Long-term Efficacy and Safety Evaluation of Arimoclomol Treatment in Patients with Niemann Pick Type C – Data from 48 Months Open Label Trial

Poster ID
21271

Marc Patterson [a], Eugen Mengel [b], Sven Guenther [c], Christine i Dali [d]

[a] Neurology, Pediatrics and Medical Genetics, Mayo Clinic, Rochester, MN, USA, [b] SpinCS, Clinical Science for LSD, Hochheim, Germany, [c] Zevra Therapeutics, Celebration, FL, USA, [d] Zevra DK, Copenhagen N, Denmark

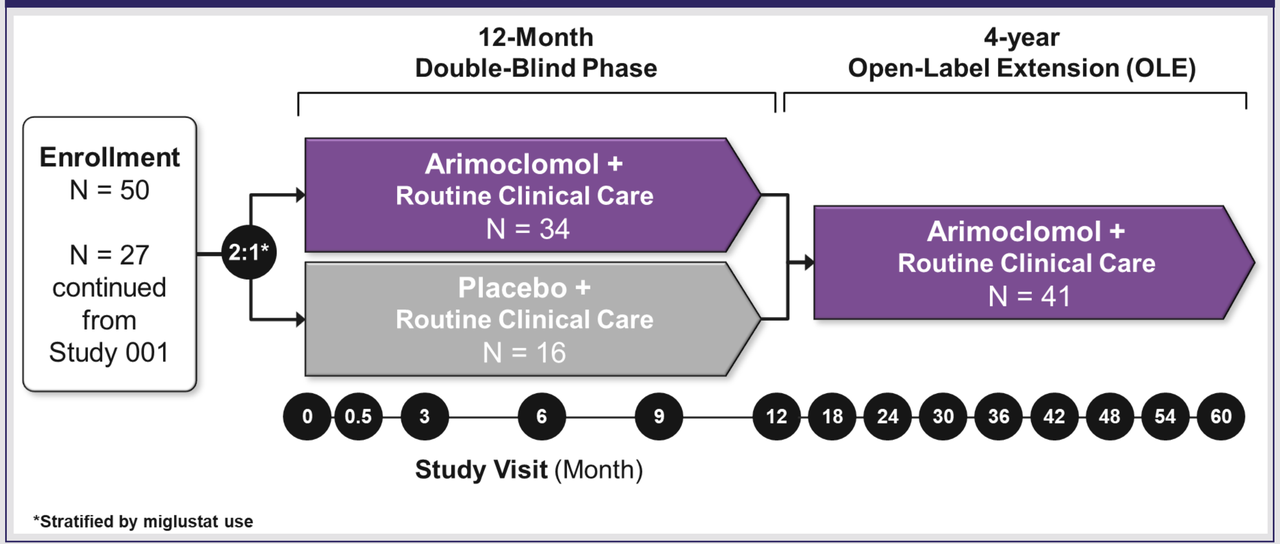
BACKGROUND

- Niemann-Pick disease type C (NPC) is an ultra-rare, autosomal recessive, progressive neurodegenerative lysosomal disease.
- Clinical presentation is heterogeneous with declining neurological function.
- Miglustat is authorized for treatment of NPC in EU and used off label in US.[1]
- With no curative treatment, there remains a high unmet need.
- Arimoclomol is an investigational orally available small molecule for the treatment of NPC.
- Results of a 12-month Double-Blind (DB) randomized trial investigating the efficacy and safety of arimoclomol showed a positive benefit-risk in patients aged 2-18 years diagnosed with NPC.[2]
- Here we present long-term efficacy data and safety of up to 48 months of Open-Label Extension (OLE) treatment with arimoclomol, introducing a modified 4-Domain severity scale 4DNPCCSS (ambulation, speech, swallowing and fine motor; Score: 0 – 20, See poster no. 21260).

METHODS

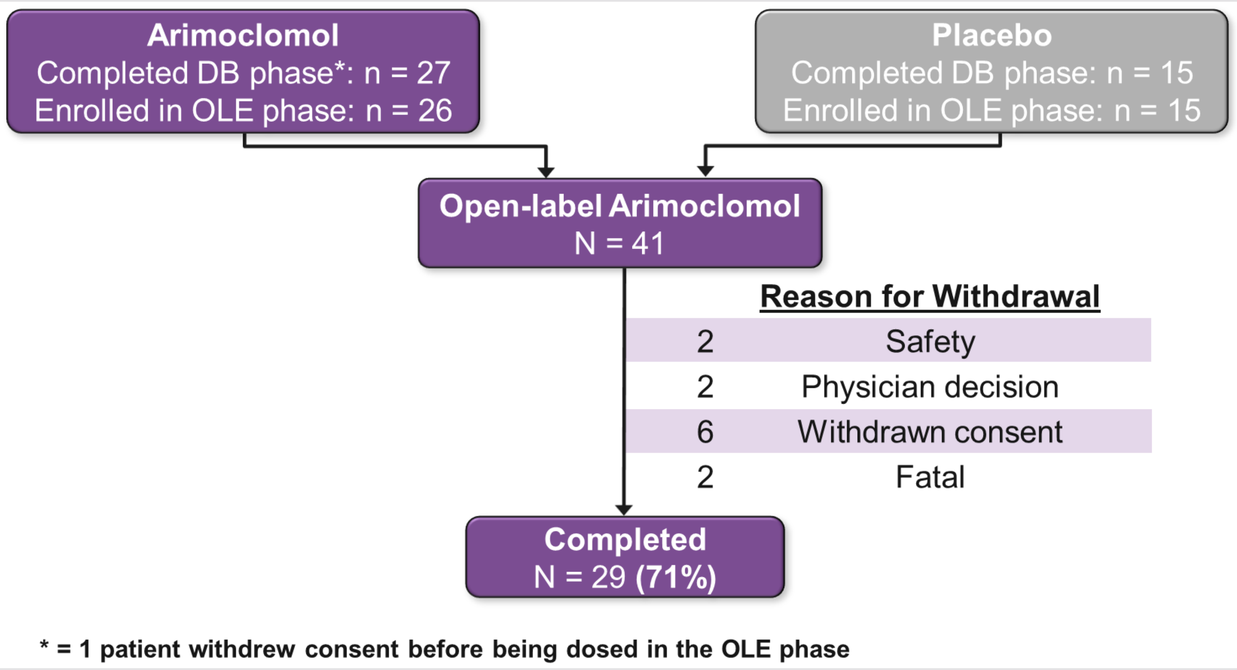
- Patients completing the DB phase were offered to continue into the OLE phase (EudraCT 2015-004438-93, NCT02612129).
- The trial was conducted at 15 sites in 9 countries (US and EU).
- Efficacy is presented as change from Baseline of DB and OLE phase and to 12, 24, 36, and 48 months of treatment.
- Safety is described by frequencies of Adverse Events (AEs) and severity.

Figure 1. NPC002 Trial design



*Stratified by miglustat use

Figure 2. NPC002 Disposition



* = 1 patient withdrew consent before being dosed in the OLE phase

Table 1. 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

REFERENCES

1. Patterson MC, Vecchio D, Jacklin E, Abel L, Chadha-Boreham H, Luzy C, et al. Long-term miglustat therapy in children with Niemann-Pick disease type C. *J Child Neurol.* 2010;25(3):300-5.
2. Mengel E, Patterson MC, Da Riol RM, Del Toro M, Deodato F, Gautschi M, 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):1463-80.

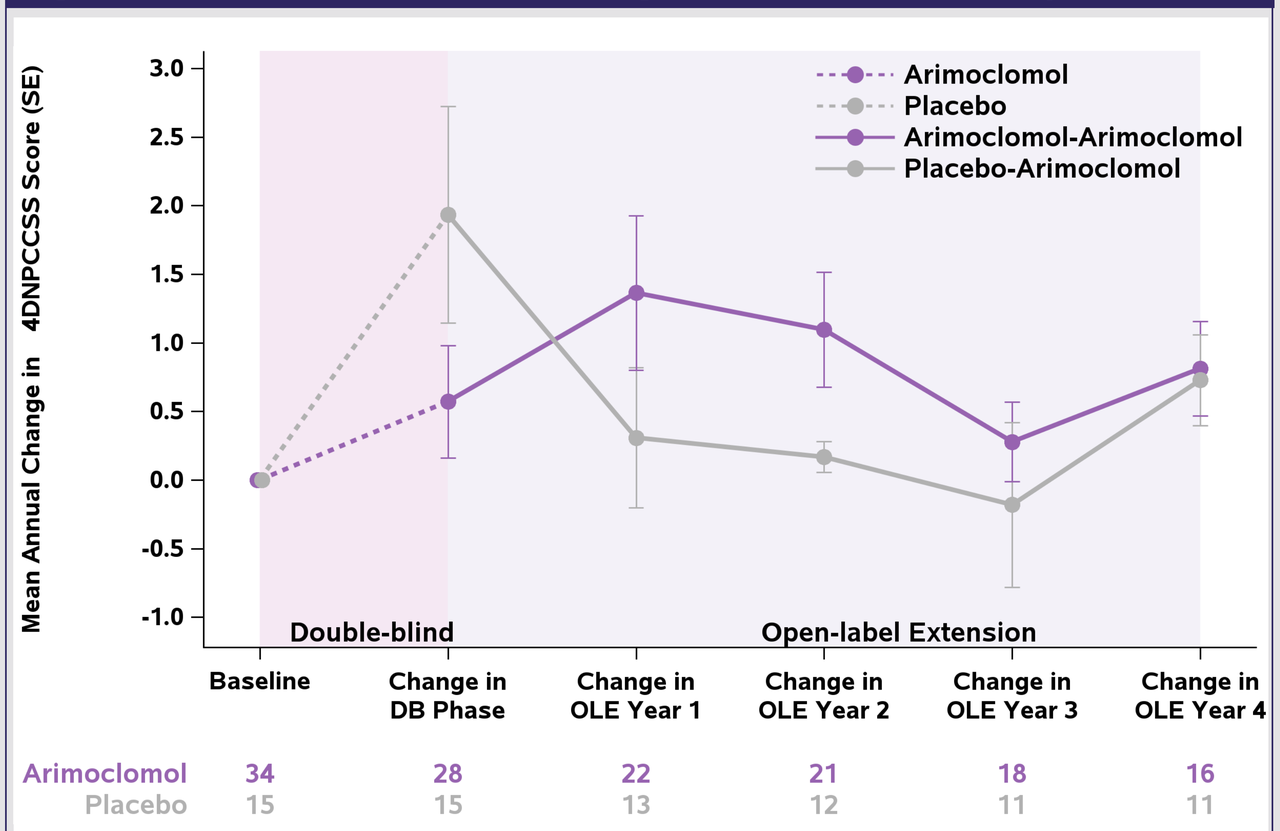
RESULTS

- A total of 41 patients continued in the OLE phase (**Figure 1**), 29 patients completed (**Figure 2**).
- Of the 12 patients withdrawn, 2 died due to disease progression (**Figure 2**).
- The mean age was 12.2 (4.8) years at start of OLE phase, 80% were concomitantly treated with miglustat and mean baseline 4DNPCCSS was 9.2 (6.5).
- Generally, the observed disease severity progressed slowly over the 48-month with a stepwise progression pattern (**Figure 3**).
- The overall pattern of AEs frequently reported were stable over the 48 months and consistent with the DB phase of the trial.
- The 3 most common AEs were diarrhea, upper respiratory tract infections and nasopharyngitis (**Table 2**).

CONCLUSIONS

- The rate of disease progression in patients treated with arimoclomol was comparable between the DB phase and the OLE phase.
- Arimoclomol was well tolerated with no new safety signals observed.

Figure 3. Mean Year-to-Year Change in 4DNPCCSS for up to 5 Years



At the end of the DB phase (12 months), the placebo group had a mean change from baseline in 4DNPCCSS of 1.9 points. From 12 months to 24 months the mean change decreased to 0.3 after starting treatment with arimoclomol (placebo-arimoclomol) and continued to be numerically smaller (potentially indicating slower disease progression) for the rest of the trial.
The arimoclomol group had a mean change from baseline in 4DNPCSS of 0.6 points at the end of the DB phase. The mean change in 4DNPCCSS scores for each year in the OLE for the arimoclomol-arimoclomol group was more variable and demonstrated an initial apparent worsening in the mean change in 4DNPCCSS of 1.4 for the first year of OLE (from end of DB to OLE Year 1). The mean year-to year change in 4DNPCCSS for the following three years of treatment in this group was 1.1, 0.3, and 0.8, respectively. The increase in disease progression during the first year of the OLE appeared to be driven in part by the few subjects who were not on miglustat as part of their routine clinical care and had rapid disease progression.

Table 2. Frequently Reported Adverse Events (>10%)

Preferred Term	Arimoclomol N = 41 n (%)
Diarrhea	10 (24.4%)
Upper respiratory infection	10 (24.4%)
Nasopharyngitis	8 (19.5%)
Epilepsy	8 (19.5%)
Corona virus infection	8 (19.5%)
Seizure	7 (17.1%)
Cough	7 (17.1%)
Bronchitis	7 (17.1%)
Weight decreased	6 (14.6%)
Epitaxis	6 (14.6%)
Constipation	6 (14.6%)
Rhinitis	5 (12.2%)
Influenza	5 (12.2%)
Vomiting	5 (12.2%)
Gastroenteritis	5 (12.2%)
Eczema	5 (12.2%)

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

SSIEM 2024
03-06 September, Porto, Portugal

MP and EM have worked under consultancy agreements for Zevra Therapeutics.
CD and SG are employees of Zevra Therapeutics.