Changing The Course of NPC: Long-term Evidence for Disease Modification in a Heterogenous Population

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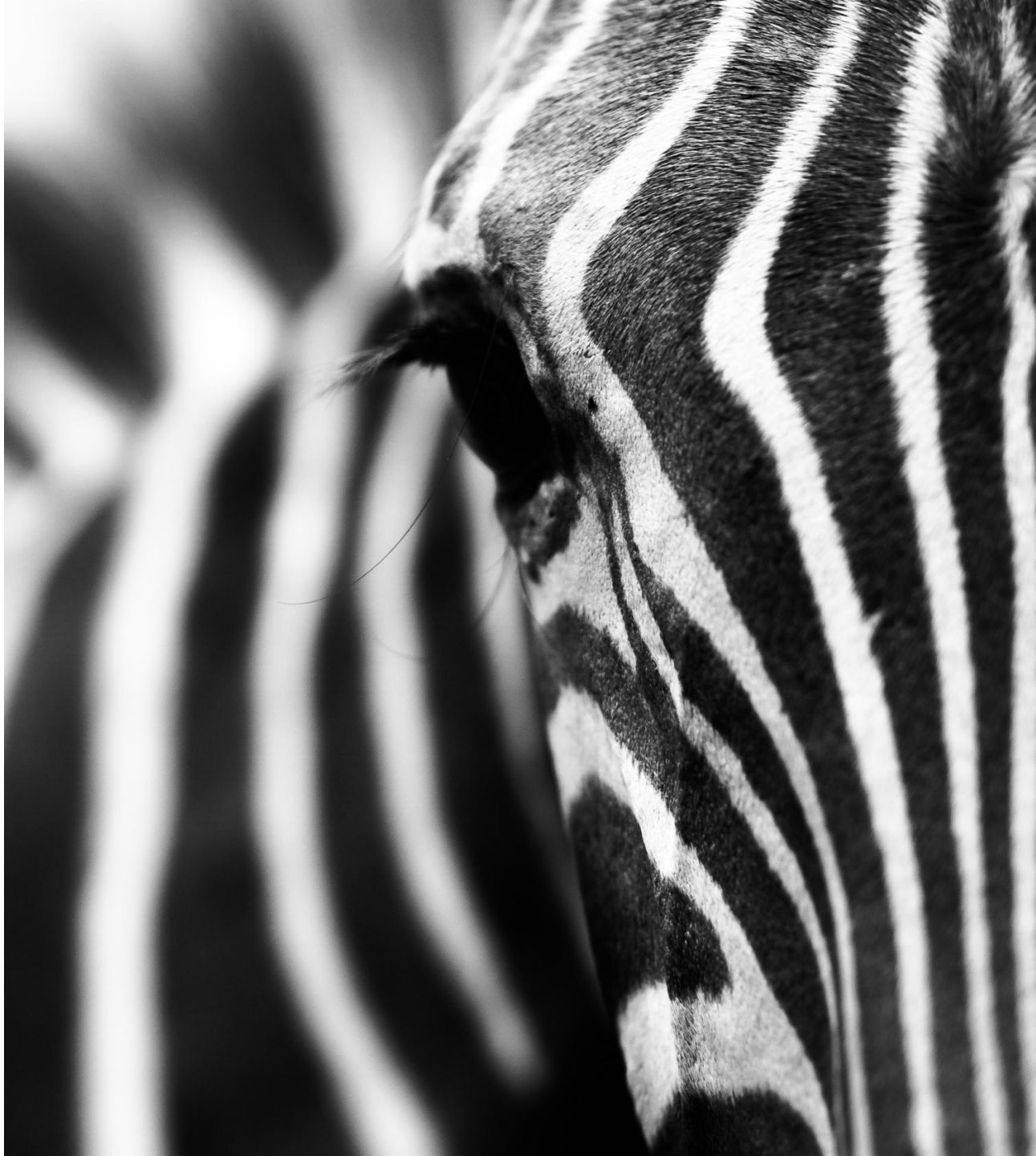
ZEVRA THERAPEUTICS



MRC-2500071 09/25

Disclaimer

- Eugen Mengel has received investigator fees and/or consultant honoraria from Cyclo Therapeutics, Amicus, Idorsia, Intrabio, Denali, JCR, Prevail, Freeline Therapeutics, Alexion, Zevra, Sanofi Genzyme, and Takeda.

Arimoclomol Improves Lysosomal Function in NPC[1]

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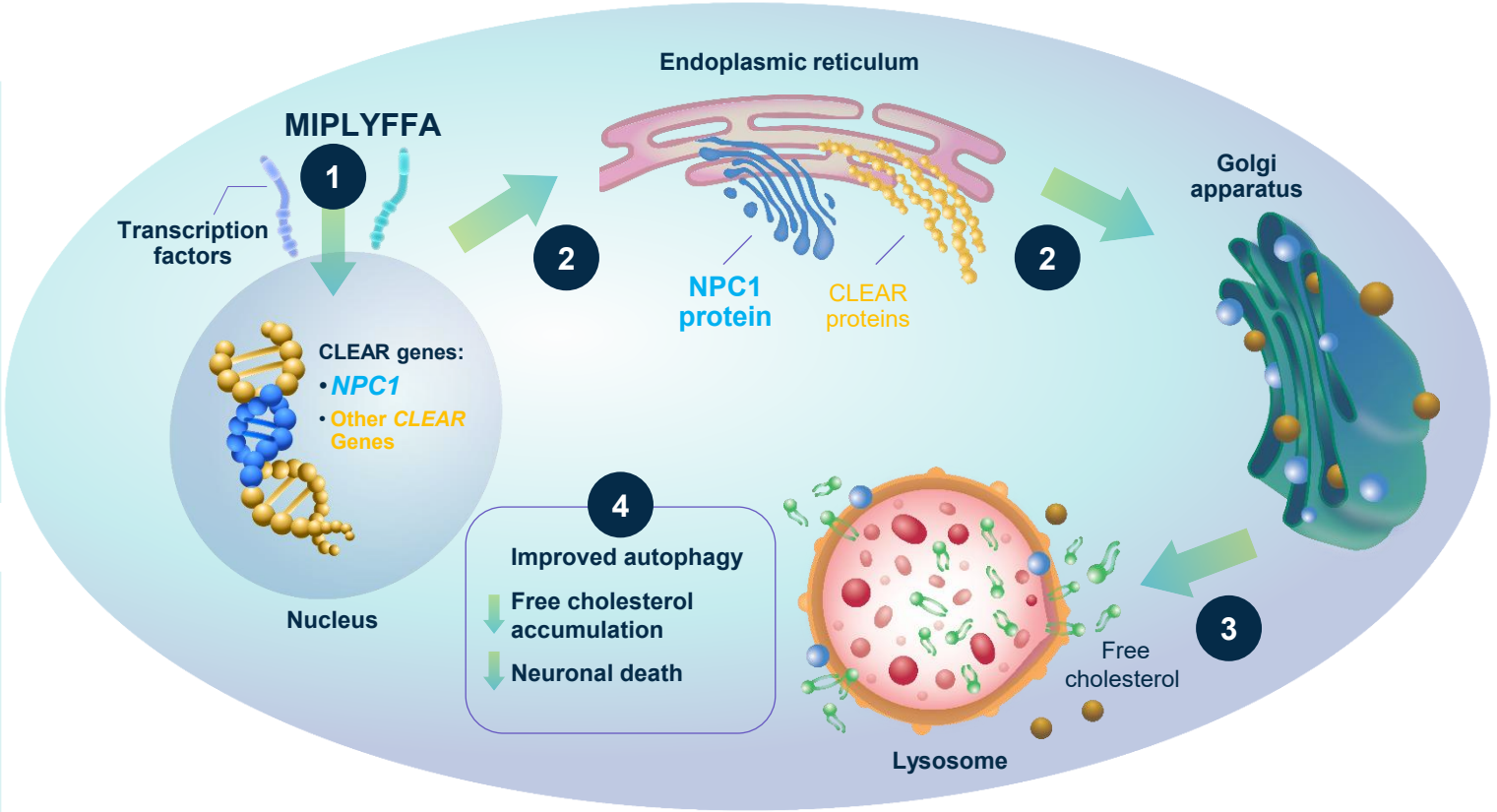
1

Arimoclomol activates transcription factors, leading to **upregulation of CLEAR network genes** (including *NPC1* gene)[1,2]



2

These genes then express more of the NPC1 protein as well as other proteins belonging to the CLEAR network[1,2]

3

In the lysosome, **NPC1 protein helps with transporting cholesterol**[1,2]

4

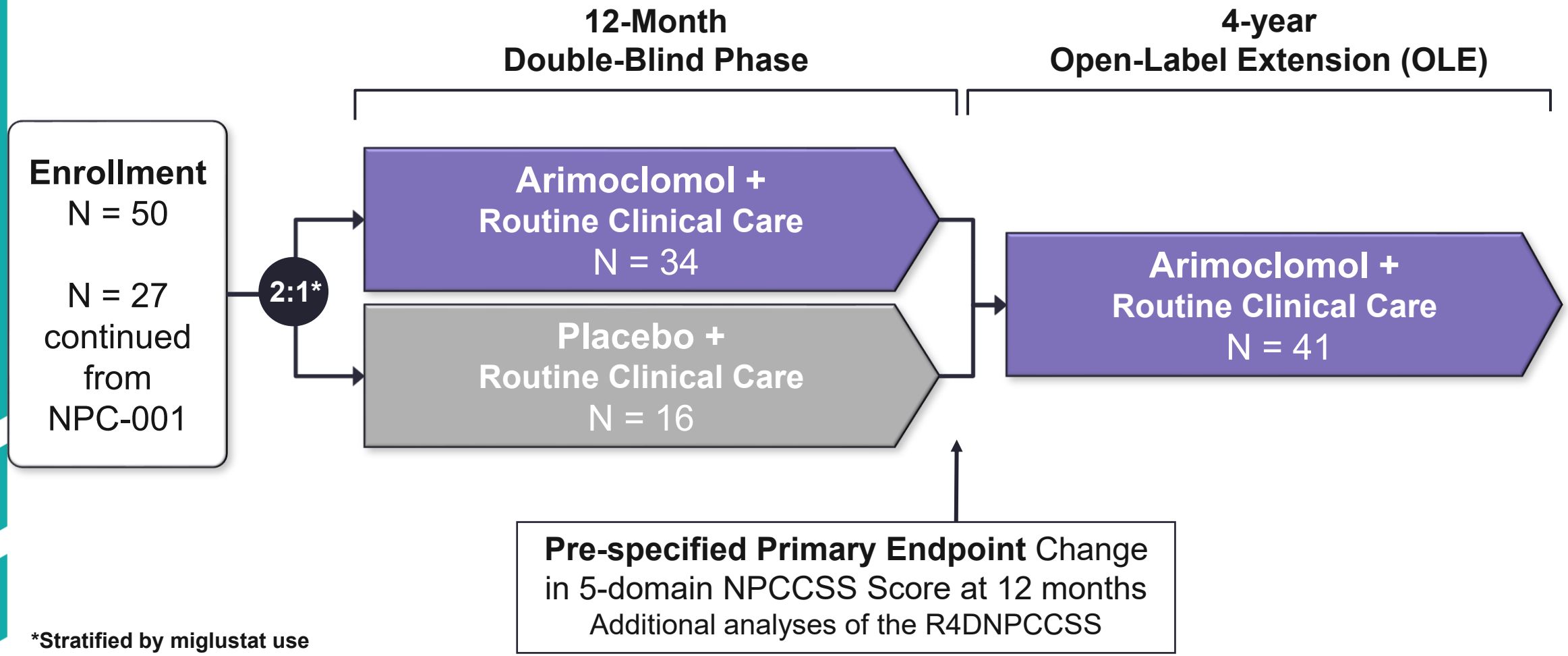
This **reduces free cholesterol accumulation and prevents cell death**[1,2]

Arimoclomol addresses the underlying pathology of NPC.[1-3]

CLEAR, coordinated lysosomal expression and regulation; ER, endoplasmic reticulum.

1. Data on file. Zevra Therapeutics, Inc. **2.** Shammas H, et al. *Mol Genet Metab*. 2025;145(1):109103. **3.** Mengel E et al. *J Inherit Metab Dis*. 2021;44(6):1463-1480.

Design of Pivotal Study 002 and Open-Label Extension[1-3]

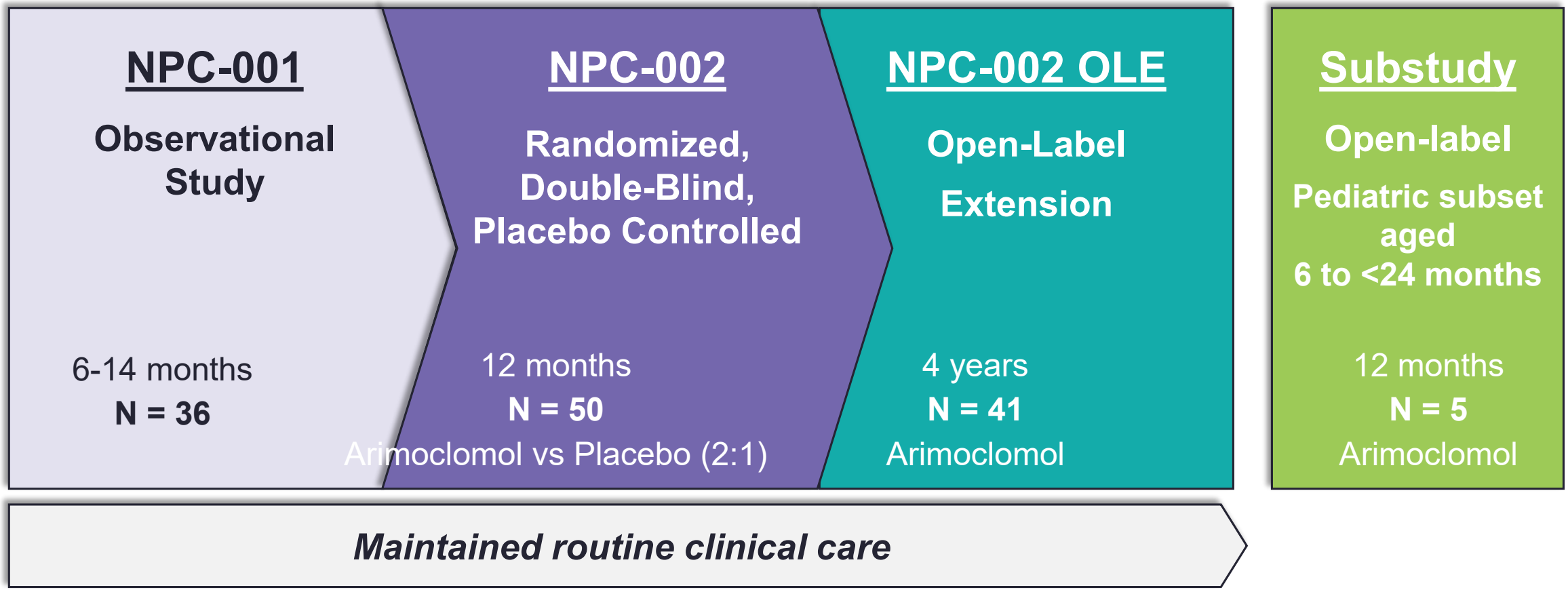


*Stratified by miglustat use

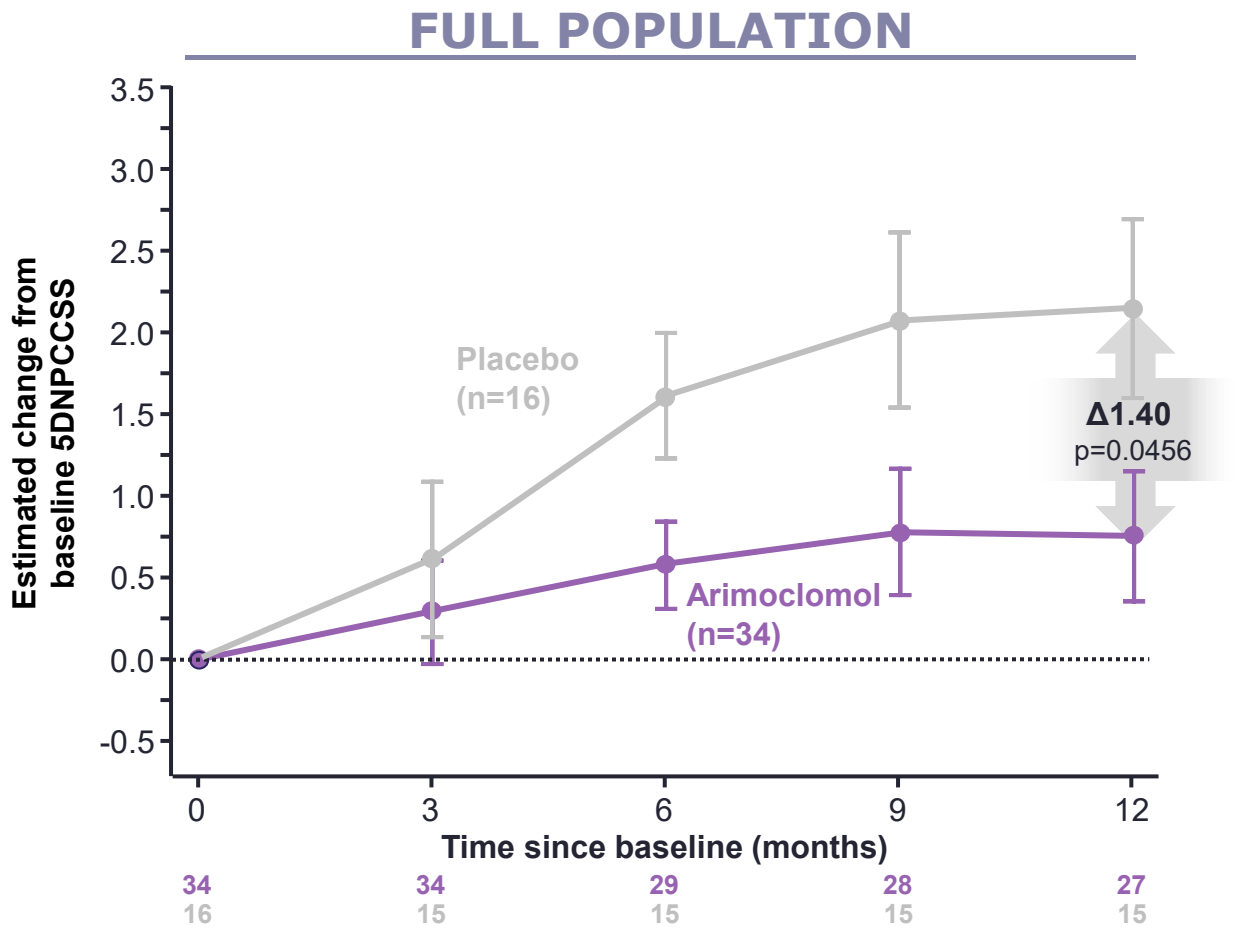
NPCCSS: Niemann Pick Disease Clinical Severity Scale

1. Mengel E et al. *J Inherit Metab Dis*. 2021;44(6):1463-1480 2. Mengel E et al. *Mol Genet Metab*. 2025;43(2025):101233. 3. Mengel E et al. *Mol Genet Metab*. 2025;145(2025):109189.

Arimoclomol Clinical Program Designed for a Broad NPC Population



Study NPC-002 Met the Pre-specified 5DNPCCSS Primary Endpoint[1]



Arimoclomol demonstrates clinically relevant slowing of disease progression in the primary analysis

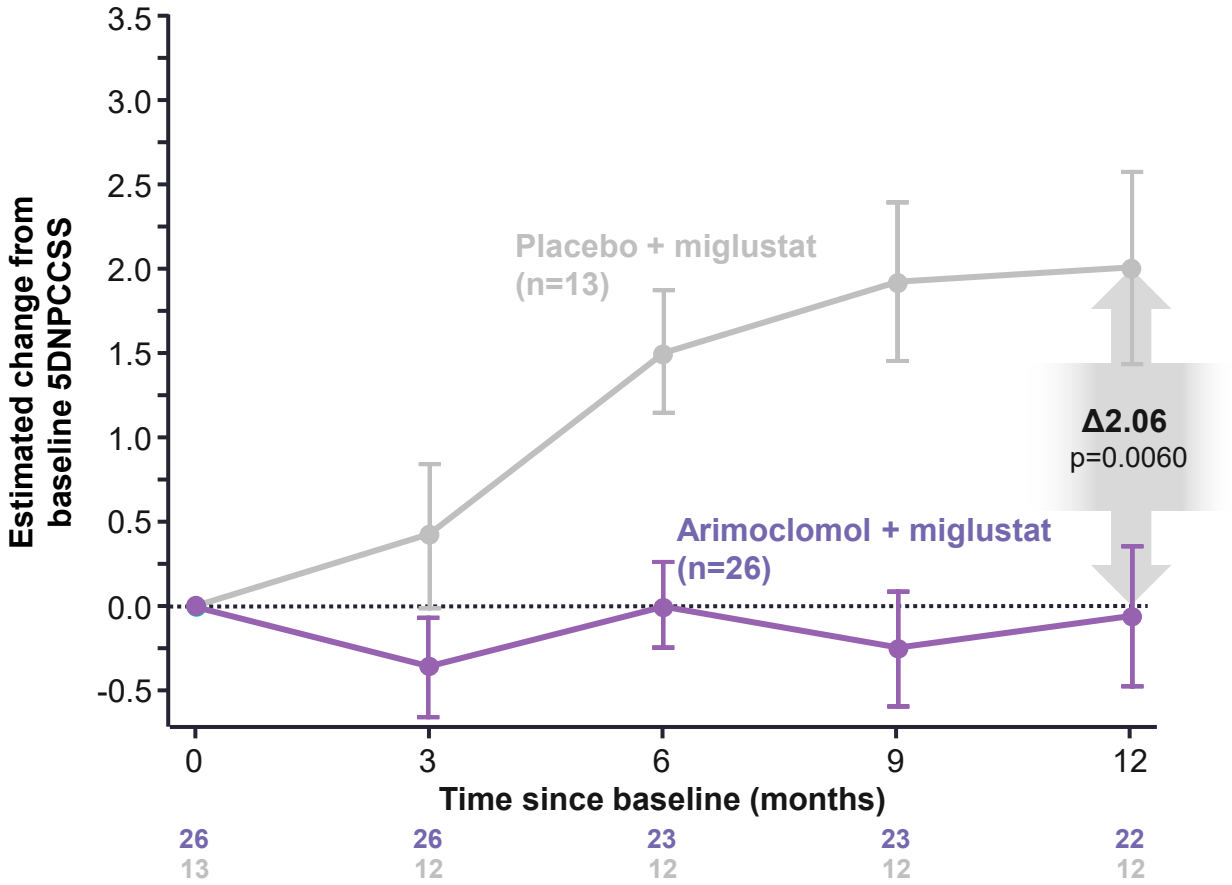
A treatment difference of ≥1 is a clinically meaningful change[2]

Error bars: standard error of the mean

1. Mengel E et al. *J Inherit Metab Dis*. 2021;44(6):1463-1480 **2.** Patterson M et al. *Orphanet J Rare Dis. 2021;16:79.*

Study NPC-002 - 5DNPCCSS Participants on Concomitant Miglustat[1]

Participants ON CONCOMITANT MIGLUSTAT



Arimoclomol demonstrates a highly significant slowing of disease progression compared with placebo in those participants taking miglustat as part of routine clinical care

Error bars: standard error of the mean

1. Mengel E et al. *J Inherit Metab Dis*. 2021;44(6):1463-1480

Adverse Events Were Generally Mild to Moderate in Severity, and Few Led to a Withdrawal of Treatment

Adverse Reaction	MIPLYFFA with miglustat n=26 n (%)	Placebo with miglustat n=13 n (%)
Upper respiratory tract infection*	**8** (31)	**2** (15)
Diarrhea	**6** (23)	**3** (23)
Decreased weight	**4** (15)	**0**
Decreased appetite	**3** (12)	**0**
Tremor	**3** (12)	**0**
Urticaria**	**3** (12)	**0**
Headache	**3** (12)	**1** (8)
Lower respiratory tract infection	**3** (12)	**1** (8)
Seizure	**3** (12)	**1** (8)

Common adverse reactions occurring in ≥8% of patients treated with MIPLYFFA and more frequently than in patients receiving placebo†

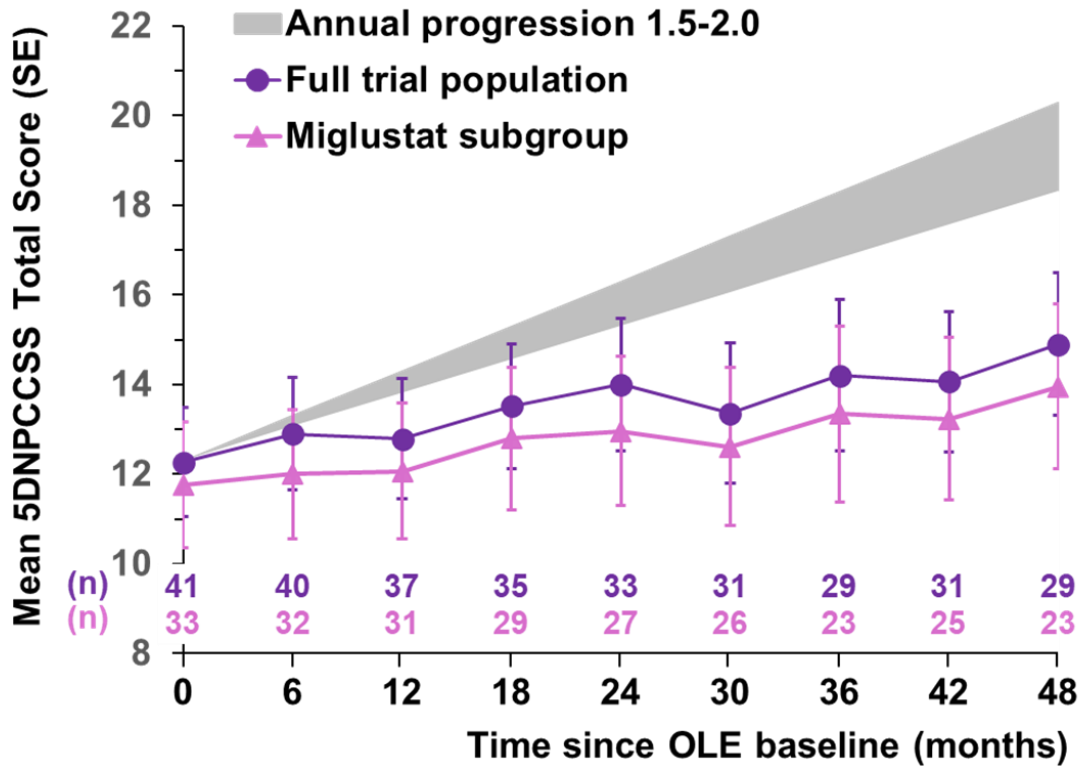
*Upper respiratory tract infection: combined incidence of upper respiratory tract infection and rhinitis.
**Urticaria: Includes one patient in which urticaria occurred alone (3%) and two patients who had urticaria with angioedema (6%).
†Placebo subgroup also received miglustat.

MIPLYFFA Full Prescribing Information. Celebration, FL, US, Zevra Therapeutics Inc.; 09/2024.

Arimoclomol has Demonstrated Long-Term Effectiveness of up to 5 years[1,2]

Continued effectiveness in open-label extension (OLE)

- Observed disease severity progressed slowly over the 48 months, with a stepwise progression pattern[2]
- Expected annual progression based on natural history and double-blind phase = 1.5-2.0 pts[1,3-4]



Error bars: standard error of the mean

1. MIPLYFFA Full Prescribing Information. Celebration, FL, US, Zevra Therapeutics Inc.; 09/2024. **2.** Mengel E et al. *Mol Genet Metab*. 2025;145(2025):109189. **3.** Mengel et al. *Orphanet J Rare Dis*. 2020;15:328. **4.** Mengel E, et al. *Mol Genet Metab Rep*. 2025;43:101233.

Arimoclomol was Well-Tolerated with No New Safety Signals Observed over 4 Years[1]

The overall pattern of frequently reported AEs was stable over the 48 months and consistent with observations from the double-blind phase of the trial.

- 38 (93%) of any AE
- 15 (37%) severe or serious AEs
- 4 (10%) AEs leading to treatment discontinuation*
- 2 (5%) AEs with fatal outcome due to disease progression

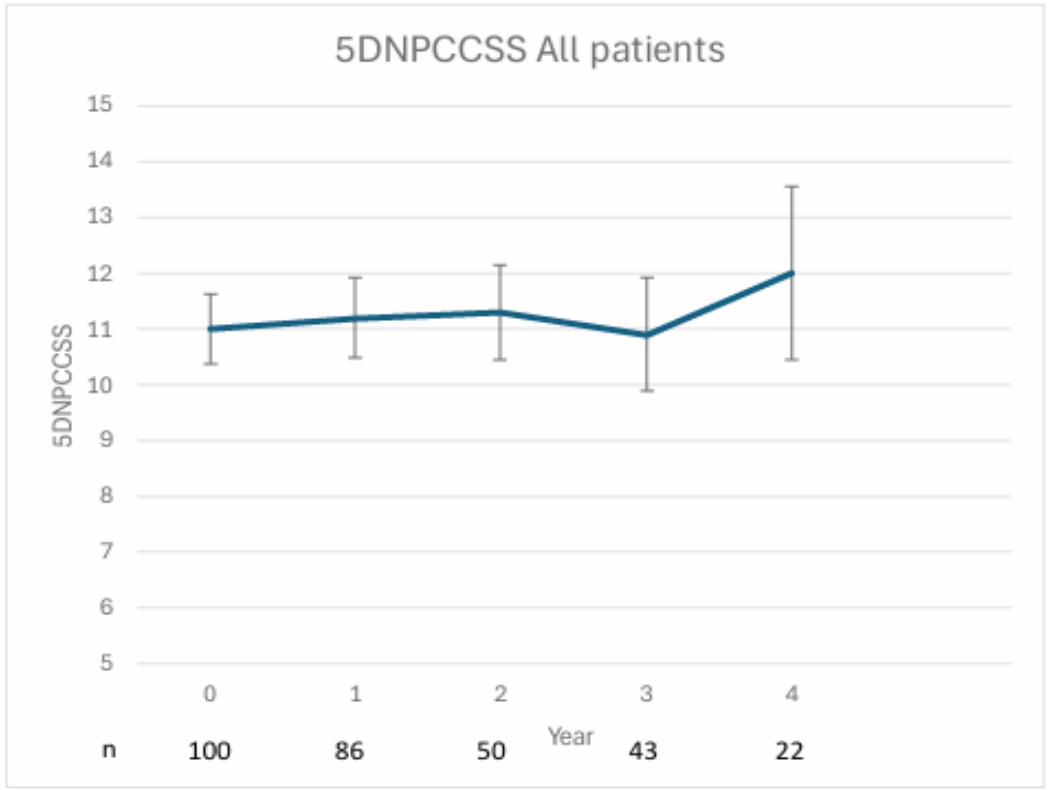
The 3 most common AEs were:	**MIPLYFFA with miglustat N=41 n (%)**
Diarrhea	**10** (24.4%)
Upper respiratory tract infection	**10** (24.4%)
Nasopharyngitis (common cold)	**8** (19.5%)

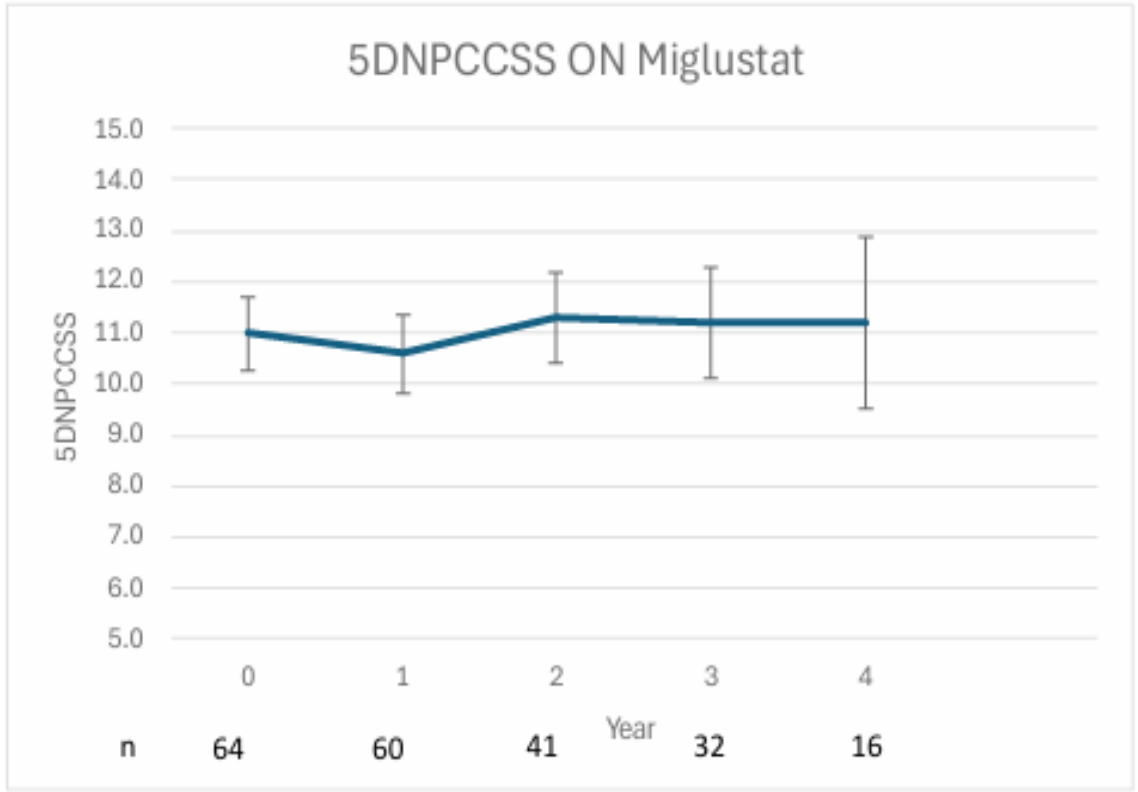
N=number of patients in the extension analysis set; n=number of patients with event; %=percentage of patients with event.
*2 patients discontinued due to safety and 2 discontinued due to physician decision.
AE=adverse event

1. Mengel E et al. *Mol Genet Metab.* 2025;145(2025):109189.

US Expanded Access Program Effectiveness

The US EAP included NPC patients ages 2 - 64.5





- There were 248 AEs with 241 being classified as treatment-emergent (TEAEs)

Error bars: standard error of the mean
Zevra Data on File

Pediatric Sub-Study

The pediatric sub-study was conducted to assess the safety and tolerability of arimoclomol treatment in children under 2 years of age with NPC.

- 5 patients, aged 14–23 months, all receiving miglustat treatment were included up to 36 months.
- Of 108 AEs reported, majority were mild and resolved and unrelated to arimoclomol.
- Most reported AEs were fever, cough, common cold, and vomiting
- 2 events in 1 patient (elevated liver enzymes) assessed as probably related to arimoclomol led to withdrawal of treatment.

Efficacy was measured using the Bayley III score for child development.

- 1 patient gained developmental skills, 2 patients were stable, 1 patient declined, and 1 patient only had the baseline visit.
- In conclusion Arimoclomol was well-tolerated in these very young patients

Summary

- Arimoclomol addresses the underlying pathology of NPC
- Arimoclomol has established effectiveness across the 12-month clinical trial, 4-year open label extension, and US Expanded Access Program datasets
- Arimoclomol is well tolerated with no new safety signals across long-term studies through 5 years
- Arimoclomol was well tolerated in children ages 14-23 months in the pediatric substudy

Zevra would like to thank all the participants, families & caregivers, clinical sites & staff who participated in our clinical trials and expanded access programs globally