Arimoclomol in adults with NPC in a real-world setting: Long-term data from an expanded access program in the USA

Kristina Julich, MD

Dell Medical School

The University of Texas at Austin

SIMD (Society for Inherited Medical Disorders)

April 15, 2024

Acknowledgements

Co-authors

- Dr. Walla Al-Hertani (Boston Children's Hospital, Harvard Medical School)
- Dr. Elizabeth Berry-Kravis (Rush University Medical Center)
- Dr. Raymond Wang (Children's Hospital of Orange County)
- Dr. Can Ficicioglu (Children's Hospital of Philadelphia)
- Dr. Damara Ortiz (UPMC Children's Hospital)
- Dr. Caroline Hastings (UCSF Benioff Children's Hospitals)
- Dr. Loren Pena (Cincinnati Children's Hospital)
- Dr. Paula Schleifer (Nicklaus Children's Hospital)
- Dr. Marc Patterson (Mayo Clinic Children's Center)
- Zevra Therapeutics: Ronan O'Reilly, Meredith Hart, Daniel Gallo
- Stratevi: Alexandra Ellis

We express our gratitude to the participants, clinical research coordinators and study sites in the arimoclomol Expanded Access Program responsible for these findings.

Funding: This study was funded by Zevra Therapeutics. The slide presentation was provided by Zevra Therapeutics.

Background

Niemann-Pick Disease Type C (NPC)

- NPC is a rare, progressive neurodegenerative disease.
- Approximately 30% of NPC patients are ≥15 years at neurological onset.[1]
  - Disease progression data in adults is sparse.
- Currently there are no FDA-approved treatments for NPC.
- Arimoclomol is an investigational, oral treatment for NPC:
  - Phase 2/3 study (NCT02612129): A statistically significant treatment difference in favor of arimoclomol was observed (mean: -1.40; 95% confidence interval: -2.76, -0.03; P = .046), corresponding to a 65% reduction in annual disease progression.[2]
    - 50 people (aged 2-19) were enrolled. 78% were treated with miglustat.
  - Prescription Drug User Fee Act (PDUFA) action date: September 21, 2024.[3]

1. Patterson MC, Mengel E, Vanier MT, et.al. Treatment outcomes following continuous miglustat therapy in patients with Niemann-Pick disease Type C: A final report of the NPC Registry. Orphanet J Rare Dis. 2020 Apr 25;15(1):104. 2. Mengel E, Patterson MC, Da Riol RM, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment. J Inherit Metab Dis. 2021 Nov;44(6):1463-1480. 3. https://investors.kempharm.com/news-releases/news-release-details/zevra-therapeutics-provides-fda-update-pdufa-action-date

Arimoclomol Expanded Access Program (EAP)

Patients enroll and consent to RWD collection in EAP and data transfer to INPDR

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Safety and effectiveness data are collected longitudinally

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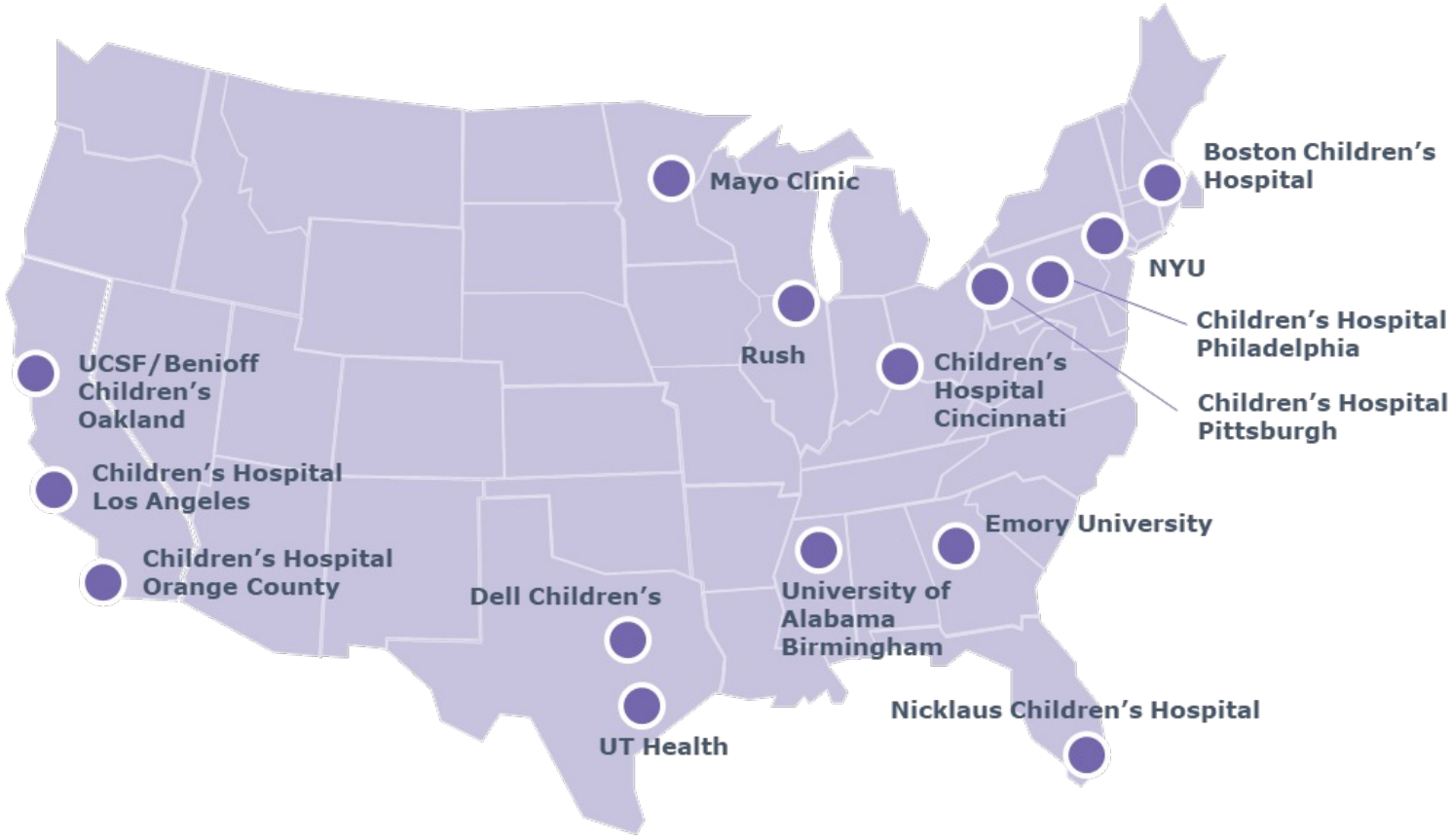
EAP Ends
Data is transferred to INPDR:
One disease registry with longitudinal multicenter data

Real-world data are primarily collected in the 15-site US EAP

- 14 out of 15 sites have enrolled patients and 13 site are currently active



EAP: Expanded Access Program; INPDR: International Niemann-Pick Disease Registry; RWD: real-world data

5-Domain NPC Clinical Severity Scale (5D NPCCSS)

Domain	Ambulation	Fine Motor Skills	Swallow	Cognition	Speech
Scoring	**0:** Normal	**0:** Normal	**0:** Normal, no dysphagia	**0:** Normal	**0:** Normal
	1: Clumsy	**1:** Slight dysmetria/dystonia (independent manipulation)	**1:** Cough while eating: *Intermittent dysphagia:* +1: w/Liquids[a] +1: w/Solids[a] *Dysphagia:* +2: w/Liquids[a] +2: w/Solids[a]	**1:** Mild learning delay, grade appropriate for age	**1:** Mild dysarthria (easily understood)
	2: Ataxic unassisted gait or not walking by 18 months	**2:** Mild dysmetria/dystonia (requires little to no assistance, able to feed without difficulty)		**3:** Moderate learning delay, individualized curriculum or modified work setting	**2:** Severe dysarthria (difficult to understand)
	4: Assisted ambulation or not walking by 24 months	**4:** Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self)	**4:** Nasogastric tube or gastric tube for supplemental feeding	**4:** Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function	**3:** Non-verbal/functional communication skills for needs
	5: Wheelchair dependent	**5:** Severe dysmetria/dystonia (gross motor limitation, requires assistance for selfcare activities)	**5:** Nasogastric tube or gastric tube feeding only	**5:** Minimal cognitive function	**5:** Minimal communication
5D NPCCSS Total Score = sum of individual domain scores, range: 0-25[b]					

[a] Score is additive (to "cough while eating"-score of 1) in subdomains 'intermittent dysphagia' and 'dysphagia' and can range from 0-5. Example: For intermittent dysphagia w/ solids and dysphagia w/ liquids a score of 4 applies (1+1+2)). [b] Higher score = more severe clinical impairment.

Analysis Objective and Methods

Objective

- Describe the effectiveness and safety of arimoclomol among US adults with NPC in the EAP.

Inclusion Criteria

- US adults with NPC aged 18 or older at the time of initiating treatment with arimoclomol.
- Baseline 5-D NPCCSS assessment and at least 1 year of follow-up.
- Data presented here are as of July 19, 2023.

Outcomes

- The physician-reported 5D NPCCSS were analyzed at baseline and 4, 7, and 12 months after treatment initiation to align with the scheduled clinical assessments. In the subset of patients with more than a year of follow-up, the scores were analyzed at these timepoints and the last observation up to 2 years after treatment initiation.
    - Higher 5D NPCCSS indicate more severe disease.
- Adverse events were summarized for all US adults with NPC in the EAP.

Patient and Treatment Characteristics

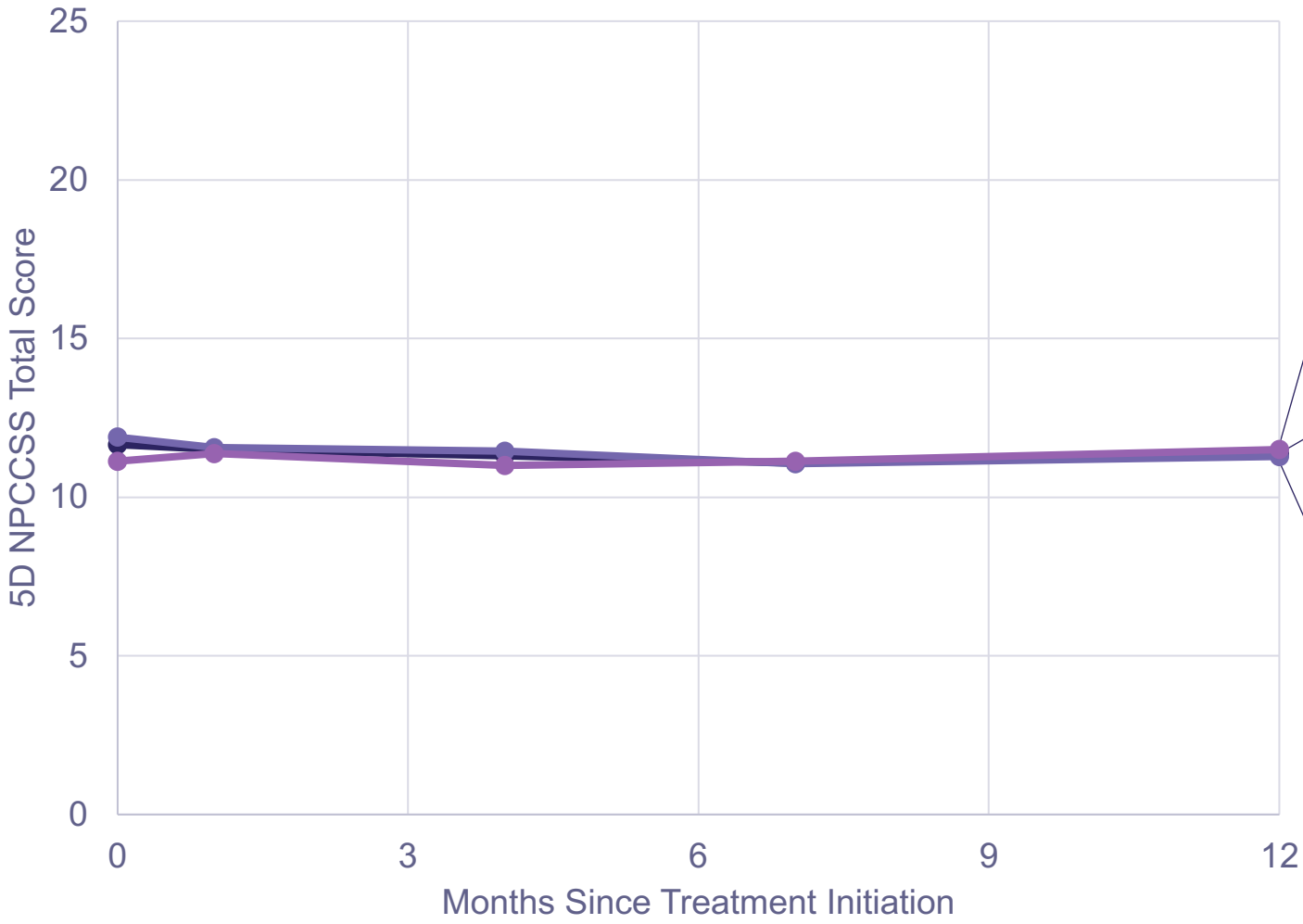
Baseline Characteristics	N=26
Age at Registration (years)	
Mean (SD)	28.5 (6.5)
Median (Range)	27.5 (18-41)
Age at NPC Diagnosis (years)	
Mean (SD)	23.7 (9.0)
Median (Range)	22.5 (8-40)
Missing, n (%)	2 (8%)
History of Neurological Symptoms [a]	
No/Unknown	3 (12%)
Yes	23 (88%)
Age (years) at First Neurological Symptom [b]	
Mean (SD)	16.8 (7.4)
Median (Range)	16 (6-37)

Treatment Characteristics	N=26
Duration of Follow-up on Arimoclomol (months)	
Mean (SD)	20.9 (6.7)
Median (Range)	23.5 (12-32)
Treatment Discontinuation	4 (15%)
Adverse Event	1 (4%)
Deceased	3 (12%)
Recorded Use of Miglustat	
Yes	18 (69%)

[a] Response to the question “Has/had the patient any neurological symptoms?” at baseline.
[b] Among those with a reported history of neurological symptoms, n=23

Data as of July 19, 2023.

1-Year Results: Mean 5-D NPCCSS (n=26)



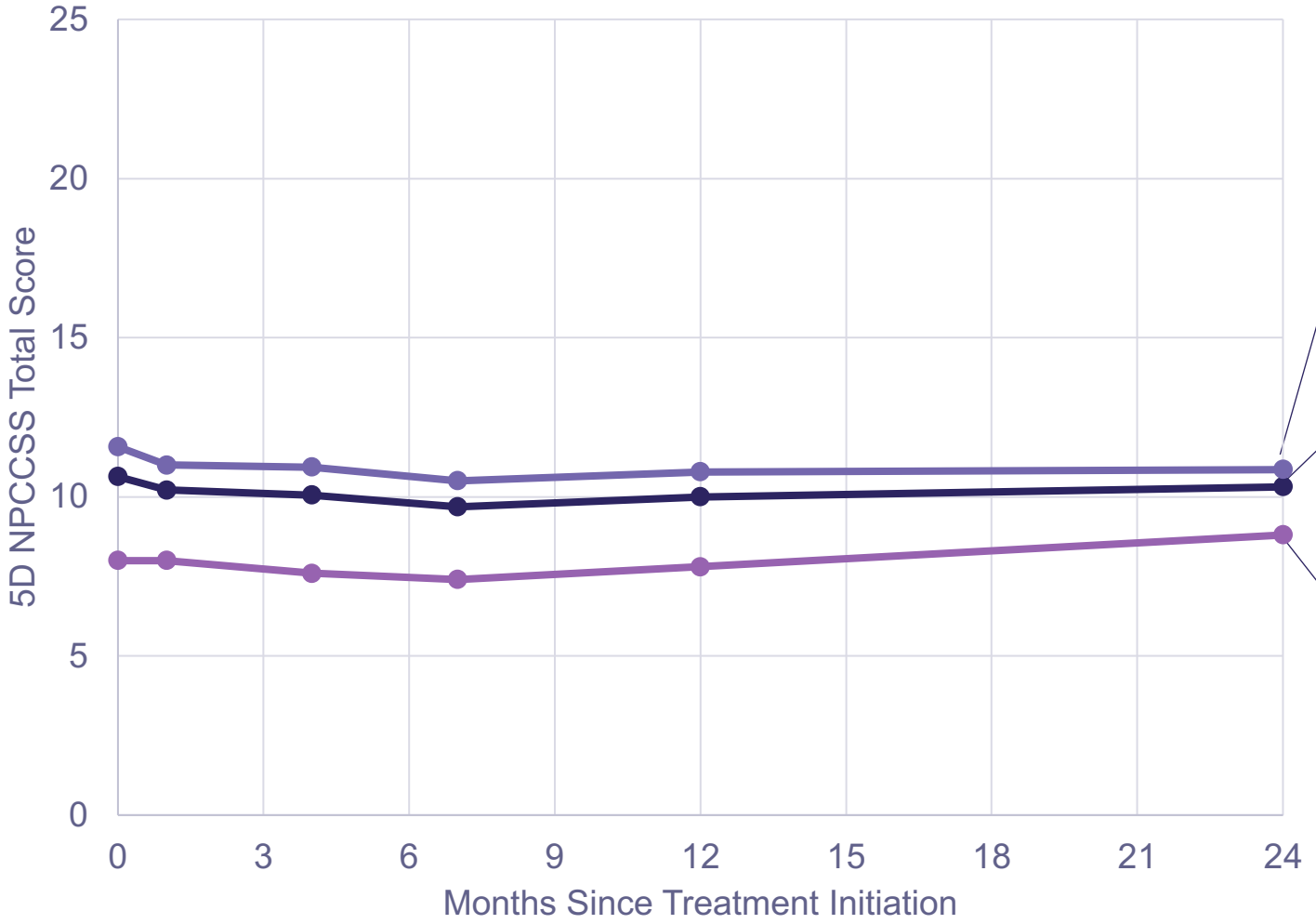
No Miglustat Use (n=8)
Baseline Total Score: 11.1 (7.2); [1, 25]
1-Year Total Score: 11.5 (8.0); [1, 25]
Change from Baseline: 0.4 (2.3); [-3, 4]

All Adults (n=26)
Baseline Total Score: 11.7 (5.6); [1, 25]
1-Year Total Score: 11.3 (5.7); [1, 25]
Change from Baseline: -0.3 (2.2); [-6, 4]

Miglustat Use (n=18)
Baseline Total Score: 11.9 (4.9); [6, 25]
1-Year Total Score: 11.3 (4.6); [5, 22]
Change from Baseline: -0.6 (2.1); [-6, 2]

Data as of July 19, 2023. Higher 5D NPCCSS scores indicate more severe disease. Results are expressed as mean (standard deviation); [range]. For patients with >1 assessment within a timeframe, the last observation within the widow was selected.

2-Year Results: Mean 5-D NPCCSS among Adults with >1 Year of Follow-up (n=19)



Miglustat Use (n=14)
Baseline Total Score: 11.6 (3.7); [6, 19]
2-Year Total Score: 10.9 (4.3); [5, 20]
Change from baseline: -0.7 (2.7); [-5, 3]

All Adults (n=19)
Baseline Total Score: 10.6 (4.4); [1, 19]
2-Year Total Score: 10.3 (4.8); [1, 20]
Change from baseline: -0.3 (2.5); [-5, 3]

No Miglustat Use (n=5)
Baseline Total Score: 8.0 (5.3); [1, 14]
2-Year Total Score: 8.8 (6.2); [1, 17]
Change from baseline: 0.8 (1.5); [-1, 3]

Data as of July 19, 2023. Higher 5D NPCCSS scores indicate more severe disease. Results are expressed as mean (standard deviation); [range]. For patients with >1 assessment within a timeframe, the last observation within the widow was selected. Median follow-up for the 2-year analysis was 20 months.

Summary of Mean Disease Progression (5D NPCCSS)

	Source	N	Age at Baseline Mean (range)	Treated with Miglustat	Range of Follow-Up Years	Mean Annual Disease Progression
Arimoclomol	EAP	26	28.5 (18-41)	69%	1.0-2.7	-0.3 (Year 1) -0.3 (Year 2)
Without Arimoclomol	NPC-001 / NPC-002	44	10.1 (2-18)	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*

*Cohort includes a wide age span. Adult patients usually have slower progression than pediatric patients.

Safety Data for US Adults in the EAP (n=41)

AEs (26 people, 60 events)

Adverse Event	N Events (% of patients)
Any	60 (63%)
By Severity	
Mild	37 (44%)
Moderate	12 (24%)
Severe	11 (22%)
Events by Preferred Term Occurring in ≥ 5% of Patients *	
COVID-19	4 (10%)
Diarrhea	4 (7%)
Nasopharyngitis	3 (7%)

*12 events (4 severe, 3 moderate, and 5 mild) have not been classified because they had no event Preferred Terms at the time the data was extracted.

Serious AEs (8 people, 10 events)

Category	N Events (% of patients)
Hospitalization or prolongation of hospitalization	6 (15%)
Death	3 (7%)
Life-threatening	1 (2%)

- None of the serious AEs were considered related to arimoclomol treatment.

Data as of July 19, 2023.

Summary and Conclusion

- This is the first study to provide data to support the effectiveness and safety of arimoclomol in adults with NPC.

- In the EAP, adults treated with arimoclomol, including those with and without miglustat use, generally had a stable disease course over two years of follow-up.
  - -0.3 mean change from baseline in 5D NPCCSS after year 1 and year 2
  - A 1-point change in the 5D NPCCSS tool represents a clinically meaningful transition.
  - This contrasts with 1.2-1.7 mean annual disease progression in NPC cohorts on routine clinical care, including children and adolescents.

- The safety profile in adult patients was consistent with that observed in the Phase 2/3 study.

Thank you