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

Poster No. 065

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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 when used 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 3 trial CT-ORZY-NPC002 (NCT02612129) was implemented.

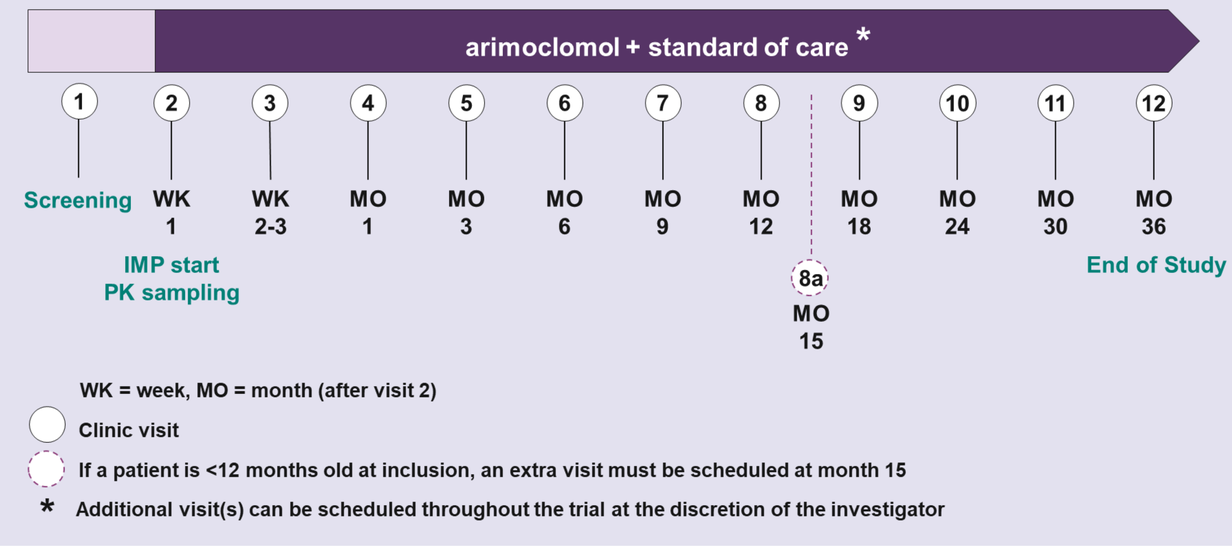
METHODS

- 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 a minimum of 12 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**).
- 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.

RESULTS

- The 5 patients were 14-23 months old at enrollment (**Table 1**). All were concomitantly treated with miglustat.
- A total of 92 AEs were reported in the substudy (**Table 2**).
- Most AEs were mild (68%) and recovered/resolved during the study.
- Most AEs and SAEs were assessed as not related to arimoclomol.
- Only 2 AEs were assessed as probably related; these were events of elevated ALT (alanine transaminase) and AST (aspartate aminotransferase), reported for the same patient (Patient 5). These 2 AEs also led to withdrawal of arimoclomol (**Table 1**).
- The most frequently reported AEs were fever, cough, common cold, and vomiting.
- None of the reported adverse events were unexpected, given the knowledge of the safety profile described in the 12-month double-blind phase and the 48-month open-label extension phase of the CT-ORZY-NPC-002 trial comprising patients aged 2 to <19 years (see also poster **229**).

Figure 1. Pediatric Substudy Design



CONCLUSIONS

- No unexpected adverse events were reported.
- Arimoclomol appeared to be well tolerated in children aged 14-23 months in the pediatric substudy.

Table 2. Adverse Event Overview

	N=5		
	n	%	e
All AEs	5	100	92
SAEs	2	40	16
Severity			
Mild	4	80	63
Moderate	4	80	19
Severe	1	20	9
Unassigned	1	20	1
AEs possibly or probably related to arimoclomol	1	20	2
AEs leading to treatment discontinuation	1	20	2

AE = adverse event; e = number of events; n = number of patients; SAE: serious adverse event; % = proportion of patients. Preliminary data, cutoff date: 06 February 2024.

REFERENCE

1. Yilmaz BS, Baruteau J, Rahim AA, Gissen P. Clinical and Molecular Features of Early Infantile Niemann Pick Type C Disease. *Int J Mol Sci*. 2020;21(14):5059. doi: 10.3390/ijms21145059.

Table 1. Patient Overview

Patient No.	Age at Enrollment (Months)	Time in Substudy[a] (Months)	Baseline Weight (kg)	Relevant Medical History	Serious Adverse Events and *Adverse Events Leading to Treatment Discontinuation*	Adverse Events Reported More Than Once
1	23	34	11.5	• Neonatal hepatitis	• Urine infection with e-coli, grade 2 (Moderate). • Fever, grade 1 (Mild). • CSF leakage from baklofen pump, grade 2 (Moderate). • Fever, grade 1 (Mild). • Common cold, grade 1 (Mild).	• Common cold • Cough • Diarrhea • Elevated AST • Fever • Vomiting
2	14	31	7.8		• Flu A, grade 3 (Severe) • Dehydration, grade 3 (Severe) • Ketotic hypoglycaemia, grade 3 (Severe) • Vomiting, grade 2 (Moderate) • Lower respiratory tract infection (respiratory syncytial virus), grade 3 (Severe) • Vomiting, grade 3 (Severe) • Blocked NJ tube, grade 3 (Severe) • Pyelonephritis, grade 3 (Severe) • Left lower lobe consolidation, grade 3 (Severe) • Diarrhoea and vomiting, grade 3 (Severe) • Recovery post procedure, grade 1 (Mild)	• Cough • Constipation • Fever • Lower respiratory tract infection • Upper respiratory tract infection • Vomiting
3	20	21	9.7	• Splenomegaly • Episode of elevated transaminases • Gaze palsy • Infections		• Common cold • Ulcus on the tongue • Upper respiratory tract infection • Vomiting
4	16	15	10.3	• Splenomegaly • Jaundice • Anemia • Developmental delay		
5	19	4	10.5	• Jaundice • Hepatosplenomegaly	• *Elevated ALT, grade 2 (Moderate)* • *Elevated AST, grade 2 (Moderate)*	

Preliminary data (cutoff date: 06 February 2024), terms are presented as reported – AEs have not yet been coded according to MedDRA terminology. [a] As of 21 February 2024, 3 patients were still ongoing.