Poster
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Safety and Efficacy of Arimoclomol in a Pediatric Substudy of Niemann-Pick Disease Type C Patients Aged 6 to <24 Months at Study Enrollment

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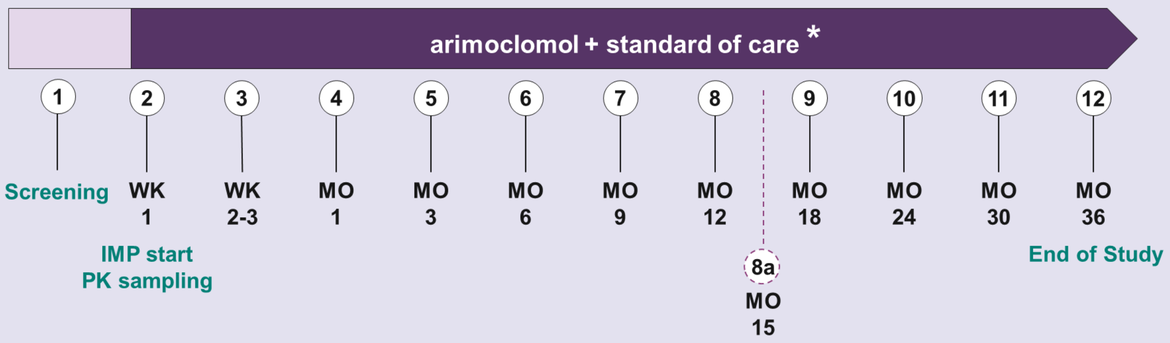
BACKGROUND

- Niemann-Pick disease type C (NPC) is an ultra-rare, progressive neurodegenerative lysosomal disease.
- Clinical presentation is heterogeneous with declining neurological functions.
- Onset of NPC symptoms can occur throughout life from the prenatal period to adulthood.
- Generally, the age of onset determines the speed of disease progression.
- For patients with early-infantile onset of NPC (onset of neurological symptoms <24 months of age) the median age of death is 48 months (range, 7-132 months).[1]
- Arimoclomol, an orally available small molecule, is the first FDA-approved treatment for NPC in patients aged ≥2 years, in combination with miglustat.
- To assess and evaluate safety and tolerability of arimoclomol treatment in children with NPC younger than 2 years, a pediatric substudy to the pivotal arimoclomol phase 2/3 trial CT-ORZY-NPC002 (NCT02612129) was implemented.

Figure 1: Pediatric Substudy Design

Open-label interventional substudy in NPC patients aged 6 to <24 months



WK = week, MO = month (after visit 2)

Clinic visit

If a patient is <12 months old at inclusion, an extra visit must be scheduled at month 15

* Additional visit(s) can be scheduled throughout the trial at the discretion of the investigator

METHODS

- The pediatric substudy is a multi-center, open-label, interventional study in patients with confirmed diagnosis of NPC, aged 6 to <24 months at study enrollment.
- The substudy enrolled 5 patients for up to 36 months of treatment with arimoclomol on top of routine clinical care.
- Eligibility criteria included: confirmed diagnosis of NPC1 or NPC2, if patients were on background treatment with miglustat the dose should have been stable for at least 1 month prior to enrollment. Start of new treatment with miglustat was not recommended during the first 12 months of arimoclomol exposure.
- Patients were followed closely with a condensed visit schedule (**Figure 1**).
- Efficacy was assessed by means of the Bayley Scales of Infant Development – Third Edition (BSID-III, Bayley III scores) every 6 months to evaluate the clinical development for each patient.
- Dosing was based on population pharmacokinetic simulation, with an arimoclomol dose of 3.2 mg/kg body weight until the age of 2 years. Arimoclomol was suspended in water and administered orally or by feeding tube.

Table 1. Adverse Event Overview

	N=5		
	n	%	E
All AEs	5	100	108
SAEs	2	40	15
Non-Serious AEs	5	100	93
Fatal AEs	0	0	0
Toxicity			
Grade 1	4	80	71
Grade 2	4	80	27
Grade 3	1	20	10
AEs possibly or probably related to arimoclomol	1	20	2
Action take with arimoclomol			
Dose not changed	4	80	106
Drug withdrawn	1	20	2

AE = adverse event; E = number of events; n = number of patients; SAE: serious adverse event; % = proportion of patients.

CONCLUSION

- Arimoclomol was well tolerated in children aged 14-23 months in the pediatric substudy with no new safety signals observed.

RESULTS

- The 5 patients were 14-23 months old at enrollment (**Table 2**). All were concomitantly treated with miglustat.
- A total of 108 AEs were reported in the substudy (**Table 1**). Most AEs were non-serious (86.1%), and mild or moderate in severity (toxicity grade 1&2, 90.7%). Most AEs (88%) resolved during the study.
- A total of 15 SAEs were reported for 2 patients. None of the SAEs were considered treatment related and all SAEs recovered/resolved without changes to arimoclomol dosing. No deaths were reported during the substudy.
- Two (2) AEs of *ALT increased* and *AST increased* were assessed as probably treatment-related. These were reported for the same patient (Patient 5); led to withdrawal of arimoclomol and resolved after cessation of treatment (**Table 1**).
- All 5 patients grew in height and increased their body weight during the trial (data not shown).
- Developmental functioning assessed with Bayley III scores (Change in Growth Scale Values [GSVs]) showed that 1 patient gained developmental skills, 2 patients were largely stable, and 1 patient declined during the substudy. Results were inconclusive for 1 patient as Bayley III was only assessed at the baseline visit.

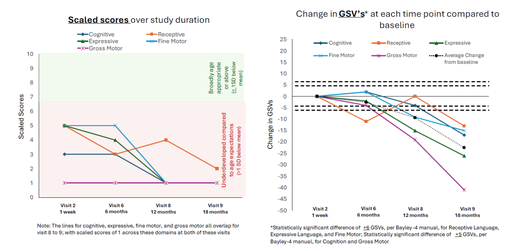
Table 2. Patient Profiles

Patient 1

Female, 23 months

Sex, Age at Enrollment	Female, 23 months
Mutation type	Missense/missense
Medical History	-
SAEs and AEs leading to treatment discontinuation	• escherichia urinary tract infection • pyrexia • device leakage • pyrexia • Nasopharyngitis

Bayley III Score

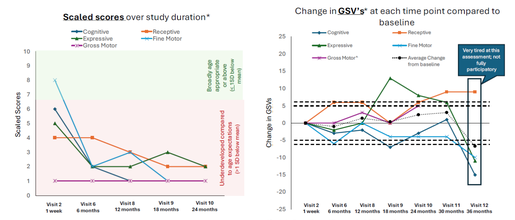


Patient 2

Female, 14 months

Sex, Age at Enrollment	Female, 14 months
Mutation type	Frameshift/frameshift
Medical History	Decreased blood iron
SAEs and AEs leading to treatment discontinuation	• influenza • vomiting • dehydration • hypoglycemia • RSV infection • device blocked • vomiting • vomiting • lung consolidation • pyelonephritis

Bayley III Score

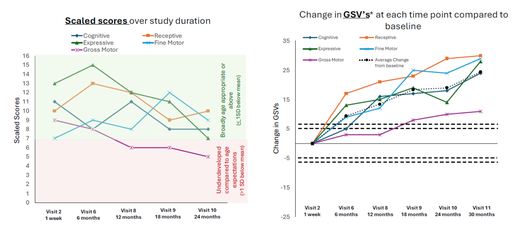


Patient 3

Female, 20 months

Sex, Age at Enrollment	Female, 20 months
Mutation Type	Missense/nonsense
Medical History	Splenomegaly, dyslipidemia, gaze palsy, eosinophilia
SAEs and AEs leading to treatment discontinuation	--

Bayley III Score

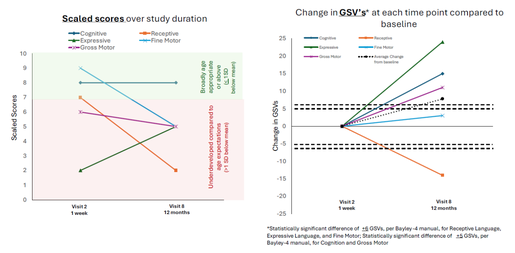


Patient 4

Male, 16 months

Sex, Age at Enrollment	Male, 16 months
Mutation Type	Missense/missense
Medical History	Splenomegaly, microcytic anemia, gross motor delay, developmental speech disorder
SAEs and AEs leading to treatment discontinuation	--

Bayley III Score

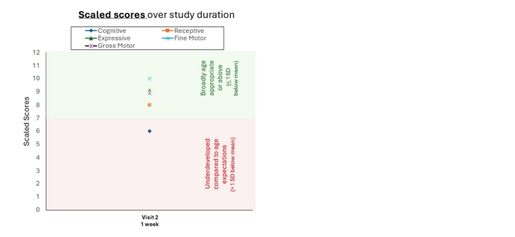


Patient 5

Male, 19 months

Sex, Age at Enrollment	Male, 19 months
Mutation Type	Missense (homozygous)
Medical History	Hepatosplenomegaly
SAEs and AEs leading to treatment discontinuation	• ALT increased • AST increased

Bayley III Score



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CONFLICT OF INTEREST STATEMENT

All authors have been involved in conducting the NPC-002 trial, which was supported by Zevra Therapeutics. Christine í Dali is an employee at Zevra Therapeutics.

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