Long-Term Effectiveness and Safety Evaluation of Arimoclomol Treatment in Patients With Niemann-Pick Disease Type C – Data From the Pivotal Study and Open-Label Extension

Eugen Mengel [1], Sven Guenther [2], Lauren Hitchins [2], Christine í Dali [3]

[1] SphinCS, Clinical Science for LSD, Hochheim, Germany, [2] Zevra Therapeutics, Celebration, FL, USA, [3] Zevra Denmark A/S, Frederiksberg, Denmark

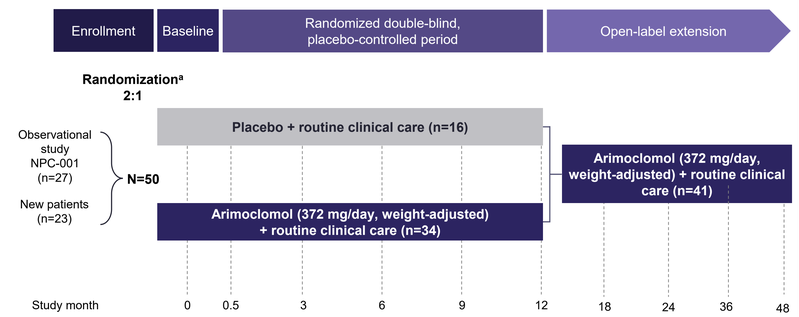
BACKGROUND

- Niemann-Pick disease Type C (NPC) is an ultra-rare, progressive, neurodegenerative disease with heterogeneous clinical presentation.
- Arimoclomol, an orally available small molecule that crosses the blood-brain barrier, is FDA-approved in combination with miglustat for the treatment of neurological manifestations of NPC in adults and children 2 years of age and older.
- This poster presents long-term safety and effectiveness data of arimoclomol in patients with NPC for up to 5 years of treatment who also received miglustat as part of their routine clinical care.

METHODS

- The safety and effectiveness of arimoclomol was studied in a 12-month, randomized, double-blind (DB), placebo-controlled clinical trial, followed by a single-arm, 48-month open-label extension (OLE) phase for up to 60 months of total treatment (**Figure 1**).
- Effectiveness assessments, including the validated rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score, were analyzed at baseline and every 3 months until 12 months of treatment; and every 6 months during the OLE phase.
- Effectiveness is presented as mean change over 12 months in R4DNPCCSS for the DB phase and as total R4DNPCCSS over 48 months for the OLE.
- Safety is described by frequency of adverse events (AEs) and severity.

Figure 1. Design of the NPC002 Trial



[a]Patients were stratified by receipt of miglustat at randomization. Adapted from: Mengel E et al. *J Inherit Metab Dis*. 2021 Nov;44(6):1463-1480.

The R4DNPCCSS is a measure of NPC disease progression that consists of the four items assessing ambulation, speech, swallow, and fine motor skills that patients with NPC, their caregivers and physicians have identified as most relevant. Score: 0-20, with higher scores representing greater severity of disease.

REFERENCES

1. Mengel E, Patterson MC, Da Riol RM, 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. doi:10.1002/jimd.12428
2. MIPLYFFA Full Prescribing Information. Celebration, FL, US, Zevra Therapeutics, Inc.; 09/2024

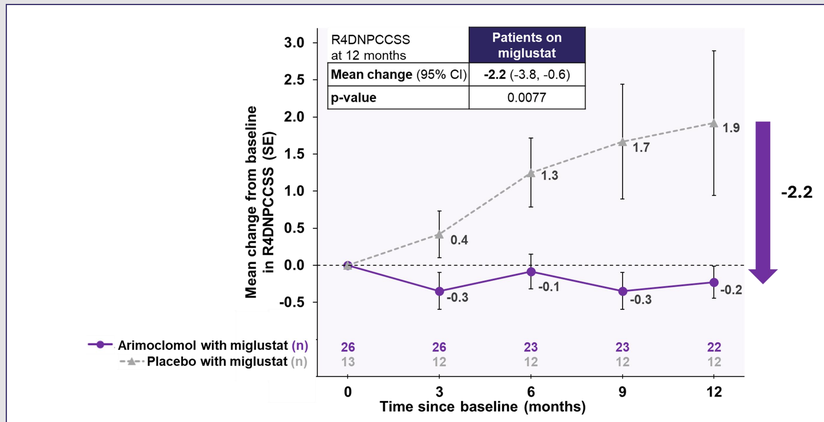
DISCLOSURES

This poster was reworded for the lay audience and was funded by Zevra Therapeutics. CD and LH are current employees of Zevra Therapeutics.

12-MONTH DOUBLE-BLIND RANDOMIZED PHASE

- The study enrolled 50 participants (2-19 yrs), randomized 2:1 to arimoclomol:placebo. 76% of patients in the arimoclomol group and 81% in the placebo group received miglustat.
- In the subgroup who received miglustat at enrollment, the mean age was 11.6 years, the mean time since first NPC symptom was 8.5 years, and the mean age at onset of first neurological symptom was 4.9 years.
- The mean baseline R4DNPCCSS score was higher in the arimoclomol group (n=26; mean=8.9) than the placebo group (n=13; mean=7), with an overall mean R4DNPCCSS score of 8.3.
- Arimoclomol, in combination with miglustat, halted disease progression through 12 months when compared to placebo treatment as measured by the R4DNPCCSS (**Figure 2**).

Figure 2. Change in R4DNPCCSS Over 12 Months in Patients Who Received Arimoclomol Plus Miglustat



Changes in R4DNPCCSS score from baseline to month 12 were compared using an analysis of variance (ANCOVA) model fitted with treatment and baseline R4DNPCCSS score as covariate.

- Adverse events were generally of mild to moderate severity. Serious adverse reactions were hypersensitivity reactions including urticaria and angioedema.
- In the arimoclomol group, 3 patients discontinued the study due to the following AEs: increased serum creatinine (one patient), and progressive urticaria and angioedema (two patients).

Table 1. Frequently Reported Adverse Events (≥8%)

Adverse reaction	Arimoclomol with miglustat n=26 n(%)	Placebo with miglustat n=13 n(%)
Upper respiratory tract infection*	8 (31)	2 (15)
Diarrhea	6 (23)	3 (23)
Decreased weight	4 (15)	0
Decreased appetite	3 (12)	0
Tremor	3 (12)	0
Urticaria**	3 (12)	0
Headache	3 (12)	1 (8)
Lower respiratory tract infection	3 (12)	1 (8)
Seizure	3 (12)	1 (8)

* Upper Respiratory Tract Infection: Combined incidence of upper respiratory tract infection and rhinitis
** Urticaria: Includes one patient in which urticaria occurred alone (3%) and two patients who had urticaria with angioedema (6%)

48-MONTH OPEN-LABEL EXTENSION PHASE

- A total of 41 patients continued in the OLE phase (**Figure 1**), 29 patients completed.
- The mean age was 12.2 (4.8) years at start of OLE phase, 80.5% were also treated with miglustat and baseline mean (SD) R4DNPCCSS was 9.2 (6.5) in the overall group and 8.9 (6.7) in the miglustat subgroup.
- The observed disease severity generally progressed slowly over the 48 months, with a stepwise progression pattern (**Figure 3**).

Figure 3. R4DNPCCSS Over 48 Months of Open-Label Extension in Patients Who Received Arimoclomol Plus Miglustat

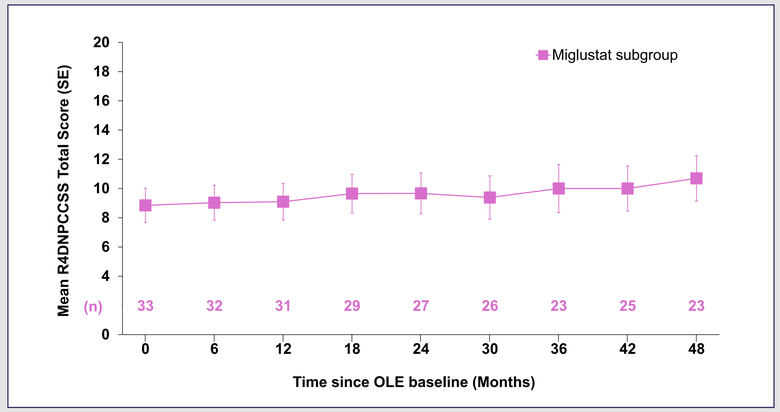


Table 2. Summary of Adverse Events

	Arimoclomol N = 41 n (%)
Any AE	38 (93%)
Severe AE	15 (37%)
Serious AE	15 (37%)
AE leading to treatment discontinuation	4 (10%)
AE with fatal outcome	2 (5%)

N = number of patients in the extension analysis set; n = number of patients with event; % = percentage of patients with event

- The overall pattern of AEs frequently reported were stable over the 48 months and consistent with observations in the DB phase
- The 3 most common AEs were (n,%); diarrhea (10, 24.4%), upper respiratory tract infection (10, 24.4%), and nasopharyngitis [also known as common cold] (8, 19.5%)

CONCLUSIONS

- In the pivotal trial, arimoclomol in combination with miglustat halted disease progression through 12 months compared with placebo as measured by the R4DNPCCSS.
- The effectiveness and safety of arimoclomol with miglustat was further confirmed in a 48-month open-label extension. Arimoclomol was generally well tolerated with no new safety signals observed during the OLE.

ACKNOWLEDGEMENTS

Authors would like to thank all participants and their caregivers who participated in this study; patient advocacy groups who supported communications and recruitment to the study; and study Investigators and site staff.