Poster 041

Real-world safety and effectiveness arimoclomol in patients with NPC: outcomes from the US early access program (EAP) over a 4-year period

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BACKGROUND AND OBJECTIVE

- Niemann-Pick disease type C (NPC) is an ultra-rare, debilitating, progressive neurodegenerative, heterogenous lysosomal disease. The estimated incidence is ~1:100,000 live births.[1]
- Arimoclomol is the first treatment approved, in combination with miglustat, by the United States Food and Drug Administration (US FDA) to treat neurological manifestations of NPC based on positive safety and effectiveness results of the 12-month Phase 2/3 randomized, double-blind placebo-controlled interventional trial which enrolled 50 participants (age 2-18).
- An early access program (EAP) was launched to provide arimoclomol to patients with NPC in the US who were not eligible for or able to participate in clinical trials or who stopped receiving treatment from the open-label extension (OLE) study.

METHODS AND STATISTICS

- Data were handled in accordance with the Regulations (US Health Insurance Portability and Accountability Act of 1996 [HIPAA] and EU General Data Protection Regulation [GDPR]) and the treating physician obtained Institutional Review Board (IRB) approval.
- Treatment decisions and therapeutic strategies for patients with NPC were made independently of participation in the study; arimoclomol was provided by the Sponsor with prescribing dose based on participant's weight and Phase 2/3 study dosing regimen.
- Physicians reported demographics, medical history, physical exam/laboratory results, adverse events (AEs), weight, concomitant medications, arimoclomol dosing, and 5-domain NPC Clinical Severity Scale (5DNPCCSS) at baseline, with ongoing clinical assessments scheduled at months 4, 7 and 12 and subsequent routine visits thereafter (however, the visit schedule was not mandatory apart from the baseline).
- Effectiveness was measured as the change from baseline in the 5DNPCCSS and rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score.
  - The 5DNPCCSS is an NPC disease-specific validated measure of disease progression[2,3] based on the five most clinically relevant domains (cognition, speech, swallow, fine motor skills and ambulation) of the 17-domain NPCCSS.
  - The R4DNPCCSS removes the cognition domain and rescores the swallow domain from the 5DNPCCSS.[4]
- Analysis was done to evaluate overall participants as well as miglustat and non-miglustat groups and pediatric and adult groups.

RESULTS

See Poster 273 for details on the pediatric and adult groups and Poster 193 for details about participants who completed multiple years of assessments.

Participants

- Fourteen sites enrolled 111 participants into the EAP (**Table 1**); 110 (99.1%) were treated and 109 (98.2%) were treated with arimoclomol and consented to real-world data (RWD) collection for inclusion in the effectiveness analysis.
- Overall demographics were well balanced with 57 male (52.3%) and 53 (48.6%) ≥ 18 years of age in the adult cohort.
- There were 71 participants who also received miglustat and 38 receiving arimoclomol only.
- At commercialization, all remaining 81 participants opted for commercially available arimoclomol. Other reasons for discontinuation were death not related to treatment with arimoclomol in 12 (11.0%) participants, AEs in 5 (4.6%) participants, withdrew consent in 3 (2.8%) and treatment initiation with another investigational treatment for NPC in 2 (1.8%) participants.

Safety

- Of 248 AEs reported, 241 were treatment-emergent (TEAEs); 95 (38.3%) AEs were serious (SAEs) in 36 (33.0%) participants; none deemed related to treatment.
- Fourteen (12.8%) participants experienced 17 AEs related to arimoclomol: 9 recovered/resolved, 3 recovering/resolving, 4 not recovered/not resolved, and 1 status of unknown; none of the 12 deaths that occurred during the study were related to arimoclomol. 5 participants withdrew due to AEs; no new safety signals were identified.

Effectiveness – 5DNPCCSS and R4DNPCCSS

- Of the 109 exposed participants, 100 (92%) had baseline 5DNPCCSS (**Figure 1**) and R4DNPCCSS (**Table 2**).
- An increase in 5DNPCCSS score is reflective of an increase in disease severity. Based on natural history studies, an annualized increase of 1.5 in total 5DNPCCSS score can be expected in pediatric NPC patients.[5]

Table 1: Demographics and Treatment Characteristics of Participants in the Arimoclomol Early Access Program

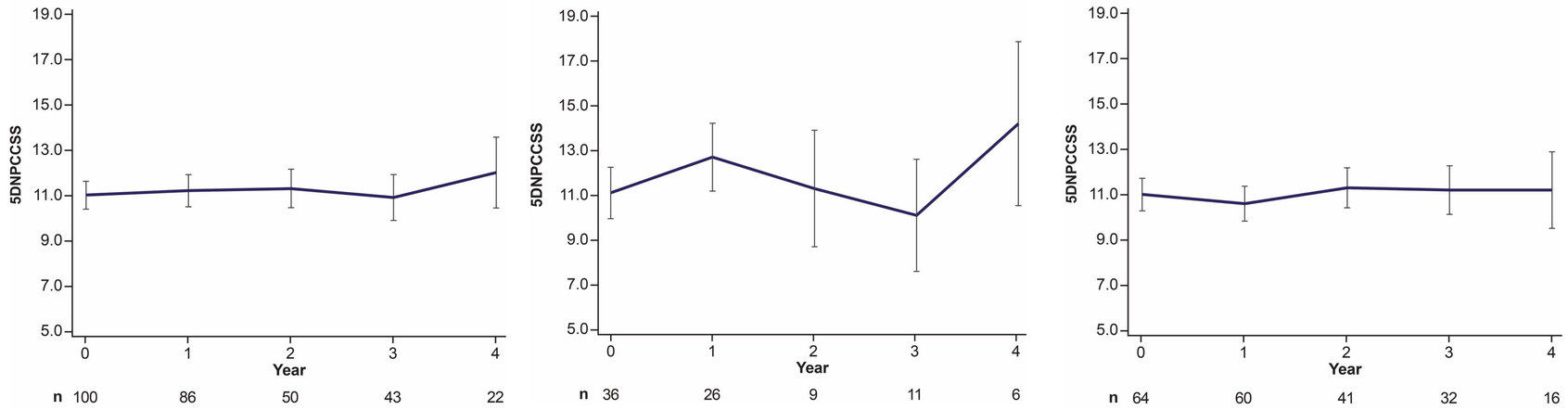
Demographic Variable Detail	Overall (N=109)	Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)
Gender – n (%)			
Male	57 (52.3)	22 (57.9)	35 (49.3)
Female	52 (47.7)	16 (42.1)	36 (50.7)
Age at diagnosis (years)			
n	106	36	70
Mean (SD)	16.4 (13.0)	19.2 (15.6)	15.0 (11.2)
Median	12.0	13.2	12.0
Min, max	0.0, 62.0	0.0, 62.0	0.1, 43.0
Year of Enrollment – n (%) *			
n	102	34	68
2020	23 (22.5)	10 (29.4)	13 (19.1)
2021	35 (34.3)	8 (23.5)	27 (39.7)
2022	10 (9.8)	3 (8.8)	7 (10.3)
2023	17 (16.7)	5 (14.7)	12 (17.6)
2024	17 (16.7)	8 (23.5)	9 (13.2)
Age at treatment initiation (years)			
n	109	38	71
Mean (SD)	19.9 (13.1)	22.1 (15.4)	18.7 (11.6)
Median	17.3	17.5	17.3
Min, max	2.0, 64.5	2.0, 64.5	2.2, 43.0
Duration of treatment with arimoclomol (days)**			
n	102	34	68
Mean (SD)	820 (539)	668 (566)	897 (513)
Median	836	460	1038
Min, max	15, 1622	15, 1622	54, 1590

* Participants with known exposure duration.
**Duration = time on treatment from the date of treatment initiation to their final dose date of arimoclomol in the EAP.

Table 2: Summary of R4DNPCCSS Total Score (Exposed Participants)

Assessment	Overall (N=109)	Arimoclomol only (N=38)	Arimoclomol + miglustat (N=71)
Treatment Initiation (Baseline)			
n	100	36	64
Mean (SD)	8.1 (4.98)	8.3 (5.64)	7.9 (4.61)
Median	7.0	7.5	7.0
Min, max	0, 20	0, 20	0, 20
Year 1			
n	86	26	60
Mean (SD)	8.2 (5.41)	9.5 (6.41)	7.6 (4.86)
Median	7.0	10.0	6.0
Min, max	0, 20	0, 20	0, 20
Year 2			
n	50	9	41
Mean (SD)	8.2 (4.95)	8.1 (6.31)	8.2 (4.70)
Median	7.0	11.0	7.0
Min, Max	0, 20	0, 18	1, 20
Year 3			
n	43	11	32
Mean (SD)	8.2 (5.53)	7.5 (6.88)	8.4 (5.10)
Median	7.0	4.0	7.0
Min, max	0, 20	0, 20	0, 17
Year 4			
n	22	6	16
Mean (SD)	9.0 (6.33)	11.5 (7.40)	8.1 (5.88)
Median	7.5	12.5	6.0
Min, max	1, 20	1, 20	1, 20

Figure 1: 5DNPCCSS Total Mean (SE) Score Over Time (Overall) by Group



DISCUSSION AND CONCLUSIONS

- The EAP enrolled a broad range of patients with NPC who are more representative of the heterogeneity in the NPC population than studied in arimoclomol clinical trials, including adults and those not currently on miglustat.[1,6-9]
- Enrollment was done in a rolling manner, and therefore only the 23 (21.1%) participants who enrolled in 2020 could have completed four 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 four years of follow-up.
- Stability of the 5DNPCCSS and R4DNPCCSS reinforces the impact of arimoclomol treatment as mean annual disease progression in natural history studies increased 1.5 points on the 5DNPCCSS in pediatric patients[5]; annual disease progression in the EAP remained below the ≥ 1-point threshold that defines a clinically meaningful increase in disability and loss of complex function.[2,10]
- Limitations of RWD collection include inconsistent reporting, quality of data collected, and biases such as selection bias.
- Limitations of this EAP and subgroup analysis include heterogeneity of NPC and a small total number of participants with data collected over the 4-year period. Lack of natural history data on disease progression in the adult NPC population limits the ability to extrapolate the impact of arimoclomol on disease severity and progression.
- Data from the EAP are consistent with the results of the Phase 2/3 clinical trials[9,11] demonstrating the positive safety profile of arimoclomol and its impact on disease stabilization in a real-world setting in a broader range of patients with NPC, including adults and those not on miglustat.

References: 1. Geberhiwot T, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis. 2018;13:50; 2. Patterson MC, et al. Validation of the 5-domain Niemann-Pick type C Clinical Severity Scale. Orphanet J Rare Dis. 2021;16(1):79; 3. Farmer C, et al. Convergent Validity of the Fine Motor, Speech, and Cognitive Domains of the 5-Domain Niemann-Pick Disease Type C Clinical Severity Scale. J Child Neurol. 2026;41(1):43-53; 4. Mengel E, et al. Efficacy results from a 12-month double-blind randomized trial of arimoclomol for treatment of Niemann-Pick disease type C (NPC): presenting a rescored 4-domain NPC Clinical Severity Scale. Mol Genet Metab Rep. 2025;43:101233; 5. Mengel E, et al. Clinical disease progression and biomarkers in Niemann-Pick disease type C: a prospective cohort study. Orphanet J Rare Dis. 2020;15(1):328; 6. Bianconi SE, et al. Evaluation of age of death in Niemann-Pick disease, type C: utility of disease support group websites to understand natural history. Mol Genet Metab. 2019;126(4):466-469; 7. Patterson MC, et al. Recommendations for the diagnosis and management of Niemann-Pick disease type C: an update. Mol Genet Metab. 2012;106(3):330-44; 8. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010;5:16; 9. Wraith JE, et al. Natural history of Niemann-Pick disease type C in a multicentre observational retrospective cohort study. Mol Genet Metab. 2009 Nov;98(3):250-4; 10. Mengel E, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment. J Inherit Metab Dis. 2021;44(6):1463-1480; 11. Mengel E, et al. Long-term efficacy and safety of arimoclomol in Niemann-Pick disease type C: final results of the phase 2/3 NPC-002 48-month open-label extension trial. Mol Genet Metab. 2025;145(4):109189. **Acknowledgements:** Funding for the EAP and analysis was provided by Zevra Therapeutics. Medical writing assistance was provided by Facet Communications.

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