Subgroup Analyses of US EAP Participants With Niemann-Pick Disease Type C Treated With Arimoclomol

Poster P-290

Caroline A. Hastings,[1] Elizabeth Berry-Kravis,[2] Nicolas Abreu,[3] Walla Al-Hertani,[4,5] Radhika Dhamija,[6] Can Ficicioglu,[7] Kristina Julich,[8] Paul Hillman,[9] Nancy Leslie,[10] Damara Ortiz,[11] Melinda Peters,[12] Paula Schleifer,[13] Ronan J. O'Reilly,[14] Blair Orr,[14] Christine í Dali[15]

[1]UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA; [2]Departments of Pediatrics, Neurological Sciences, Anatomy and Cell Biology and the RUSH Pediatric Neurosciences F.A.S.T. Center for Translational Research, Rush University Medical Center, Chicago, IL, USA; [3]NYU Grossman School of Medicine, New York, NY, USA; [4]Division of Metabolic Disorders, Children's Hospital of Orange County (CHOC®), Rady Children's Health, Orange, CA, USA; [5]Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; [6]Department of Neurology and Clinical Genomics, Mayo Clinic, Rochester, MN, USA; [7]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [8]Department of Neurology, Dell Medical School, The University of Texas at Austin, TX, USA; [9]Department of Pediatrics, Division of Medical Genetics, McGovern Medical School UTHealth Houston, Houston, TX, USA; [10]Cincinnati Children's Hospital, Cincinnati, OH, USA; [11]Medical Genetics and Genomics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA; [12]Boston Children's Hospital, Boston, MA, USA; [13]Department of Neurology, Nicklaus Children's Hospital, Miami, FL, USA; [14]Zevra Therapeutics, Celebration, FL, USA; [15]Zevra Denmark, Frederiksberg, Denmark

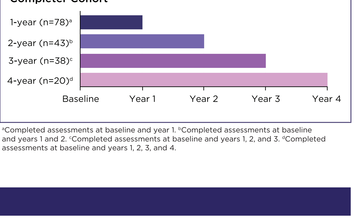
INTRODUCTION

- Niemann-Pick disease type C (NPC) is an ultra-rare, progressive, neurodegenerative lysosomal disorder caused by pathological variants in the *NPC1* or *NPC2* genes[1]
- In 2024, arimoclomol 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 with miglustat[2,3]
- The protocol-driven US Early Access Program (EAP; NCT04316637) was a prospective, real-world study designed to provide early access to arimoclomol for patients with NPC who were not eligible for or unable to participate in clinical trials[4,5]
  - Enrollment was initiated in July 2020 and was closed at the time of commercial approval in September 2024[4]
- Here we present effectiveness and safety data from patients with NPC treated in the US EAP with arimoclomol over a 4-year period

METHODS

- Participants in the EAP were enrolled on a rolling basis over the 4-year duration of the program; all participants received arimoclomol orally plus their routine clinical care
- Eligible participants were aged ≥2 years with a confirmed diagnosis of NPC and ≥1 neurological symptom
  - If taking miglustat, the patient must have been on the target dose for the previous 6 weeks
  - If history of seizures existed, the condition must have been adequately controlled
- A completer analysis was performed in which effectiveness was measured as the change from baseline in the physician-reported 5-domain NPC Clinical Severity Scale (5DNPCCSS) in patients who had available assessments at baseline and at ≥1-year follow-up (**Figure 1**)
  - Subgroup analyses were performed according to
    - Treatment: arimoclomol alone and arimoclomol plus miglustat
    - Age: <18 years (pediatrics) and ≥18 years (adults)
  - Effectiveness was also assessed in a subgroup aligned with pivotal trial criteria (pediatric participants aged 2-19 years on concomitant miglustat)[6]
- All adverse events (AEs) were recorded during the US EAP and summarized
- Descriptive statistics were performed; comparisons between groups and across timepoints were descriptive and observational only

Figure 1. Multiyear Completer Cohorts



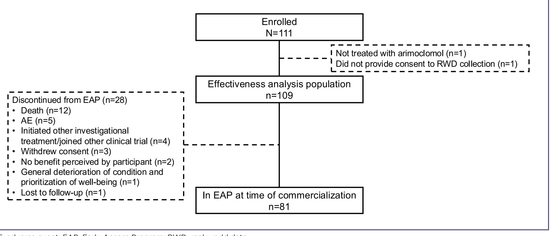
[a]Completed assessments at baseline and year 1. [b]Completed assessments at baseline and years 1 and 2. [c]Completed assessments at baseline and years 1, 2, and 3. [d]Completed assessments at baseline and years 1, 2, 3, and 4.

RESULTS

Disposition

- A total of 111 participants from 14 sites were enrolled in the EAP (**Figure 2**)
  - Of these, 110 (99.1%) were treated with arimoclomol and 109 (98.2%) consented to real-world data collection
  - At the time of commercialization of arimoclomol, all participants still active in the EAP (n=81) transitioned to commercial treatment

Figure 2. Disposition of Participants



AE, adverse event; EAP, Early Access Program; RWD, real-world data.

Baseline Demographics

- Overall, demographics were well balanced by sex and age; 52.3% (n=57) were male, and 48.6% (n=53) were ≥18 years of age (**Table 1**)
- Overall mean exposure was 820 days (2.2 years; range: 15-1622 days) among participants with known final dose dates (n=102)
- A total of 71 participants (65%) received concomitant miglustat; 38 (35%) received arimoclomol only

Table 1. Demographics and Baseline Characteristics

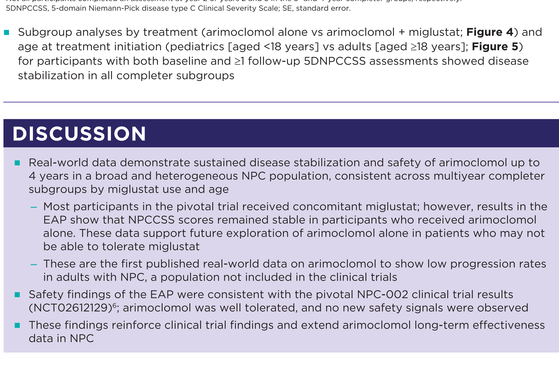
Variable	Overall (N=109)	Arimoclomol only (n=38)	Arimoclomol + miglustat (n=71)	Pediatric (n=56)	Adult (n=53)
Sex, n (%)					
Male	57 (52.3)	22 (57.9)	35 (49.3)	29 (51.8)	28 (52.8)
Female	52 (47.7)	16 (42.1)	36 (50.7)	27 (48.2)	25 (47.2)
Age at diagnosis, years,[a] mean± SD	16.4±13.0 (n=106)	19.2±15.6 (n=36)	15.0±11.2 (n=70)	7.2±4.6 (n=54)	26.0±11.9 (n=52)
Age at treatment initiation, years, mean±SD	19.9±13.1 (n=109)	22.1±15.4 (n=38)	18.7±11.6 (n=71)	9.4±4.7 (n=56)	31.1±9.2 (n=53)
Duration of treatment with arimoclomol,[a,b] days, mean±SD	820±539 (n=102)	668±566 (n=34)	897±513 (n=68)	760±536 (n=52)	883±541 (n=50)
5DNPCCSS score at treatment initiation,[a] mean±SD	11.0±6.2 (n=100)	11.1±6.9 (n=36)	11.0±5.7 (n=64)	10.1±6.9 (n=52)	11.9±5.2 (n=48)
R4DNPCCSS score at treatment initiation,[a] mean±SD	8.1±5.0 (n=100)	8.3±5.6 (n=36)	7.9±4.6 (n=64)	7.4±5.6 (n=52)	8.8±4.2 (n=48)

[a]Sample sizes for those with available data. [b]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 Niemann-Pick disease type C Clinical Severity Scale; EAP, Early Access Program; R4DNPCCSS, rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale; SD, standard deviation.

Outcome Measures

- Analysis of those with both baseline and ≥1 follow-up 5DNPCCSS assessments demonstrated minimal changes in disease severity over time (**Figure 3**)
  - Among the 78 participants with baseline and year 1 data, mean±standard error (SE) scores were 11.2±0.72 and 11.1±0.75 at baseline and year 1, respectively; similar patterns were observed for participants with baseline and year 2, year 3, or year 4 assessments

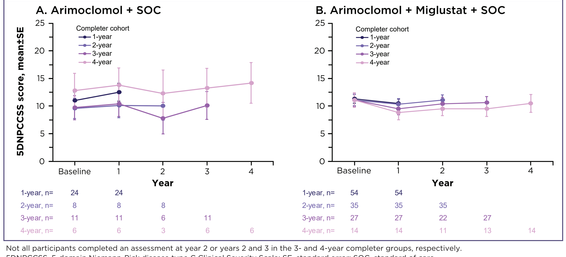
Figure 3. Completer Analysis: Overall



Not all participants completed an assessment at year 2 or years 2 and 3 in the 3- and 4-year completer groups, respectively. 5DNPCCSS, 5-domain Niemann-Pick disease type C Clinical Severity Scale; SE, standard error.

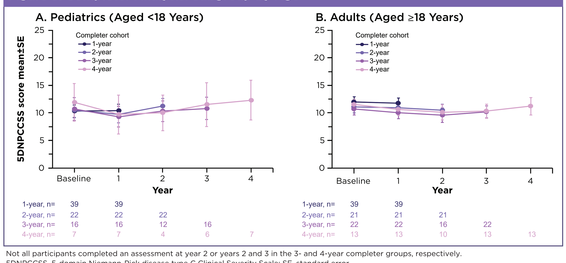
- Subgroup analyses by treatment (arimoclomol alone vs arimoclomol + miglustat; **Figure 4**) and age at treatment initiation (pediatrics [aged <18 years] vs adults [aged ≥18 years]; **Figure 5**) for participants with both baseline and ≥1 follow-up 5DNPCCSS assessments showed disease stabilization in all completer subgroups

Figure 4. Completer Analysis: Subgroup by Treatment



Not all participants completed an assessment at year 2 or years 2 and 3 in the 3- and 4-year completer groups, respectively. 5DNPCCSS, 5-domain Niemann-Pick disease type C Clinical Severity Scale; SE, standard error; SOC, standard of care.

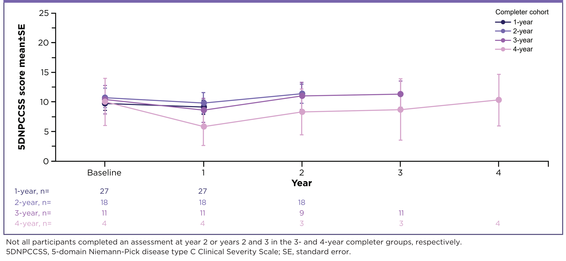
Figure 5. Completer Analysis: Subgroup by Age



Not all participants completed an assessment at year 2 or years 2 and 3 in the 3- and 4-year completer groups, respectively. 5DNPCCSS, 5-domain Niemann-Pick disease type C Clinical Severity Scale; SE, standard error.

- Of interest, in a pediatric subgroup aligned with pivotal trial criteria (aged 2-19 years; on miglustat), scores were 9.7±1.16 vs 9.1±1.20 at year 1 (n=27) and 10.0±3.94 vs 10.3±4.33 at year 4 (n=4), consistent with stabilization observed in the pivotal trial and its 4-year, open-label extension (**Figure 6**)

Figure 6. Completer Analysis: Pediatric (Aged 2-19 Years) Subgroup, Arimoclomol + Miglustat



Not all participants completed an assessment at year 2 or years 2 and 3 in the 3- and 4-year completer groups, respectively. 5DNPCCSS, 5-domain Niemann-Pick disease type C Clinical Severity Scale; SE, standard error.

Safety

- A total of 248 AEs were reported during the EAP, of which 241 were classified as treatment-emergent based on known date of administration; 5 AEs led to discontinuation for 5 (4.6%) participants (**Table 2**)
- A total of 13 participants (11.9%) reported a total of 17 AEs deemed related to arimoclomol
- The most common treatment-related AEs were diarrhea (n=3 participants [2.8%]), increased blood creatinine (n=2 [1.8%]), and rash (n=2 [1.8%])
- A total of 36 (33.0%) participants reported 95 serious AEs, none of which were deemed related to arimoclomol.
- There were 12 deaths (4 pediatric, 8 adult participants), all unrelated to treatment
  - Ages at death varied from 6 to 42 years old; the latest recorded 5DNPCCSS total score before death ranged from 10 to 25

Table 2. Safety Overview

Event	Overall (N=109) n (%)	Number of events, n
Any AE	109 (100)	248
Treatment-related AEs	13 (11.9)	17
Any SAEs	36 (33.0)	95
Treatment-related SAEs	0	0
AEs leading 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

[a]Treatment-related AEs occurring in >1 participant are included.
AE, adverse event; SAE, serious adverse event.

DISCUSSION

- Real-world data demonstrate sustained disease stabilization and safety of arimoclomol up to 4 years in a broad and heterogeneous NPC population, consistent across multiyear completer subgroups by miglustat use and age
  - Most participants in the pivotal trial received concomitant miglustat; however, results in the EAP show that NPCCSS scores remained stable in participants who received arimoclomol alone. These data support future exploration of arimoclomol alone in patients who may not be able to tolerate miglustat
  - These are the first published real-world data on arimoclomol to show low progression rates in adults with NPC, a population not included in the clinical trials
- Safety findings of the EAP were consistent with the pivotal NPC-002 clinical trial results (NCT02612129)[6]; arimoclomol was well tolerated, and no new safety signals were observed
- These findings reinforce clinical trial findings and extend arimoclomol long-term effectiveness data in NPC

References

1. Hiwot T, et al. *J Inherit Metab Dis.* 2026;49(3):e70185. **2.** Miplyffa. Prescribing information. Zevra Therapeutics, Inc; 2026. **3.** Mengel E, et al. *Mol Genet Metab.* 2025;145(4):109189. **3.** Zevra Therapeutics, Inc. Data on file. **4.** ClinicalTrials.gov. Accessed May 28, 2026. https://clinicaltrials.gov/study/NCT04316637. **5.** Mengel E, et al. *J Inherit Metab Dis.* 2021;44(6):1463-1480.

Disclosures

CAH served as a PI on the EAP and on the advisory board of Zevra Therapeutics; previously served on the advisory board of IntraBio; global (and site) PI for current open phase 3 trial in NPC investigating intravenous HPBCD and advisory board at Cyclo Therapeutics; site PI for current open phase 3 trial for NPC and GM1/2 investigating nizubaglustat and advisory board at Azafaros. **EBK** has received funding from Acadia Pharmaceuticals, Arbor Pharmaceuticals, Biogen, BioMarin Pharmaceutical, GeneTx, Engrail, EryDel, Healx, IntraBio, Ionis Pharmaceuticals, Jaguar, Kisbee Therapeutics, Majhi Therapeutics, Mirum Pharmaceuticals, Moment Biosciences, Neuren Pharmaceuticals, Neurogene, Novartis, Ono Pharmaceutical, Orphazyme/KemPharm/Zevra Therapeutics, Oak Hill Bio, Praxis Precision Medicines, PTC Therapeutics, PYC Therapeutics, QurAlis, Roche, Taysha Gene Therapies, Tetra, Shionogi, Ultragenyx, Vtesse/Sucampo/Mallinckrodt/Mandos Pharmaceuticals, Yamo Pharmaceuticals, and Zyneyba/Harmony Biosciences 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. **NA** has received funding from Amicus Therapeutics, BioMarin Pharmaceutical, Sangamo Therapeutics, Sanofi, and Takeda Pharmaceuticals; has served on advisory boards for Beren Therapeutics and Sanofi; and serves as a consultant to Takeda Pharmaceutical. **WAH** served as advisor to Aygamy Pharma, Amicus Therapeutics, Azafaros, Cyclo Therapeutics, HCU Network America, IntraBio, National Niemann-Pick Disease Foundation, Takeda Pharmaceutical, and Ultragenyx; as PI for Beam Therapeutics; and has served on a genetics evaluation committee for Denali Therapeutics, collaborator for Sanofi, and advisor and steering committee for Zevra Therapeutics. **RD** has no conflicts of interest. **CF** has no conflicts of interest. **KJ** has served as a consultant for Cyclo Therapeutics and Zevra Therapeutics. She is a fellow of the Clarke Family Foundation. **PH** serves on the speaker bureau and advisory board for Mirum Pharmaceuticals; advisory boards for Amicus Therapeutics and Chiesi USA; and speaker bureau for Sanofi and Zevra Therapeutics. **NL** has no conflicts of interest. **DO** received research grants from 4DMT, Alexion, Amicus, BioMarin Pharmaceutical, Freeline, GC Biopharma, Protalix/Chiesi, Sangamo, Sanofi, Sentynl Therapeutics, Takeda Pharmaceutical, and UniQure; speaker bureau for Zevra Therapeutics; and advisory board for Sanofi and Takeda. **MP** has served on the advisory board for Cyclo Therapeutics and Zevra Therapeutics. **PS** has served on advisory boards and/or as a consultant for Acadia Pharmaceuticals, Sanofi, Taysha Gene Therapies, and Zevra Therapeutics; served as a site PI for Ionis Pharmaceuticals, Mandos Health, Neurogene, and Ultragenix; and served for the US EAP for Zevra Therapeutics. **RJO** is a consultant for Zevra Therapeutics. **BO** is a consultant for Zevra Therapeutics. **CID** is an employee and shareholder of Zevra Denmark A/S.

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