, BioMarin, GeneTx, Engrail, Erydel, Healx, Intrabio, Ionis, Jaguar, Kisbee, Mazhi, Mirum, Moment Biosciences Neuren, Neurogene, Novartis, Ono, Orphazyme/Kempharm/Zevra, Oak Hill, Praxis, PTC Therapeutics, PYC Therapeutics, Quralis, Roche, Taysha, Tetra, Shionogi, Ultragenyx, Vtesse/Sucampo/Mallinckrodt/Mandos Pharmaceuticals, Yamo, and Zynerba/Harmony, to consult on trial design or run clinical trials in genetic neurodevelopmental or neurodegenerative disorders, all of which is directed to RUMC in support of rare disease programs; she receives no personal funds and RUMC has no relevant financial interest in any of the commercial entities listed;

Nicolas J. Abreu has received funding from Takeda Pharmaceuticals, BioMarin Pharmaceutical, Sanofi, Sangamo Therapeutics, and Amicus Therapeutics, has served on advisory boards for Sanofi and Beren Therapeutics, and serves as a consultant to Takeda Pharmaceuticals.

Walla Al-Hertani served as advisor to Agyany Pharma, Amicus Therapeutics, Azafaros, CycloTherapeutics, HCU Network America, Intrabio, National Nicmann-Pick Disease Foundation, Takeda Pharmaceuticals, Ultragenyx, as PI for Beam Therapeutics, Genetics evaluation committee for Denali Therapeutics, collaborator for Sanofi, and advisor and steering committee for Zevra Therapeutics.

Radhika Dhamija has no conflicts of interest related to this publication.

Can Ficicioglu has no conflicts of interest related to this publication.

Kristina Julich has served as a consultant for Zevra Therapeutics and Cyclo Therapeutics. She is a fellow of the Clarke Family Foundation.

Caroline Hastings served as a PI on the EAP and advisory board of Zevra, previously on advisory board of IntraBio, global (and site) PI for current open Phase 3 trial in NPC investigating intravenous HPBCD and advisory board at CycloTherapeutics, site PI for current open Phase 3 trial for NPC and GM1/2 investigating Nizubaglustat and advisory board at Azafaros.

Paul R. Hillman serves on the speaker bureau and advisory board for Mirum Pharmaceuticals, advisory boards for Chiese USA and Amicus Therapeutics, and speaker bureau for Sanofi and Zevra Pharmaceuticals.

Nancy Leslie has no conflicts of interest related to this publication.

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Melinda Peters has served at advisory board for Zevra Therapeutics and CycloTherapeutics.

Paula Schleifer has served on advisory boards and or as a consultant for Sanofi, Taysha Gene Therapies, Acadia Pharmaceuricals, Zevra Therapeutics, and served as a site PI for Mandos Health, Ultragenix, Ionis Pharmaceuticals, Neurogene and for the US EAP for Zevra Therapeutics.

Ronan O'Reilly is a consultant of Zevra Therapeutics Inc.

Blair C. Ornstein is a consultant of Zevra Therapeutics Inc.

Christine í Dali is an employee and shareholder of Zevra Denmark A/S.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2026.110223.

Data availability

The data that support the findings of this trial are available upon reasonable request on a case-by-case basis from Zevra but restrictions apply to the availability of these data, which were used under license for the current trial, and so are not publicly available. Data requests that risk sharing participant level data or proprietary information will not be approved.

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Supplementary materials

Table S1. Real-world data collected in the EAP

Timing	Assessment
Baseline only	Demographics
	Non-NPC medical history/NPC disease history
	Height (if <18 years)
	Weight
	General physical examination
Baseline; Month 1, 4 and 7	Laboratory tests (renal, hepatic, hematology)[a]
	Pregnancy test for treatment initiation, if required
Within 1 business day after event[b]	AEs, special situations
Based on site and local standard of care	Weight
	Concomitant Medication
	Arimoclomol dosing
	Patient-Reported Outcomes (PROs)[c]
	- Questionnaire on Quality of Life and Activities of Daily Living
	- Financial Impact of Disease
	Physician-Reported Outcomes
	- 5DNPCCSS and R4DNPCCSS

5DNPCCSS: 5-domain NPC Clinical Severity Scale; EAP: Early Access Program; NPC: Niemann-Pick disease type C; R4DNPCCSS: rescored 4-domain NPC Clinical Severity Scale

[a]Laboratory tests included creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, platelets, haemoglobin, differential leukocyte count (bands, neutrophils, basophils, eosinophils, monocytes, and lymphocytes), expressed as a percentage of white blood cells

[b]Serious adverse events had to be reported within 24 hours after the event

[c]Insufficient data collection precluded analysis of PROs

Table S2. Number of participants in the EAP with available treatment initiation and stop dates by year of enrollment

Year of enrollment, n (%)	Overall (N=102)	Arimoclomol only (N=34)	Arimoclomol + miglustat (N=68)	Pediatric (N=52)	Adult (N=50)
2020	23 (22.5)	10 (29.4)	13 (19.1)	10 (19.2)	13 (26.0)
2021	35 (34.3)	8 (23.5)	27 (39.7)	15 (28.8)	20 (40.0)
2022	10 (9.8)	3 (8.8)	7 (10.3)	4 (7.7)	6 (12.0)
2023	17 (16.7)	5 (14.7)	12 (17.6)	11 (21.2)	6 (12.0)
2024	17 (16.7)	8 (23.5)	9 (13.2)	12 (23.1)	5 (10.0)

Table S3. Adverse events related to treatment by System Organ Class and Preferred Term (all participants exposed to arimoclomol; N=109)

SOC PT	Overall (N=109) n (%) e	Arimoclomol only (N=38) n (%) e	Arimoclomol + miglustat (N=71) n (%) e	Pediatric (N=56) n (%) e	Adult (N=53) n (%) e	Male (N=57) n (%) e	Female (N=52) n (%) e
Subjects with any AE related to arimoclomol	13 (11.9) 17	6 (15.8) 6	8 (11.3) 12	8 (14.3) 9	6 (11.3) 9	7 (12.3) 10	7 (13.5) 8
Gastrointestinal disorders	5 (4.6) 5	2 (5.3) 2	3 (4.2) 3	3 (5.4) 3	2 (3.8) 2	3 (5.3) 3	2 (3.8) 2
Diarrhea	3 (2.8) 3	1 (2.6) 1	2 (2.8) 2	2 (3.6) 2	1 (1.9) 1	2 (3.5) 2	1 (1.9) 1
Abdominal pain upper	1 (0.9) 1	1 (2.6) 1	0	1 (1.8) 1	0	0	1 (1.9) 1
Breath odor	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	1 (1.8) 1	0
Investigations	4 (3.7) 7	2 (5.3) 2	2 (2.8) 5	2 (3.6) 2	2 (3.8) 5	3 (5.3) 6	1 (1.9) 1
Blood creatinine increased	2 (1.8) 2	1 (2.6) 1	1 (1.4) 1	1 (1.8) 1	1 (1.9) 1	1 (1.8) 1	1 (1.9) 1
Aspartate aminotransferase increased	1 (0.9) 1	1 (2.6) 1	0	1 (1.8) 1	0	1 (1.8) 1	0
Lymphocyte count decreased	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	1 (1.8) 1	0
Neutrophil count increased	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	1 (1.8) 1	0

SOC PT	Overall (N=109) n (%) e	Arimoclomol only (N=38) n (%) e	Arimoclomol + miglustat (N=71) n (%) e	Pediatric (N=56) n (%) e	Adult (N=53) n (%) e	Male (N=57) n (%) e	Female (N=52) n (%) e
Platelet count decreased	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	1 (1.8) 1	0
White blood cell count increased	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	1 (1.8) 1	0
Skin and subcutaneous tissue disorders	2 (1.8) 2	0	2 (2.8) 2	1 (1.8) 1	1 (1.9) 1	0	2 (3.8) 2
Rash	2 (1.8) 2	0	2 (2.8) 2	1 (1.8) 1	1 (1.9) 1	0	2 (3.8) 2
General disorders and administration site conditions	1 (0.9) 1	0	1 (1.4) 1	1 (1.8) 1	0	0	1 (1.9) 1
Fatigue	1 (0.9) 1	0	1 (1.4) 1	1 (1.8) 1	0	0	1 (1.9) 1
Infections and infestations	1 (0.9) 1	0	1 (1.4) 1	1 (1.8) 1	0	0	1 (1.9) 1
Upper respiratory tract infection	1 (0.9) 1	0	1 (1.4) 1	1 (1.8) 1	0	0	1 (1.9) 1
Psychiatric disorders	1 (0.9) 1	1 (2.6) 1	0	0	1 (1.9) 1	1 (1.8) 1	0
Agitation	1 (0.9) 1	1 (2.6) 1	0	0	1 (1.9) 1	1 (1.8) 1	0

AE: adverse event; e: incidence; n: number of patients with available data; PT: Preferred Term; SOC: System Organ Class

Table S4. Fatal adverse events by System Organ Class and Preferred Term (all exposed participants)

SOC PT	Overall (N=109) n (%) e	Arimoclomol only (N=38) n (%) e	Arimoclomol + miglustat (N=71) n (%) e	Pediatric (N=56) n (%) e	Adult (N=53) n (%) e	Male (N=57) n (%) e	Female (N=52) n (%) e
Subjects with any fatal AE	12 (11.0) 17	3 (7.9) 4	9 (12.7) 13	4 (7.1) 5	8 (15.1) 12	4 (7.0) 7	8 (15.4) 10
Infections and infestations	6 (5.5) 7	2 (5.3) 2	4 (5.6) 5	0	6 (11.3) 7	3 (5.3) 4	3 (5.8) 3
Sepsis	2 (1.8) 2	1 (2.6) 1	1 (1.4) 1	0	2 (3.8) 2	2 (3.5) 2	0
COVID-19	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	0	1 (1.9) 1
Influenza	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	1 (1.8) 1	0
Pneumonia aspiration	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	0	1 (1.9) 1
Pneumonia bacterial	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	0	1 (1.9) 1
Pneumonia haemophilus	1 (0.9) 1	1 (2.6) 1	0	0	1 (1.9) 1	1 (1.8) 1	0
Respiratory, thoracic and mediastinal disorders	6 (5.5) 6	1 (2.6) 1	5 (7.0) 5	2 (3.6) 2	4 (7.5) 4	3 (5.3) 3	3 (5.8) 3
Acute respiratory failure	4 (3.7) 4	1 (2.6) 1	3 (4.2) 3	1 (1.8) 1	3 (5.7) 3	2 (3.5) 2	2 (3.8) 2
Choking	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	1 (1.8) 1	0
Pneumonitis	1 (0.9) 1	0	1 (1.4) 1	1 (1.8) 1	0	0	1 (1.9) 1
General disorders and administration site conditions	3 (2.8) 3	1 (2.6) 1	2 (2.8) 2	2 (3.6) 2	1 (1.9) 1	0	3 (5.8) 3
Death	2 (1.8) 2	1 (2.6) 1	1 (1.4) 1	2 (3.6) 2	0	0	2 (3.8) 2
Disease progression	1 (0.9) 1	0	1 (1.4) 1	0	1 (1.9) 1	0	1 (1.9) 1
Cardiac disorders	1 (0.9) 1	0	1 (1.4) 1	1 (1.8) 1	0	0	1 (1.9) 1
Cardio-respiratory arrest	1 (0.9) 1	0	1 (1.4) 1	1 (1.8) 1	0	0	1 (1.9) 1

AE: adverse event; e: incidence; n: number of patients with available data; PT: Preferred Term; SOC: System Organ Class

Table S5. Summary of 5DNPCCSS total scores over time (all exposed participants)

Assessment window Statistic	Overall (N=109)	Treatment subgroups		Age at treatment initiation subgroups	
		Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)	Pediatric (N=56)	Adult (N=53)
Treatment initiation (Baseline)					
n	100	36	64	52	48
Mean (SD)	11.0 (6.15)	11.1 (6.89)	11.0 (5.74)	10.1 (6.86)	11.9 (5.17)
Median	10.0	10.0	10.0	9.0	11.0
Min, Max	0, 25	0, 25	0, 25	0, 25	1, 25
Year 1					
n	86	26	60	42	44
Mean (SD)	11.2 (6.57)	12.7 (7.73)	10.6 (5.96)	10.5 (7.24)	11.9 (5.88)
Median	10.0	13.5	9.0	9.0	11.0
Min, Max	0, 25	1, 25	0, 25	0, 25	1, 25
Year 2					
n	50	9	41	26	24
Mean (SD)	11.3 (6.00)	11.3 (7.81)	11.3 (5.65)	12.3 (6.84)	10.2 (4.82)
Median	11.0	15.0	11.0	13.0	9.0
Min, Max	1, 25	1, 22	1, 25	1, 25	1, 22
Year 3					
n	43	11	32	19	24
Mean (SD)	10.9 (6.62)	10.1 (8.31)	11.2 (6.06)	12.2 (8.13)	10.0 (5.09)
Median	10.0	8.0	10.0	15.0	8.0
Min, Max	1, 25	1, 25	1, 22	1, 25	1, 22
Year 4					
n	22	6	16	8	14
Mean (SD)	12.0 (7.32)	14.2 (8.98)	11.2 (6.75)	13.9 (9.88)	10.9 (5.53)
Median	9.5	14.5	8.0	14.5	8.0
Min, Max	2, 25	2, 25	2, 25	2, 25	6, 22

5DNPCCSS: 5-domain NPC Clinical Severity Scale; Max, maximum; Min, minimum; n: number of patients with available data; SD: standard deviation

Of the 109 exposed participants, 100 had a Baseline 5DNPCCSS score and are included in this analysis.

Participants had different maximum possible follow-up durations depending on when they entered the EAP

Table S6. Summary of 5DNPCCSS by domain (all exposed participants)

Assessment window Statistic	Overall (N=109)	Treatment subgroups		Age at treatment initiation subgroups	
		Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)	Pediatric (N=56)	Adult (N=53)
Ambulation					
Treatment Initiation (Baseline)					
n	100	36	64	52	48
Mean (SD)	2.4 (1.63)	2.5 (1.86)	2.4 (1.51)	2.2 (1.66)	2.6 (1.60)
Median	2.0	2.0	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 1					
n	86	26	60	42	44
Mean (SD)	2.4 (1.66)	2.7 (1.99)	2.3 (1.49)	2.2 (1.73)	2.6 (1.59)
Median	2.0	4.0	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 2					
n	50	9	41	26	24
Mean (SD)	2.3 (1.54)	2.0 (1.94)	2.4 (1.46)	2.5 (1.65)	2.2 (1.43)
Median	2.0	2.0	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 4
Year 3					
n	43	11	32	19	24
Mean (SD)	2.4 (1.76)	2.3 (2.10)	2.4 (1.66)	2.4 (1.92)	2.4 (1.66)
Median	2.0	1.0	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 4					
n	22	6	16	8	14
Mean (SD)	2.4 (1.84)	3.2 (2.14)	2.1 (1.71)	2.8 (2.25)	2.2 (1.63)
Median	2.0	4.0	2.0	3.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Fine Motor Skills					
Treatment Initiation (Baseline)					
n	100	36	64	52	48

Assessment window Statistic	Overall (N=109)	Treatment subgroups		Age at treatment initiation subgroups	
		Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)	Pediatric (N=56)	Adult (N=53)
Mean (SD)	2.2 (1.52)	2.3 (1.75)	2.2 (1.39)	2.1 (1.62)	2.4 (1.41)
Median	2.0	2.0	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 1					
n	86	26	60	42	44
Mean (SD)	2.4 (1.57)	2.8 (1.85)	2.2 (1.40)	2.1 (1.62)	2.6 (1.50)
Median	2.0	3.0	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 2					
n	50	9	41	26	24
Mean (SD)	2.3 (1.51)	2.1 (2.09)	2.3 (1.39)	2.4 (1.63)	2.2 (1.40)
Median	2.0	2.0	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 3					
n	43	11	32	19	24
Mean (SD)	2.4 (1.69)	2.3 (2.15)	2.4 (1.54)	2.7 (1.91)	2.1 (1.47)
Median	2.0	2.0	2.0	4.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 4					
n	22	6	16	8	14
Mean (SD)	2.6 (1.73)	3.3 (1.86)	2.4 (1.67)	2.9 (2.10)	2.5 (1.56)
Median	2.0	4.0	2.0	3.0	2.0
Min, Max	0, 5	1, 5	0, 5	0, 5	1, 5
Cognition					
Treatment Initiation (Baseline)					
n	100	36	64	52	48
Mean (SD)	2.7 (1.48)	2.7 (1.72)	2.8 (1.34)	2.6 (1.53)	2.9 (1.43)
Median	3.0	3.0	3.0	3.0	3.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 1					

Assessment window Statistic	Overall (N=109)	Treatment subgroups		Age at treatment initiation subgroups	
		Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)	Pediatric (N=56)	Adult (N=53)
n	86	26	60	42	44
Mean (SD)	2.8 (1.47)	3.0 (1.64)	2.8 (1.40)	2.9 (1.39)	2.8 (1.55)
Median	3.0	3.0	3.0	3.0	3.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 2					
n	50	9	41	26	24
Mean (SD)	2.9 (1.37)	2.8 (1.64)	2.9 (1.33)	3.0 (1.33)	2.7 (1.43)
Median	3.0	4.0	3.0	3.0	3.0
Min, Max	0, 5	0, 4	0, 5	0, 5	0, 5
Year 3					
n	43	11	32	19	24
Mean (SD)	2.6 (1.51)	2.4 (1.80)	2.7 (1.42)	2.7 (1.56)	2.5 (1.50)
Median	3.0	1.0	3.0	3.0	3.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 4					
n	22	6	16	8	14
Mean (SD)	2.9 (1.52)	2.5 (2.07)	3.0 (1.32)	3.3 (1.58)	2.6 (1.50)
Median	3.0	2.5	3.0	3.5	3.0
Min, Max	0, 5	0, 5	0, 5	1, 5	0, 4
Speech					
Treatment Initiation (Baseline)					
n	100	36	64	52	48
Mean (SD)	1.6 (1.24)	1.7 (1.33)	1.6 (1.19)	1.6 (1.38)	1.7 (1.07)
Median	1.0	1.0	1.0	1.0	1.5
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 1					
n	86	26	60	42	44
Mean (SD)	1.6 (1.29)	1.9 (1.60)	1.5 (1.11)	1.6 (1.53)	1.6 (1.02)
Median	1.0	1.5	1.0	1.0	1.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5

Assessment window Statistic	Overall (N=109)	Treatment subgroups		Age at treatment initiation subgroups	
		Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)	Pediatric (N=56)	Adult (N=53)
Year 2					
n	50	9	41	26	24
Mean (SD)	1.8 (1.25)	2.0 (1.66)	1.7 (1.16)	2.1 (1.53)	1.4 (0.72)
Median	1.0	2.0	1.0	2.0	1.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 3
Year 3					
n	43	11	32	19	24
Mean (SD)	1.7 (1.13)	1.5 (1.51)	1.7 (1.00)	2.1 (1.49)	1.3 (0.55)
Median	1.0	1.0	1.0	2.0	1.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 2
Year 4					
n	22	6	16	8	14
Mean (SD)	2.0 (1.46)	2.5 (2.17)	1.8 (1.13)	2.5 (1.85)	1.6 (1.15)
Median	1.0	2.0	1.0	2.5	1.0
Min, Max	0, 5	0, 5	1, 5	0, 5	1, 5
Swallow					
Treatment Initiation (Baseline)					
n	100	36	64	52	48
Mean (SD)	2.0 (1.62)	1.9 (1.66)	2.0 (1.61)	1.6 (1.79)	2.4 (1.32)
Median	2.0	2.0	2.0	1.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 1					
n	86	26	60	42	44
Mean (SD)	2.0 (1.78)	2.3 (1.85)	1.9 (1.76)	1.7 (1.83)	2.3 (1.70)
Median	2.0	3.0	2.0	1.5	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 2					
n	50	9	41	26	24
Mean (SD)	2.1 (1.77)	2.4 (1.81)	2.0 (1.77)	2.4 (1.88)	1.7 (1.60)
Median	2.0	2.0	2.0	2.0	2.0

Assessment window Statistic	Overall (N=109)	Treatment subgroups		Age at treatment initiation subgroups	
		Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)	Pediatric (N=56)	Adult (N=53)
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 3					
n	43	11	32	19	24
Mean (SD)	1.9 (1.73)	1.6 (1.69)	2.0 (1.76)	2.2 (1.99)	1.7 (1.49)
Median	2.0	1.0	2.0	2.0	2.0
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5
Year 4					
n	22	6	16	8	14
Mean (SD)	2.1 (1.81)	2.7 (1.63)	1.9 (1.88)	2.5 (2.33)	1.9 (1.49)
Median	2.0	3.0	1.0	2.5	1.5
Min, Max	0, 5	0, 5	0, 5	0, 5	0, 5

5DNPCCSS: 5-domain NPC Clinical Severity Scale; Max: maximum; Min: minimum; n: number of patients with available data; SD: standard deviation
Of the 109 exposed participants, 100 had a Baseline 5DNPCCSS score and are included in this analysis
Participants had different maximum possible follow-up durations depending on when they entered the EAP

Table S7. Demographics and treatment characteristics of participants who completed Baseline and Year 1 assessments (Long-term follow-up population; N=78) and those who completed assessments at Baseline and Year 4 (Extended follow-up population; N=20)

Demographic variable	Long-term follow-up (N = 78)	Extended follow-up (N = 20)
Gender – n (%)		
Male	39 (50.0)	7 (35.0)
Female	39 (50.0)	13 (65.0)
Age at diagnosis (years)		
n	77	19
Mean (SD)	16.5 (12.7)	18.4 (11.4)
Median (min, max)	12.3 (0.0, 62.0)	15.0 (3.2, 40.9)
Age at treatment initiation (years)		
n	78	20
Mean (SD)	20.1 (12.9)	21.9 (11.3)
Median (min, max)	18.0 (2.2, 64.5)	23.5 (2.2, 41.8)
Duration of treatment with arimoclomol (days)[a]		
n	75	20
Mean (SD)	965 (481)	1471 (87)
Median (min, max)	1146 (54, 1622)	1479 (1339, 1622)

Demographic variable	Long-term follow-up (N = 78)	Extended follow-up (N = 20)
5DNPCCSS score at treatment initiation		
n	78	20
Mean (SD)	11.2 (6.3)	11.6 (5.8)
Median (min, max)	10.0 (0, 25)	11.5 (2, 25)
R4DNPCCSS score at treatment initiation		
n	78	20
Mean (SD)	8.2 (5.2)	8.7 (4.6)
Median (min, max)	7.0 (0, 20)	8.5 (2, 20)

Table S8. Summary of 5DNPCCSS total score for participants with Baseline and follow-up data

Participants with data at baseline and Year x	Year	0	1	2	3	4
Year 1	n	78	78			
	Mean (SD)	11.2 (6.33)	11.1 (6.63)			
Year 2	n	43	43	43		
	Mean (SD)	10.8 (5.76)	10.3 (5.99)	10.9 (5.90)		
Year 3	n	38	38	28	38	
	Mean (SD)	10.7 (6.44)	9.7 (6.00)	9.9 (5.78)	10.4 (6.47)	
Year 4	n	20	20	14	19	20
	Mean (SD)	11.6 (5.75)	10.3 (6.01)	10.1 (4.73)	10.7 (6.38)	11.6 (6.98)

5DNPCCSS: 5-domain NPC Clinical Severity Scale; n: number of patients with available data; SD: standard deviation

Participants had different maximum possible follow-up durations depending on when they entered the EAP

Table S9. Summary of 5DNPCCSS total score for participants with Baseline and follow-up data in age and treatment subgroups

Participants with data at baseline and Year x	Year	0	1	2	3	4
Arimoclomol only						
Year 1	n	24	24			
	Mean (SD)	11.0 (7.69)	12.5 (7.98)			
Year 2	n	8	8	8		
	Mean (SD)	9.6 (5.24)	10.1 (6.17)	10.0 (7.17)		
Year 3	n	11	11	6	11	
	Mean (SD)	9.7 (7.13)	10.4 (7.45)	7.80 (6.97)	10.1 (8.31)	
Year 4	n	6	6	3	6	6
	Mean (SD)	12.8 (7.65)	13.8 (7.55)	12.3 (7.37)	13.3 (8.64)	14.2 (8.98)
Arimoclomol + miglustat						
Year 1	n	54	54			
	Mean (SD)	11.3 (5.7)	10.5 (5.92)			
Year 2	n	35	35	35		
	Mean (SD)	11.1 (5.91)	10.3 (6.04)	11.1 (5.68)		
Year 3	n	27	27	22	27	
	Mean (SD)	11.1 (6.23)	9.5 (5.44)	10.4 (5.47)	10.6 (5.74)	
Year 4	n	14	14	11	13	14
	Mean (SD)	11.1 (4.98)	8.8 (4.76)	9.5 (4.03)	9.5 (4.98)	10.5 (6.00)
Pediatric						
Year 1	n	39	39			
	Mean (SD)	10.3 (7.00)	10.4 (7.45)			
Year 2	n	22	22	22		
	Mean (SD)	10.5 (6.58)	9.7 (7.08)	11.2 (6.78)		
Year 3	n	16	16	12	16	
	Mean (SD)	10.7 (8.20)	9.3 (7.51)	10.3 (6.58)	10.8 (8.11)	
Year 4	n	7	7	4	6	7
	Mean (SD)	11.9 (9.01)	9.7 (9.23)	10.0 (6.38)	11.5 (9.77)	12.3 (9.50)

Participants with data at baseline and Year x	Year	0	1	2	3	4
Adult						
Year 1	n	39	39			
	Mean (SD)	12.0 (5.54)	11.8 (5.71)			
Year 2	n	21	21	21		
	Mean (SD)	11.1 (4.89)	10.9 (4.70)	10.5 (4.97)		
Year 3	n	22	22	16	22	
	Mean (SD)	10.7 (5.00)	10.00 (4.79)	9.6 (5.32)	10.2 (5.16)	
Year 4	n	13	13	10	13	13
	Mean (SD)	11.5 (3.43)	10.6 (3.78)	10.1 (4.33)	10.3 (4.55)	11.2 (5.63)

5DNPCCSS: 5-domain NPC Clinical Severity Scale; n: number of patients with available data; SD: standard deviation

Participants had different maximum possible follow-up durations depending on when they entered the EAP

Table S10. Summary of in R4DNPCCSS total score (all exposed participants)

Assessment window Statistic	Overall (N=109)	Treatment subgroups		Age at treatment initiation subgroups	
		Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)	Pediatric (N=56)	Adult (N=53)
Treatment initiation (Baseline)					
n	100	36	64	52	48
Mean (SD)	8.1 (4.98)	8.3 (5.64)	7.9 (4.61)	7.4 (5.56)	8.8 (4.20)
Median	7.0	7.5	7.0	6.0	8.5
Min, Max	0, 20	0, 20	0, 20	0, 20	0, 20
Year 1					
n	86	26	60	42	44
Mean (SD)	8.2 (5.41)	9.5 (6.41)	7.6 (4.86)	7.6 (6.11)	8.7 (4.65)
Median	7.0	10.0	6.0	6.0	8.5
Min, Max	0, 20	0, 20	0, 20	0, 20	0, 20
Year 2					
n	50	9	41	26	24
Mean (SD)	8.2 (4.95)	8.1 (6.31)	8.2 (4.70)	9.2 (5.81)	7.2 (3.68)
Median	7.0	11.0	7.0	9.0	7.0
Min, Max	0, 20	0, 18	1, 20	0, 20	0, 17
Year 3					
n	43	11	32	19	24
Mean (SD)	8.2 (5.53)	7.5 (6.88)	8.4 (5.10)	9.4 (6.69)	7.2 (4.32)
Median	7.0	4.0	7.0	11.0	5.5
Min, Max	0, 20	0, 20	0, 17	0, 20	0, 17
Year 4					
n	22	6	16	8	14
Mean (SD)	9.0 (6.33)	11.5 (7.40)	8.1 (5.88)	10.6 (8.38)	8.1 (4.94)
Median	7.5	12.5	6.0	11.0	6.0
Min, Max	1, 20	1, 20	1, 20	1, 20	3, 18

Max, maximum; Min, minimum; n: number of patients with available data; R4DNPCCSS: rescored 4-domain NPC Clinical Severity Scale; SD: standard deviation

Of the 109 exposed participants, 100 had a Baseline 5DNPCCSS score and are included in this analysis.

Participants had different maximum possible follow-up durations depending on when they entered the EAP

Table S11. Summary of R4DNPCCSS total score for participants with Baseline and follow-up data

Participants with data at baseline and Year x	Year	0	1	2	3	4
Year 1	n	78	78			
	Mean (SD)	8.2 (5.17)	8.1 (5.52)			
Year 2	n	43	43	43		
	Mean (SD)	7.7 (4.72)	7.3 (5.02)	7.8 (4.81)		
Year 3	n	38	38	28	38	
	Mean (SD)	7.9 (5.27)	6.9 (4.99)	7.0 (4.72)	7.7 (5.38)	
Year 4	n	20	20	14	19	20
	Mean (SD)	8.7 (4.55)	7.5 (4.90)	7.1 (3.57)	8.1 (5.45)	8.6 (6.13)

n: number of patients with available data; R4DNPCCSS: rescored 4-domain NPC Clinical Severity Scale; SD: standard deviation; SE: standard error
Participants had different maximum possible follow-up durations depending on when they entered the EAP

Table S12. Phenotype subgroup analysis: Demographics, treatment characteristics and 5DNPCCSS and R4DNPCCSS total scores at Baseline and Year 1

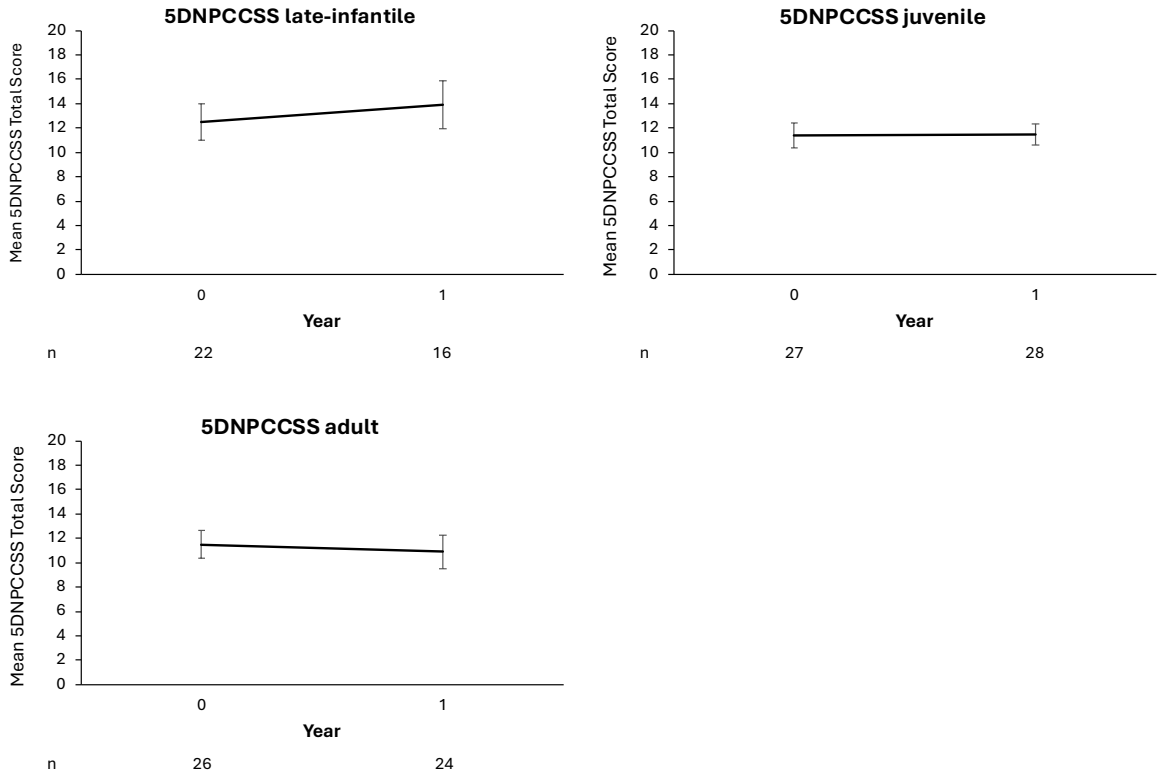
Variable	Phenotype subgroups (by onset of neurological symptoms)		
	Late-infantile (N=22)	Juvenile (N=30)	Adult (N=29)
Gender – n (%)			
Male	9 (40.9)	15 (50.0)	18 (62.1)
Female	13 (59.1)	15 (50.0)	11 (37.9)
Age at first neurological symptoms (years)			
n	22	30	29
Mean (SD)	3.5 (1.2)	8.4 (2.4)	25.4 (10.6)
Median (min, max)	3.5 (2, 5)	8.0 (6.0, 15.0)	23.0 (16.0, 57.0)
Age at diagnosis (years)			
n	22	29	29
Mean (SD)	6.9 (5.4)	14.3 (7.5)	31.1 (10.8)
Median (min, max)	7.3 (0.0, 21.1)	11.5 (5.0, 36.2)	30.0 (12.0, 62.0)
Age at treatment initiation (years)			
n	22	30	29
Mean (SD)	10.5 (6.5)	19.2 (8.6)	34.4 (9.8)
Median (min, max)	9.0 (2.7, 26.6)	17.4 (9.0, 38.4)	33.8 (18.9, 64.5)
Duration of treatment with arimoclomol (days)[a]			
n	20	29	28
Mean (SD)	539 (443)	951 (462)	845 (584)

Variable	Phenotype subgroups (by onset of neurological symptoms)		
	Late-infantile (N=22)	Juvenile (N=30)	Adult (N=29)
Median (min, max)	403 (70, 1370)	1082 (15, 1590)	813 (71, 1622)
5DNPCCSS score at treatment initiation			
n	22	27	26
Mean (SD)	12.5 (6.9)	11.4 (5.2)	11.5 (5.7)
Median (min, max)	11.0 (0, 25)	10.0 (1, 25)	11.0 (0, 25)
5DNPCCSS score at Year 1			
n	16	28	24
Mean (SD)	13.9 (7.92)	11.5 (4.63)	10.9 (6.71)
Median (min, max)	13.5 (2, 25)	11.0 (4, 22)	9.5 (1, 25)
R4DNPCCSS score at treatment initiation			
n	22	27	26
Mean (SD)	9.5 (5.5)	8.1 (4.6)	8.7 (4.5)
Median (min, max)	8.0 (0, 20)	7.0 (2, 20)	5.5 (0, 20)
R4DNPCCSS score at Year 1			
n	16	28	24
Mean (SD)	10.5 (6.75)	8.1 (4.29)	8.2 (5.23)
Median (min, max)	9.5 (1, 20)	7.5 (1, 17)	6.5 (0, 20)

[a]Duration of exposure is defined as time on treatment from the date of treatment initiation to final dose date of arimoclomol in the EAP

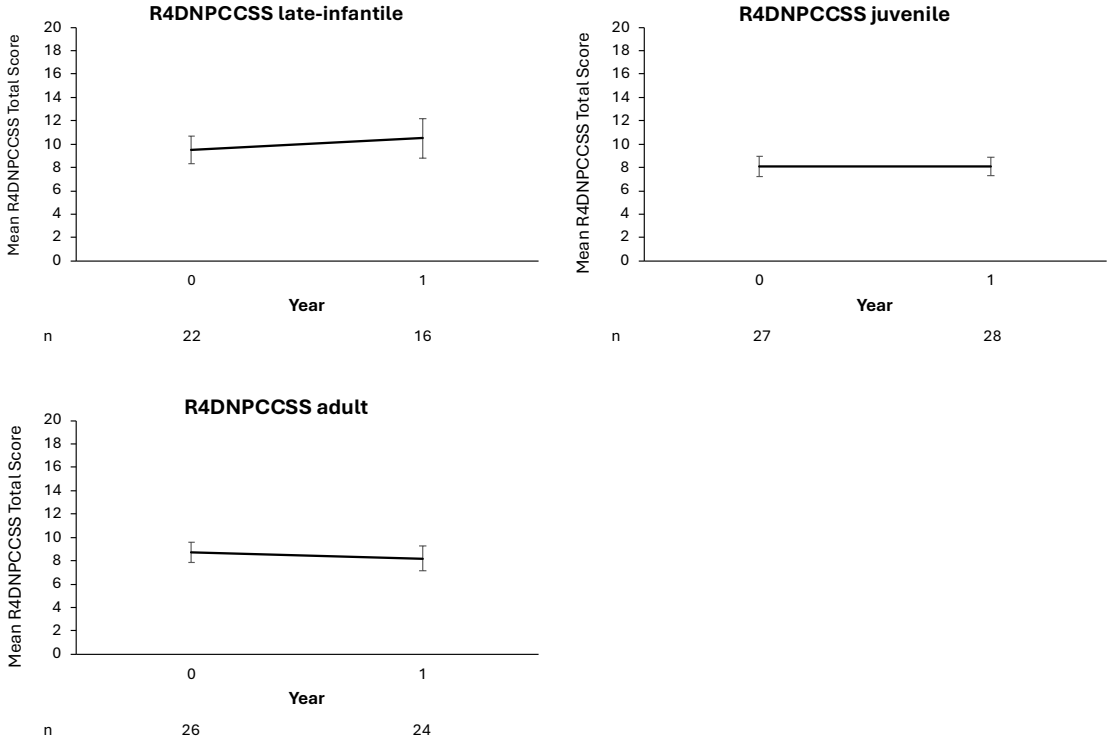
5DNPCCSS: 5-domain NPC Clinical Severity Scale; EAP: Early Access Program; max: maximum; min: minimum; N indicates the number of participants that could be allocated to any of the phenotype subgroups based on the availability of information on their age at neurological onset; n: number of participants with available data; R4DNPCCSS: rescored 4-domain NPC Clinical Severity Scale; SD: standard deviation

Figure S1. Mean total (SE) 5DNPCCSS scores at Baseline and Year 1 in the participants with neurological onset phenotype ≥2–<6 years (late-infantile), juvenile ≥6–16 years (juvenile), and ≥16 years of age(adult)



n: number of patients with available data; 5DNPCCSS: 5-domain NPC Clinical Severity Scale; SE: standard error

Figure S2. Mean total (SE) R4DNPCCSS scores at Baseline and Year 1 in the participants with neurological onset phenotype ≥2–<6 years (late-infantile), juvenile ≥6–16 years (juvenile), and ≥16 years of age(adult)



n: number of patients with available data; R4DNPCCSS: rescored 4-domain NPC Clinical Severity Scale; SE: standard error