

Arimoclomol for the Treatment of NPC in a Real-World Setting: Long-Term Outcomes from an Expanded Access Program in the USA

Walla Al-Hertani¹, Elizabeth M. Berry-Kravis², Raymond Wang³, Marc Patterson⁴, Can Ficicioglu⁵, Loren Pena⁶, Kristina Julich⁷, Damara Ortiz⁸, Paula Schleifer⁹, Caroline Hastings¹⁰, Paul Hillman¹¹, Ronan O'Reilly¹², Christine Dalí¹², Daniel Gallo¹²

¹ Boston Children's Hospital, Harvard Medical School, MA, USA, ²Rush University Medical Center, IL, USA, ³Children's Hospital of Orange County, CA, USA, ⁴Mayo Clinic Children's Center, MN, USA, ⁵Children's Hospital of Philadelphia, PA, USA, ⁶Cincinnati Children's Hospital, OH, USA, ⁷Dell Medical School, The University of Texas at Austin, TX, USA, ⁸UPMC Children's Hospital, PA, USA, ⁹Nicklaus Children's Hospital, FL, USA, ¹⁰UCSF Benioff Children's Hospitals, CA, USA, Department of Pediatrics, ¹¹Division of Medical Genetics, McGovern Medical School, University of Texas Health Science Center at Houston (UTHealth Houston) and Children's Memorial Hermann Hospital, Houston, TX, ¹²Zevra Therapeutics, FL, USA

The Society for the Study of Inborn Errors of Metabolism (SSIEM)
September 3rd-6th, Porto, Portugal

BACKGROUND AND OBJECTIVE

- Niemann-Pick disease Type C (NPC) is an ultra-rare, progressive neurodegenerative lysosomal storage disease with no FDA-approved treatments and persisting unmet medical need.
- Arimoclomol is an investigational orally available small molecule for the treatment of NPC.
- Rare disease data are sparse and data collection opportunities limited.
- The US arimoclomol Expanded Access Program (EAP), initiated in June 2020 (NCT04316637) provides drug access to eligible NPC patients.
- Optional real-world data (RWD) collected in an ongoing protocol-driven EAP aimed to expand the understanding of NPC, including populations not previously studied in randomized clinical trials, for patients consenting to RWD collection.
- Here we present effectiveness and safety data from pediatric and adult NPC patients treated in the US EAP with arimoclomol over a 3-year period.

METHODS

- The protocol-driven US EAP is an ongoing, prospective real-world study designed to provide expanded access to arimoclomol for NPC patients who were not eligible for or unable to participate in clinical trials.
- The 15-site US EAP was designed to also collect RWD for those participants who consented to data collection.
- Effectiveness was measured as the change from baseline in the physician-reported 5-domain NPC Clinical Severity Scale (5DNPCSS) and 4-domain NPC Clinical Severity Scale (4DNPCSS).
- Scores were analyzed at 1-year (<13 months), 2-year (≥13 to <25 months), and 3-year (≥25 to <37 months) post-treatment initiation for patients with a minimum of 1 year of follow-up using descriptive statistics.
- All adverse events were recorded during the US EAP and were summarized.

RESULTS

Table 1: Key EAP Eligibility and Ineligibility Criteria*

Eligibility Criteria	Ineligibility Criteria
Confirmed NPC diagnosis and at least 1 neurological symptom, age ≥ 2 years, permanent US resident, if taking miglustat (Zavesca®), the patient must have been on the target dose for the past 6 weeks, if history of seizures, the condition must be adequately controlled	Severe liver disease; kidney disease; known or suspected allergy or intolerance to arimoclomol; pregnancy, planning to become pregnant or currently breastfeeding; treatment with other investigational drug during the EAP or in the 4 weeks prior to arimoclomol treatment start

* Eligibility and ineligibility criteria described are not inclusive of all criteria. Refer to NCT04316637 for complete criteria

Table 2: NPCCSS Assessments

5 Domain Niemann Pick Type C Clinical Severity Scale (5DNPCSS)				
Ambulation	Cognition*	Fine Motor	Speech	Swallow**
Domain Scoring: Individual domains: 0 (normal) – 5 (worst)			Total Score: 0 (normal) – 25 (worst)	

*4DNPCSS assessments exclude the cognition domain resulting in a maximal worst score of 20.

**In an effort to improve the linearity of the swallow domain the scoring algorithm was simplified for the 4D NPCCSS; applying 0 to no impairment, 1 for cough while swallowing, 2 for intermittent dysphagia, 3 for dysphagia, 4 for supplemental feeding via gastric or nasogastric tube, and 5 for feeding exclusively via gastric or nasogastric tube.

Table 3: US EAP Efficacy Analysis Participant Characteristics & Demographics

Analysis Outputs	Patients Initiated to Treatment	Arimoclomol	Arimoclomol + miglustat as part of routine clinical care
Number of Participants	56 (100 %)	17 (30.4%)	39 (70%)
Age at Treatment Initiation (Years)			
Mean (SD)	20.18 (11.22)	22.88 (11.00)	19.0 (11.25)
Median (Range)	20.5 (2 - 41)	24.0 (7 - 41)	20.0 (2 - 41)
Exposure to Arimoclomol (Months)			
Mean (SD)	32.7 (8.80)	29.7 (12.19)	34.04 (6.61)
Median (Range)	34.83 (12.3 - 44.97)	30.40 (12.3 - 44.97)	35.40 (14.87 - 44.1)
NPCCSS at baseline*			
5DNPCSS Total score	11.2 (6.2); 10.5 [1, 25]	11.7 (6.5); 11.0 [1, 25]	11.0 (6.1); 10 [1, 25]
4DNPCSS Total score	8.2 (5.1); 8 [0, 20]	8.5 (5.6); 9.0 [0, 20]	8.1 (4.9); 7.0 [1, 20]

*-Data reported as Mean (SD); Median [Range]

Table 4: US EAP Patient Safety

	Patients treated with Arimoclomol (N = 56) n (%)	Adverse Event Summary (Serious and non-serious)	Patients treated with Arimoclomol (N = 56) n (%)
Adverse Events Reported	42 (75 %)	Corona virus infection	10 (17.9%)
Non-Serious Adverse Events Reported	22 (39.3%)	Pneumonia	8 (14.3%)
Serious Adverse Events Reported	20 (35.7%)	Diarrhea	5 (8.9 %)
Treatment Emergent Adverse Events (TEAE) Reported	41 (73.2%)	Fall	5 (8.9 %)
Fatal Serious Adverse Events Reported	6 (10.7 %)	Rash	4 (7.1 %)
		Seizure	4 (7.1 %)
		Vomiting	4 (7.1 %)

Adverse event data are reported as counts of the number of patients that experienced the event(s) and % of patients.

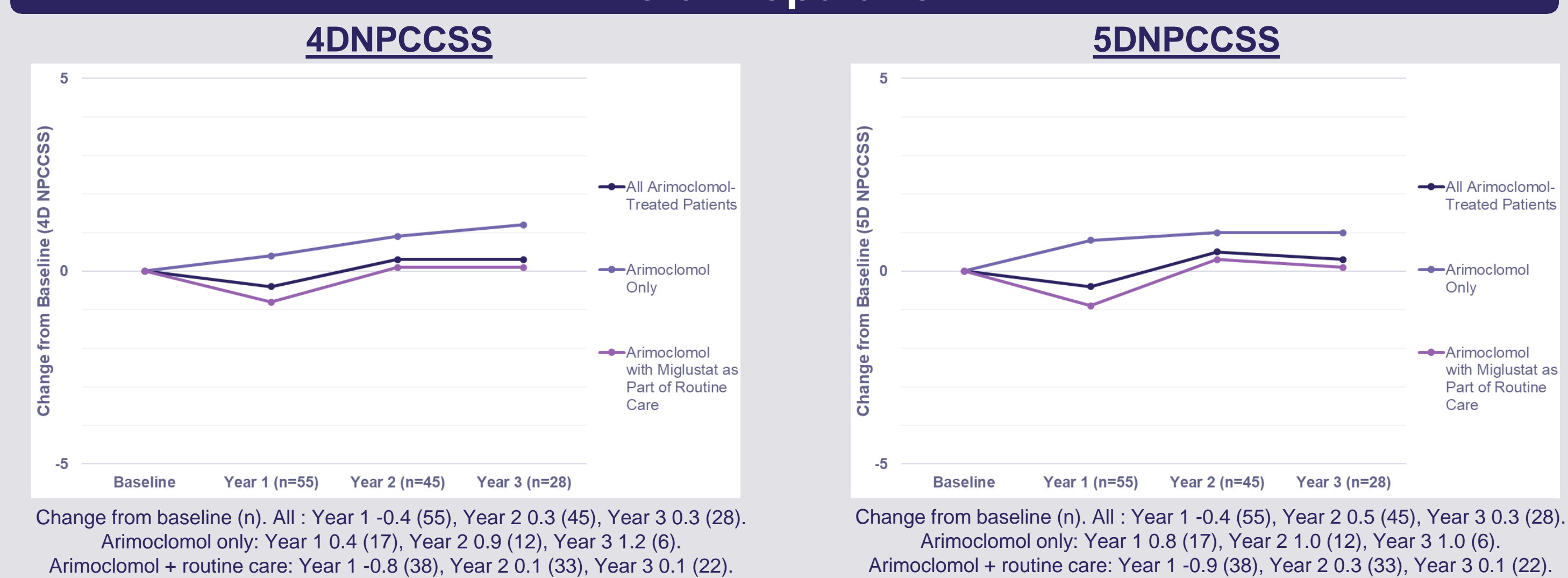
Description of Fatalities: Pneumonia- 3, COVID-19- 2, acute respiratory failure- 2, disease progression- 1, sepsis-1.

Note that 9 serious fatal adverse events occurred in a total of 6 patients, 1 patient experienced 3 events and 1 patient experienced 2 events with a fatal outcome. No fatalities were determined to have a causal relationship to arimoclomol.

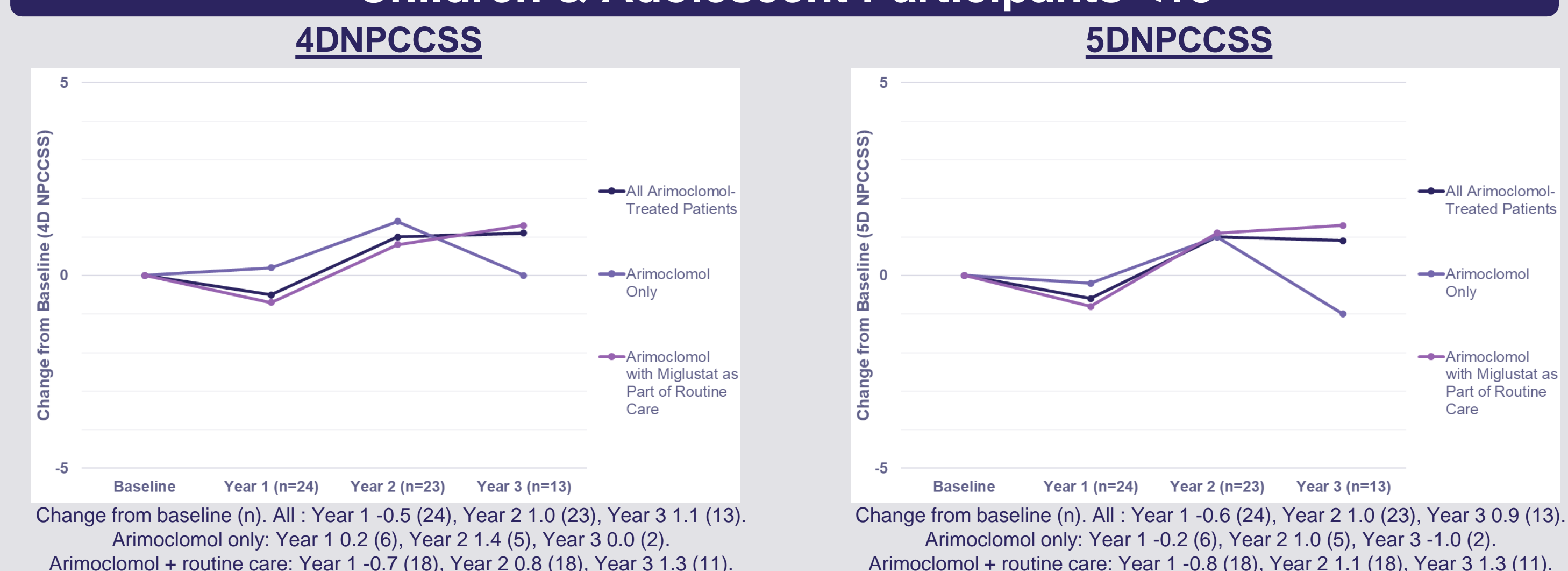
RESULTS

- Results are presented with the current data as of May 8, 2024.
- 56 patients (60%) had a baseline 5DNPCSS assessment and at least one year of follow-up (Table 3).
- A total of 55 patients were included in the 1-year analysis, 45 in the 2-year analysis, and 28 in the 3-year analysis.
- 31 patients (55%) were ≥18 years of age and 25 patients (45%) were under 18 at the time of arimoclomol initiation in the US EAP.
- 17 patients (30.4%) were treated with arimoclomol monotherapy and 39 patients (70%) used arimoclomol and miglustat as part of routine clinical care (Table 3).
- Similar results were observed using the 5DNPCSS and 4DNPCSS.
- Arimoclomol was well tolerated during the US EAP with no new safety signals identified.

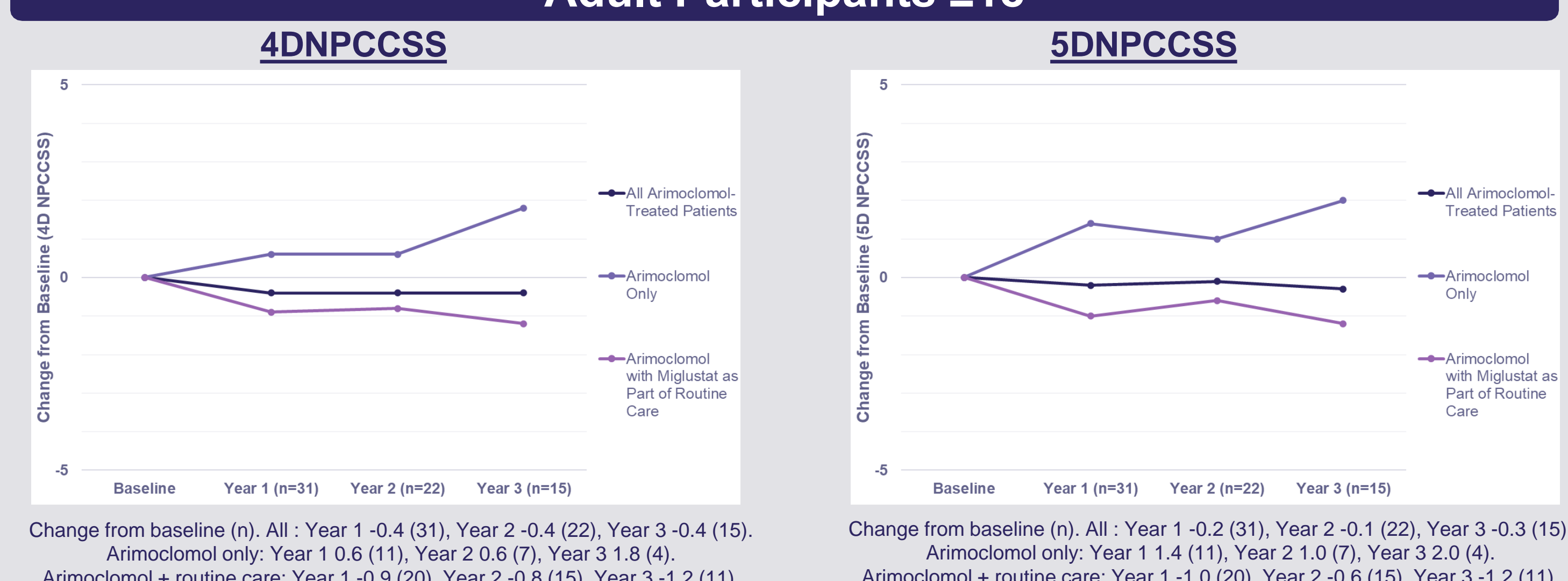
Total Population



Children & Adolescent Participants <18



Adult Participants ≥18



CONCLUSIONS

- Patients treated with arimoclomol in the US EAP, including those with and without miglustat as a component of routine clinical care, experienced relatively stable disease through the up to 3 years of follow-up reported here.
- Published natural history indicates that on average patients progress between ~1.0-2.0 points per year on the 5DNPCSS.^{1,2}
- A 1-2 point change in the 5DNPCSS represents a clinically meaningful change or progression; any slowing of disease is considered meaningful³
- Real-world outcomes from the arimoclomol NPC US EAP indicate that arimoclomol stabilizes disease with and without miglustat, representing a reduction in disease progression relative to natural history data.

Disclosures: Poster was prepared by Zevra Therapeutics
Zevra would like to thank the research sites including all study coordinators and staff involved in the expanded access program. We also thank all participants and families who have contributed to the data presented.

References: 1. Mengel E, et al. Clinical Disease progression and biomarkers in Niemann-Pick type C: a prospective cohort study. *Orphanet J Rare Dis.* 2020 Nov 23;15(1):328. 2. Yanjanin NM, et al. Linear clinical progression, independent of age of onset, in Niemann-Pick disease, type C. *Am J Med Genet B Neuropsychiatr Genet.* 2010 Jan 5;153B(1):132-40. 3. Patterson MC, et al. Validation of the 5-domain Niemann-Pick type C Clinical Severity Scale. *Orphanet J Rare Dis.* 2021 Feb 12;16(1):79.