Poster
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Efficacy Results Across a 12-Month Double-Blind Randomized Trial and an Open-Label Extension Phase of Arimoclomol for Treatment of Niemann-Pick Disease Type C in Patients Treated with Miglustat

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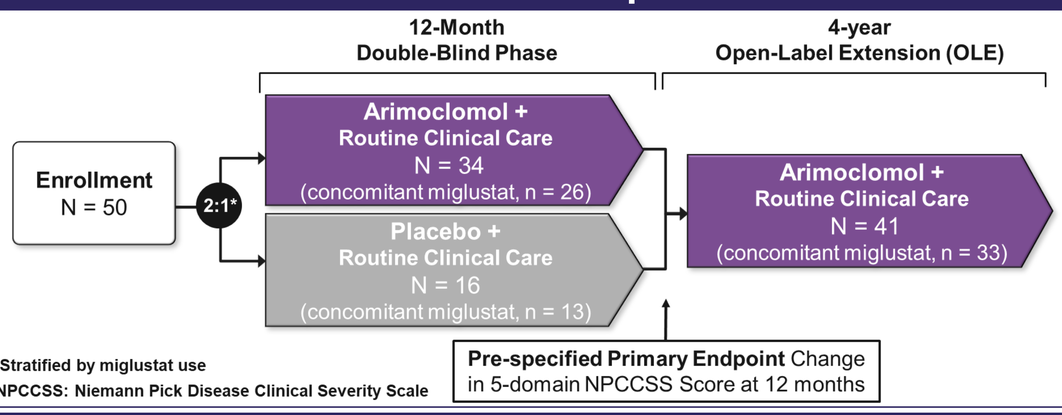
15th International Congress of Inborn Errors of Metabolism, 2025, Kyoto, Japan

BACKGROUND

- Niemann-Pick disease type C (NPC) is an ultra-rare, progressive neurodegenerative lysosomal disease with heterogeneous clinical presentation.
- The NPC Clinical Severity Scale (NPCCSS) is a disease-specific, clinician-reported outcome measure used to quantify disease progression.
- A validated 5-domain (5DNPCCSS [Swallow, Fine Motor Skills, Speech, Ambulation, and Cognition domains]), and a validated rescored 4-domain (R4DNPCCSS [Swallow, Fine Motor Skills, Speech and Ambulation domains]) version, including domains rated as the most important by patients, caregivers, and clinicians were used in the 12-month double-blind (DB), randomized, placebo-controlled trial investigating efficacy and safety of arimoclomol (NPC002, NCT02612129)[1,2] and the open-label extension (OLE) of this trial.
- Arimoclomol, an orally available small molecule, is the first FDA-approved treatment for NPC when used in combination with miglustat.
- Here we present the prespecified efficacy analysis of patients on routine clinical care with miglustat, treated with arimoclomol versus placebo from NPC002.
- Within-patient comparisons for patients switching from placebo (with concomitant miglustat) to addition of arimoclomol across the NPC002 DB and OLE trial phases are also presented.

Figure 1: NPC002 Double-Blind and Open-Label Extension Phase



METHODS

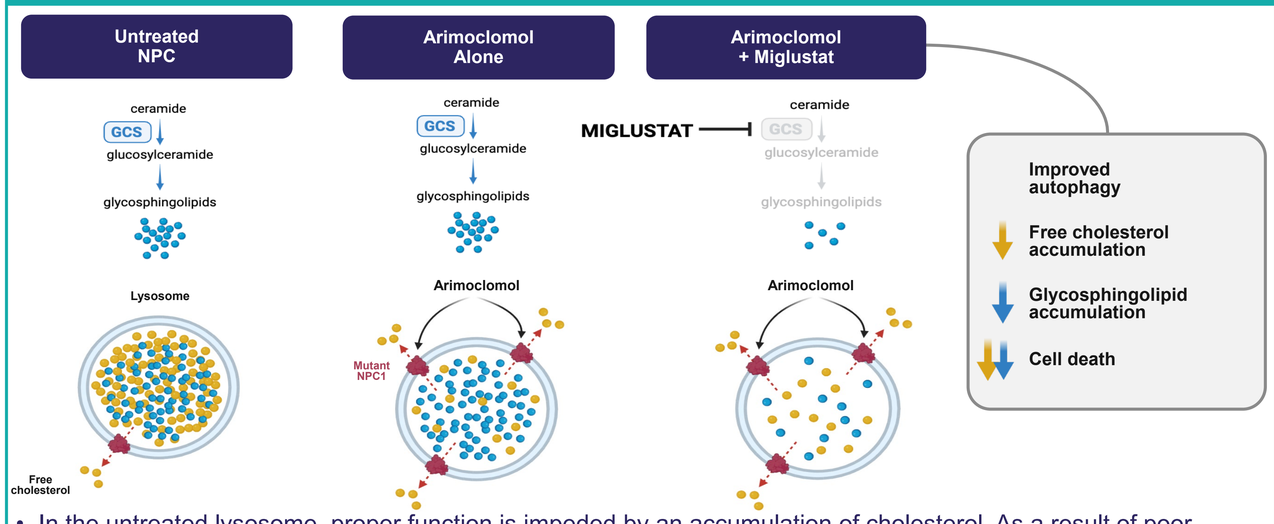
- The trial was conducted at 15 sites in 9 countries (US and EU).
- Patients completing the DB phase were offered to continue into the OLE phase.
- Efficacy for patients concomitantly treated with miglustat from the NPC002 DB trial is presented as mean change over 12 months in 5DNPCSS and R4DNPCCSS.
- While the pre-specified primary analysis for the difference in change in 5DNPCCSS was a mixed model for repeated measures (MMRM), the R4DNPCCSS was analyzed with an analysis of covariance (ANCOVA).
- All patients in the placebo group who completed the DB phase of NPC002 continued in the OLE phase, where they received arimoclomol treatment.
- Therefore, within-patient comparisons of mean annual change in 5DNPCCSS were made between placebo and subsequent arimoclomol treatment in patients on concomitant miglustat.
- Patients and investigators were unaware of their randomized assignment during the DB and for the first 2 years of the OLE phase.

Table 1: Demographic and Baseline Characteristics – Patients on Concomitant Miglustat - NPC002

	Arimoclomol (N=26)	Placebo (N=13)
Age, mean (SD)	12.8 (4.7)	9.1 (3.6)
< 4 years, n (%)	2 (7.7%)	2 (15.4%)
4 to < 8 years, n (%)	3 (11.5%)	1 (7.7%)
8 to < 12 years, n (%)	7 (26.9%)	7 (53.8%)
≥ 12 years, n (%)	16 (61.5%)	2 (15.4%)
Female, n (%)	14 (53.8%)	8 (61.5%)
Race, n (%)		
White	24 (92.3%)	10 (76.9%)
Asian	1 (3.8%)	1 (7.7%)
Native Hawaiian or other pacific islander	0	1 (7.7%)
Unknown	1 (3.8%)	1 (7.7%)
BMI; mean (SD)	19.23 (4.57)	18.78 (3.06)
Age at first neurological symptom, mean (SD)	5.25 (3.34)	4.04 (3.20)
NPCCSS full scale score, mean (SD)[a]	20.4 (12.1)	17.2 (12.2)
5DNPCCSS score, mean (SD)	11.7 (7.2)	9.6 (7.1)

[a] NPCCSS total score = all 17 domains minus Auditory Brainstem Response and Hearing. BMI = body mass index; N = number of patients; NPCCSS = Niemann-Pick Disease type C Clinical Severity Scale; 5DNPCCSS = 5-domain Niemann-Pick disease type C Clinical Severity Scale; SD = standard deviation.

PUTATIVE MODE OF ACTION OF COMBINED TREATMENT WITH ARIMOCLOMOL AND MIGLUSTAT



- In the untreated lysosome, proper function is impeded by an accumulation of cholesterol. As a result of poor lysosomal function, other lipid by-products also accumulate. Glycosphingolipids are one of these by-products (**blue dots**).
- With arimoclomol treatment, cholesterol clearance is enhanced by increased NPC1-mediated transport of cholesterol out of the lysosomal compartment (**yellow dots**).[3]
- Miglustat, through its MOA in inhibiting glucosylceramide synthase, creates less glycosphingolipids (**blue dots**) and enhances lysosomal function by improving overall lipid homeostasis in the lysosomes.
- Arimoclomol and miglustat have two different, apparently complimentary, MOAs leading to improved cell health.

RESULTS

- 33 patients were on concomitant miglustat during the DB phase of the NPC002 study, 26 in the arimoclomol group and 13 in the placebo group (**Figure 1** and **Table 1**). Mean age (SD) was 12.8 (4.7) and 9.1 (3.6) years, respectively. Mean disease severity at baseline was comparable (**Table 1**).
- Statistically significant differences in change from baseline between arimoclomol and placebo groups were seen with both the 5DNPCCSS and R4DNPCCSS (**Figure 2**).
- 12 patients from the NPC002 DB placebo group who were on concomitant treatment with miglustat went on to receive arimoclomol in the OLE phase (**Figure 3**).
- Patients switching from placebo in the DB phase to arimoclomol in the OLE, while on continued concomitant miglustat treatment experienced a decline in annual disease progression (**Figure 3**).
- The mean annual change decreased from 1.9 to -0.1 after starting treatment with arimoclomol and continued to be numerically smaller for the rest of the trial.

Figure 2: Change from baseline in 5DNPCCSS and R4DNPCCSS - Patients on Concomitant Miglustat – NPC002

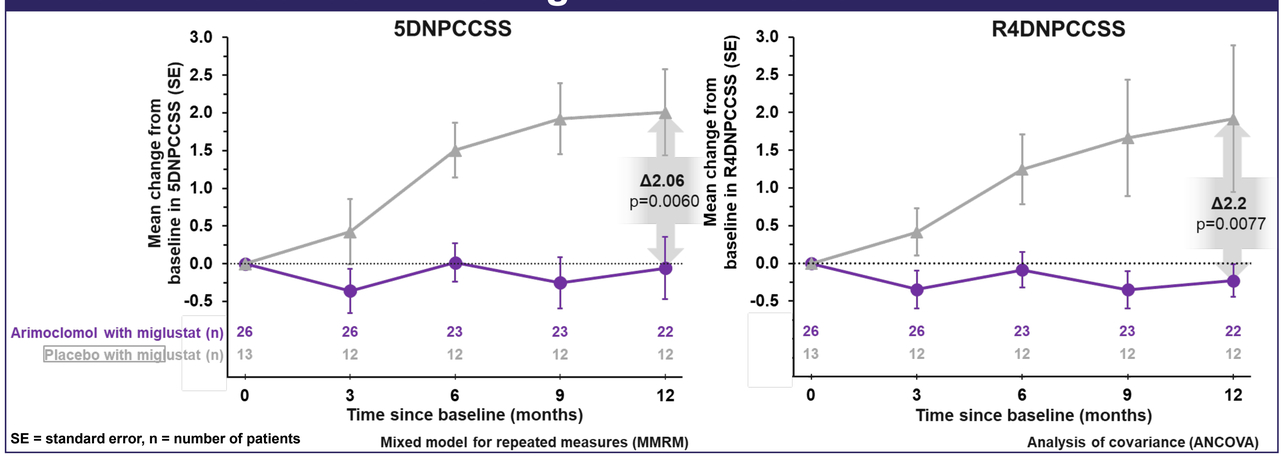
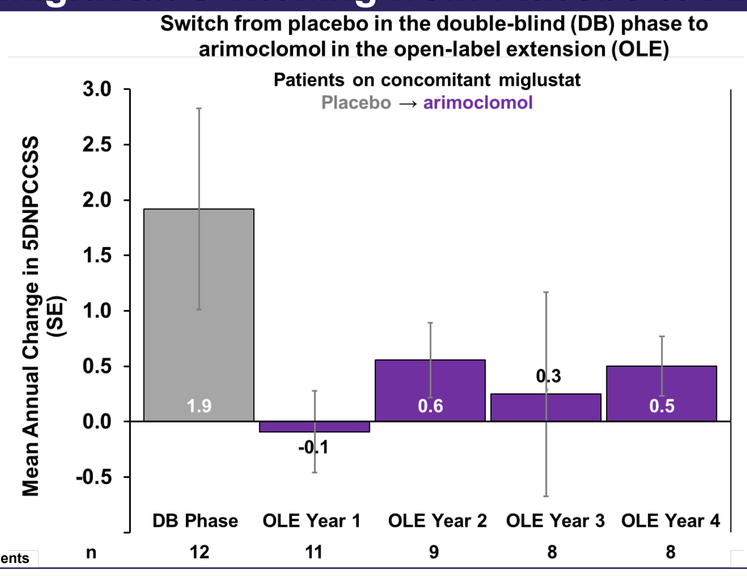


Figure 3: Annual Change in 5DNPCCSS - Patients on Concomitant Miglustat Switching from Placebo to Arimoclomol



CONCLUSION

- These data demonstrate that arimoclomol treatment as add-on to routine clinical care with miglustat slowed NPC disease progression.

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ACKNOWLEDGEMENTS

We want to thank Dr. Marc Pattterson for his support and contributuions to the NPC002 trial.

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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. Sven Guenther was an employee of Zevra Therapeutics at the time of the project and currently a consultant of Zevra Therapeutics.