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Evaluation of the Long-Term Effect of Arimoclomol in NPC - 48 Months Data from CT-ORZY-NPC-002

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Background and Purpose

- Niemann-Pick disease type C (NPC) is a rare, progressive neurodegenerative disease.
- NPC-002, a 12-month, double-blind, placebo-controlled trial (ClinicalTrials.gov: NCT02612129) demonstrated a statistically significant and clinically meaningful effect of arimoclomol in NPC.
- Here we evaluate the long-term effect of arimoclomol leveraging up to 48 months of exposure data from the combined DB and OLE phases of the trial.

Methods

- Disease progression was assessed with the 5-domain NPC Clinical Severity Scale (5DNPCCSS).
- Data from 2 clinical trials (NPC-001 and NPC-002, **Figure 1**) and 1 observational cohort (ASIS-01) were included.
- **Observational ASIS-01 cohort:** 22 patients followed for a period of 2-7 years. Assessments were performed during clinic visits.
- **Observational NPC-001 trial:** 36 patients on routine clinical care, with or without miglustat, were assessed at baseline, 31 patients assessed again at between 6 and 14 months.
- **NPC-002 trial:** Patients were randomized to 12 months of double-blind treatment with either arimoclomol (34 patients) or placebo (16 patients). After the double-blind period, all patients were offered 4 years of open-label arimoclomol treatment with assessments every 6 months.
- **Disease progression:**
- To estimate disease progression without arimoclomol treatment (referred to as "**untreated patients**"), data from patients in NPC-001 (including 1 screen failure with assessment) and placebo patients in NPC-002 were pooled (**Figure 1**, orange fill). The annual progression rate was then calculated from a linear regression model and extrapolated up to 48 moths (**Figure 2**).
  - This was similarly estimated for the subgroup of untreated patients on concomitant treatment with miglustat.
- To estimate the progression with arimoclomol treatment (referred to as "**arimoclomol treated patients**"), data were pooled for all patients treated with arimoclomol at any timepoint during NPC-002 (**Figure 1**, **blue** fill) and presented relative to initiation of arimoclomol.
- The progression trajectory of the arimoclomol-treated patients based on a mixed model repeated measures (MMRM) analysis was then compared graphically to the progression rate for untreated NPC-001/NPC-002 patients (**Figure 2**).
  - This was similarly done for the subgroup of arimoclomol treated patients on concomitant treatment with miglustat.
- The progression rate for the untreated NPC-001/NPC-002 cohort was compared with corresponding progression rates for the ASIS-01 cohort and literature reports (**Table 2**).

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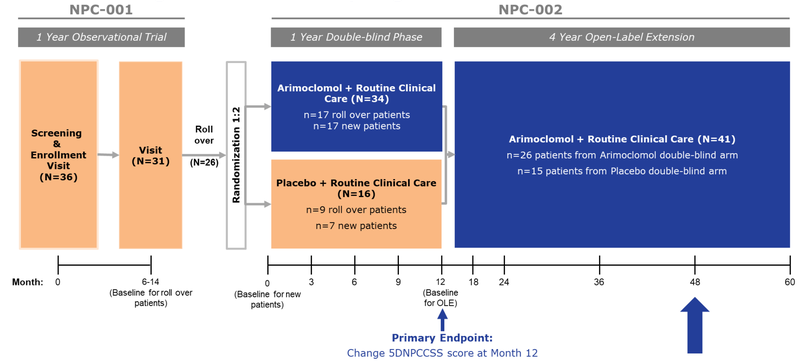
Disclosures: MP and EM were investigators in arimoclomol trials and have consultancy agreements with KemPharm. CD is an employee of KemPharm.

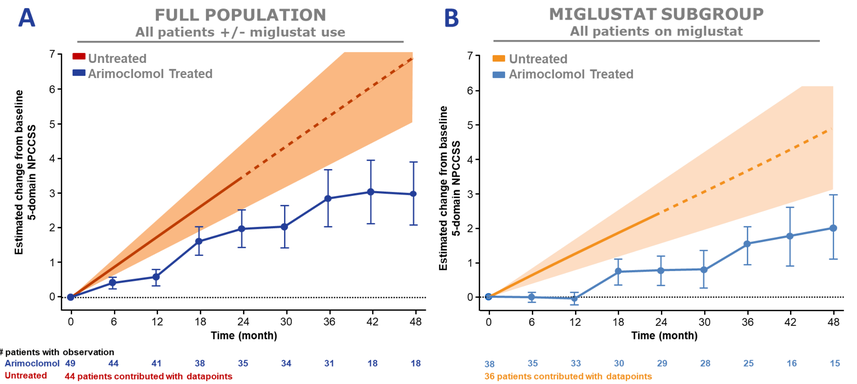
Figure 1: Clinical Efficacy Program for Arimoclomol in NPC



Results

- **Figure 2** shows the estimated disease progression in the full population of untreated patients in NPC-001/NPC-002 (**Figure 2 A, red line**), and in the subgroup on miglustat (**Figure 2 B, orange line**).
- Also shown in **Figure 2 A** and **B,** respectively, are disease progression for patients treated with arimoclomol in the full population (**dark blue line**) and in the subgroup on miglustat (**light blue line**).
- A lower progression rate was observed for the subgroup of patients treated with miglustat vs the full population (**Figure 2 B** vs **A**).
- Disease progression for patients treated with arimoclomol was lower vs estimated annual progression rate for untreated patients (**Figure 2 A**).
- Patients treated with both arimoclomol and miglustat had a lower progression rate than patients treated with miglustat alone (**Figure 2 B**).

Figure 2: Disease Progression in Untreated Patients (Linear Model) and Arimoclomol Treated Patients (MMRM)



Untreated: Linear regression model, random slope and intercept. Shaded areas represent standard error.
Arimoclomol Treated: MMRM adjusted for baseline score and miglustat use. Error bars represent standard error.

Results (Cont.)

- Baseline characteristics were overall similar between arimoclomol treated and untreated patients (**Table 1**).
- Untreated patients were slightly younger and with slightly lower disease severity at baseline as expected, due to the patient overlap between the 2 groups.

Table 1: Baseline Characteristics - Arimoclomol Treated and Untreated Patients

NPC-001/NPC-002	N	Age, mean (SD)	Treated with miglustat, n (%)	5DNPCCSS, mean (SD)	Full NPCCSS excluding hearing domains, mean (SD)	ASIS Score, mean (SD)
Arimoclomol treated	49	11.6 (5.1)	38 (77.6%)	11.9 (7.0)	20.8 (11.9)	2.1 (1.7)
Untreated	44	10.1 (4.8)	36 (81.8%)	9.6 (6.1)	17.0 (10.1)	2.0 (1.7)

ASIS: annual severity increment score; N: number of patients in cohort; n: number of patients with outcome; NPCCSS: NPC clinical severity scale; SD: standard deviation.

- Disease progression rates for untreated patients in the NPC-001/NPC-002 cohort were comparable to cohorts with similar age ranges (The ASIS-01 cohort ≤18 years and Ory et al., 2017) (**Table 2**).
- Data from Ory et al., 2017 and Yanjanin et al., 2010, on the full NPCCSS, confirm age range impacts the progression rate (**Table 2**).

Table 2: Disease Progression - Comparison Across Cohorts

Source	N	Age at baseline Mean (range)	Treated with miglustat	Duration of follow-up Years	Annual disease progression
5DNPCCSS					
Untreated NPC-001/NPC-002	44	10.1 (2-18)[a]	82%	0.5-2	**1.73**
ASIS-01 cohort ≤18 years	20	7.3 (1-17)	80%	1.7-7	**1.66**
ASIS-01 cohort	28	13.2 (1-46)	82%	1.7-7	**1.17**[b]
Full NPCCSS excluding hearing domains					
Untreated NPC-001/NPC-002	44	10.1 (2-18)[a]	82%	0.5-2	**2.88**
ASIS-01 cohort ≤18 years	20	7.3 (1-17)	80%	1.7-7	**2.99**
ASIS-01 cohort	28	13.2 (1-46)	82%	1.7-7	**2.14**[b]
Ory et al. 2017[1]	21	10.7 (4-22)	76%	0.5-2	**2.67**
Full NPCCSS					
Ory et al. 2017[1]	21	10.7 (4-22)	76%	Unknown	**2.92**
Yanjanin et al. 2010[2]	18	12.9 (4-51)	44%	1 - >10	**1.4**[b]
Yanjanin et al. 2010[2]	19	14.7 (2-38)	Not reported	1 - >10	**1.9**[b]

[a] Calculated using discrete age values at baseline [b] Cohort includes a wide age span. Adult patients usually have slower progression than pediatric patients.

1. Ory D, et al. *Lancet* 2017;390:1758-68.
2. Yanjanin NM, et al. *Am J Med Genet B Neuropsychiatr Genet*. 2010;153B:132–140.

Conclusions

- Data from similar cohorts of NPC patients show similar progression rates on the population level.
  - These cohorts were comparable with regards to age, standard of care, and disease severity.
- This dataset suggests that long-term progression may be reduced in patients treated with arimoclomol.
- Patients treated with arimoclomol may experience additional benefits from concomitant treatment with miglustat.