Efficacy results from a 12-month double-blind randomized trial of arimoclomol for the treatment of Niemann-Pick disease type C

– Presenting a rescored 4-domain NPC Clinical Severity Scale

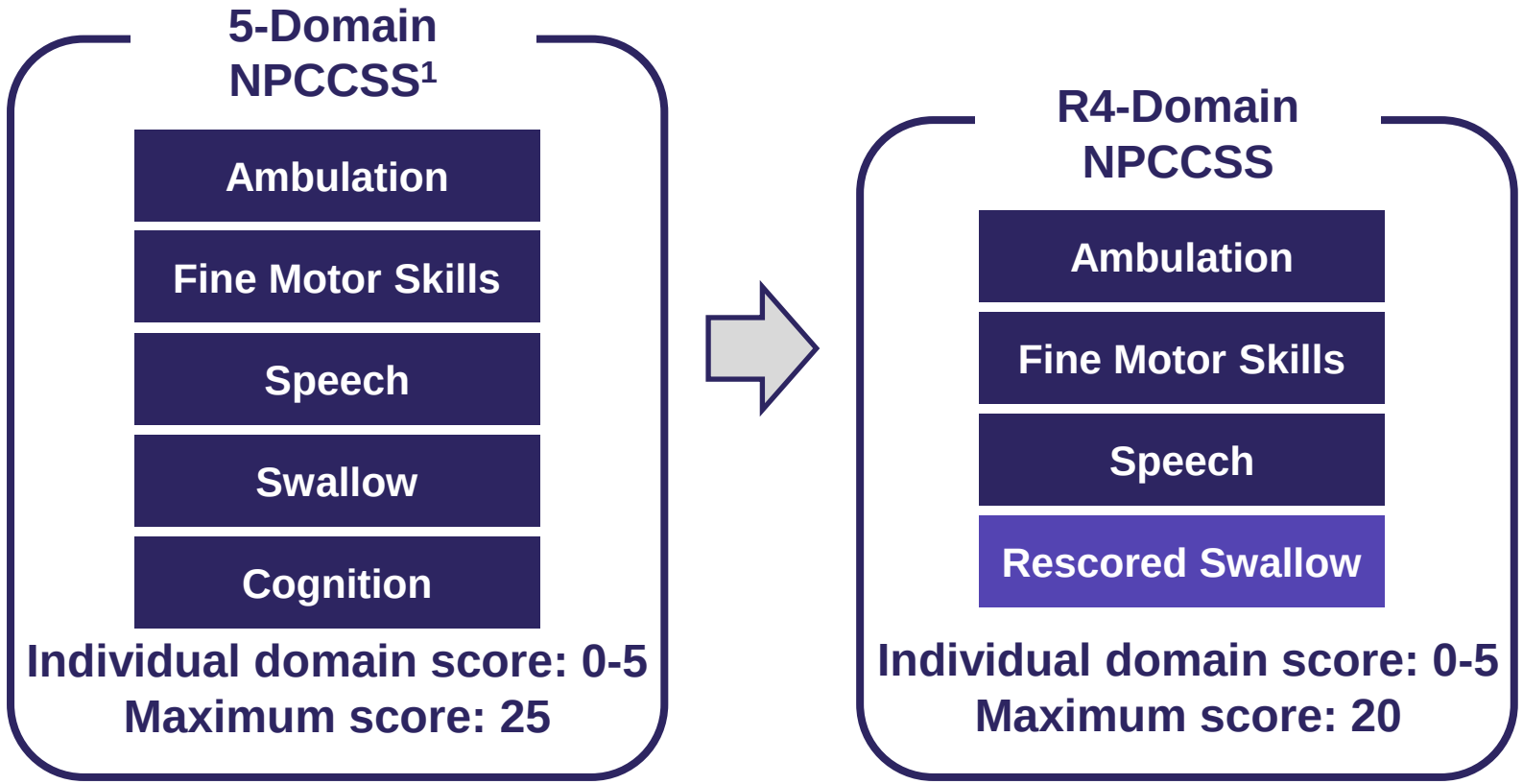
Dr. Eugen Mengel, MD
SphinCS, Clinical Science for LSD
Hochheim, Germany

Introduction

- Niemann-Pick disease type C (NPC) is an ultra-rare, progressive neurodegenerative lysosomal disease
  - Clinical presentation is heterogeneous with declining neurological functions
- A validated 5-domain version of NPCCSS (5DNPCCSS)[1] including the Swallow, Fine Motor Skills, Speech, Ambulation, and Cognition domains was used in 12-month double-blind, randomized, placebo-controlled trial investigating the efficacy and safety of arimoclomol (NPC-002, NCT02612129)[2]
- Arimoclomol is an orally available small molecule
  - The first FDA-approved treatment for NPC when used in combination with miglustat

1. Patterson MC, Lloyd-Price L, Guldberg C, et al. *Orphanet J Rare Dis*. 2021;16(1):79. doi:10.1186/s13023-021-01719-2
2. Mengel E, Patterson MC, Da Riol RM, et al. *J Inherit Metab Dis*. 2021;44(6):1463-1480. doi:10.1002/jimd.12428

From the Clinician-Reported 5DNPCCSS to R4DNPCCSS



1. Evans W, Patterson M, Platt F, et al. *Orphanet J Rare Dis*. 2021;16(1):482. doi:10.1186/s13023-021-02115-6

Methods: Update of the scoring methodology for the swallow domain

- Swallow domain validated by performance tests[1]:
  - Modified PAS score (NIH-adapted Penetration Aspiration Scale)
  - ASHA-NOMS (American Speech-Language-Hearing Association National Outcome Measure)

- Original scoring methodology for the Swallow domain could yield inaccurate equivalencies in disease severity
- To improve linearity in swallow domain:
  - Qualitative study with swallow experts and clinical NPC experts informed new scoring algorithm
  - Experts **only reviewed the swallow scoring methodology**

1. Solomon BI, Muñoz AM, Sinaii N, et al. *Orphanet J Rare Dis*. 2022;17(1):342. doi:10.1186/s13023-022-02472-w

Original swallow domain scoring could yield inaccurate equivalencies in disease severity

Original Swallow	Score	Patient A	Patient B
Normal, no dysphagia	0		
Cough while eating	1	1	
Intermittent dysphagia with liquids	+ 1		
Intermittent dysphagia with solids	+ 1		
Dysphagia with liquids	+ 2	+ 2	
Dysphagia with solids	+ 2	+ 2	
Nasogastric tube or gastric tube for supplemental feeding	4		
Nasogastric tube or gastric tube feeding only	5		5
		Total = 5	Total = 5

A patient who does not require feeding tube ***at any time*** ≠
to patient who requires feeding tube ***all of the time***

Rescored swallow domain

Updated Swallow	Score
Normal, no dysphagia	0
Cough while eating	1
Intermittent dysphagia	2
Dysphagia	3
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5

Scores clearly delineated

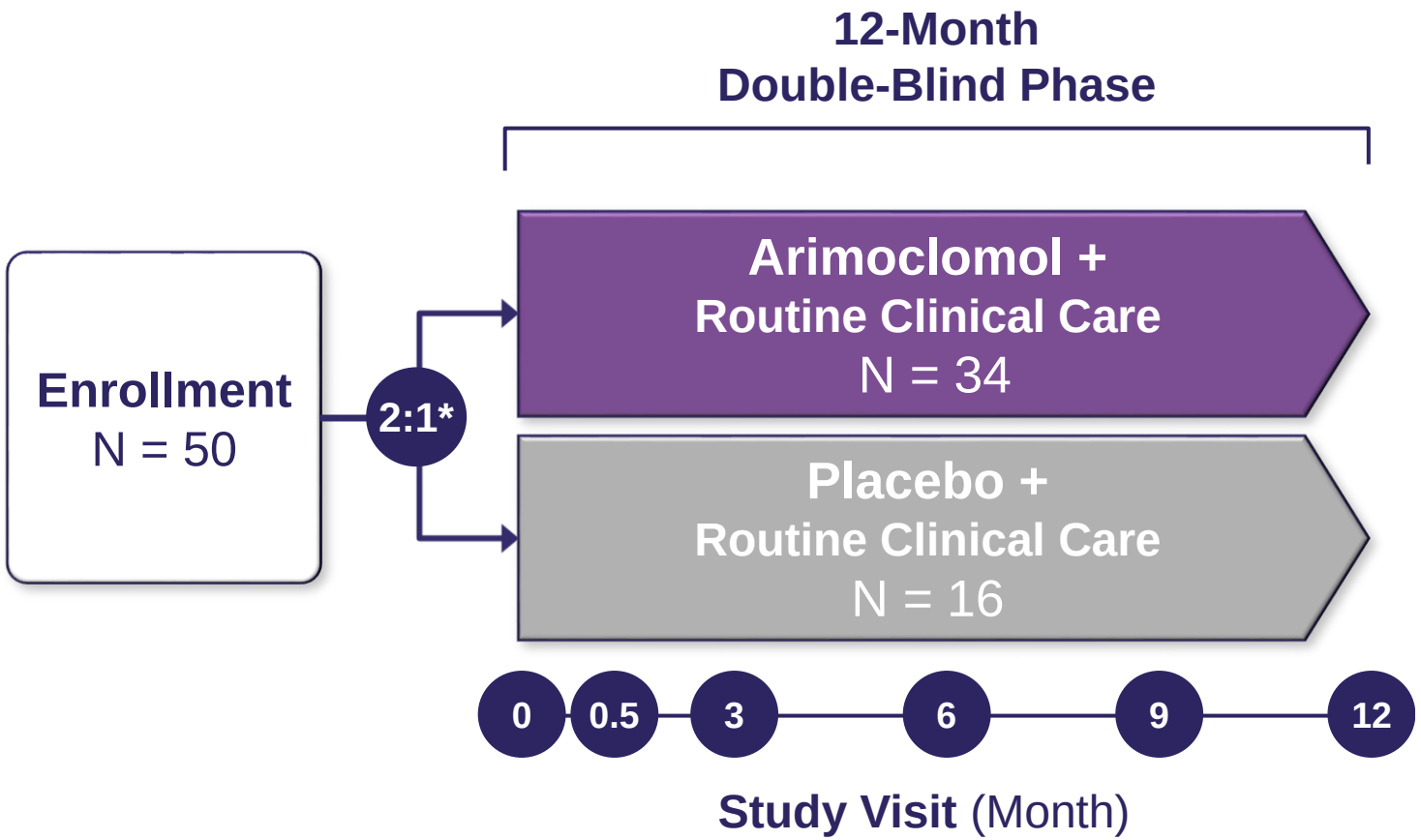
- Each step-wise increase in swallow dysfunction matched with numeric point increase in score

R4DNPCCSS is a reliable and validated tool[1]

NPCCSS Domain (score range)	Performance	Polychoric and Spearman Correlation at 0, 6 and 12 months
Ambulation (0-5, a score of 3 is not an option)	SARA GAIT (0-8)	0.85-0.97
Fine motor skills (0-5, a score of 3 is not an option)	SARA Finger chase (0-4)	0.58-0.93
	SARA Nose-finger test (0-4)	
	SARA Fast alternating hand movements (0-4)	
	9-HPT (seconds)	0.45-0.84
Speech (0-5, a score of 4 is not an option)	SARA Speech disturbance	0.89-0.99

1. Patterson MC, Lloyd-Price L, Guldberg C, et al. *Orphanet J Rare Dis*. 2021;16(1):79. Published 2021 Feb 12. doi:10.1186/s13023-021-01719-2

NPC-002 Trial



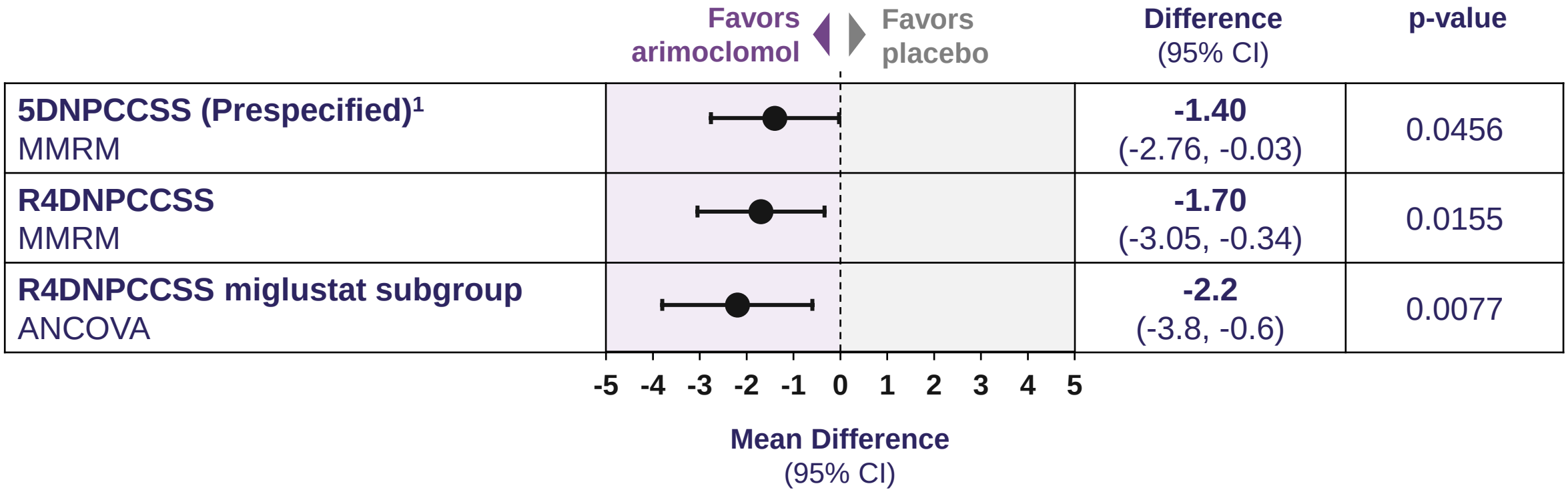
*Stratified by miglustat use

Results:[1]

- **Prespecified primary endpoint:**
  - Statistically significant change from baseline in 5DNPCCSS at Month 12 using MMRM model
- **Arimoclomol is well-tolerated:**
  - Similar incidences of adverse events for arimoclomol and placebo

1. Mengel E, Patterson MC, Da Riol RM, et al. *J Inherit Metab Dis*. 2021;44(6):1463-1480. doi:10.1002/jimd.12428

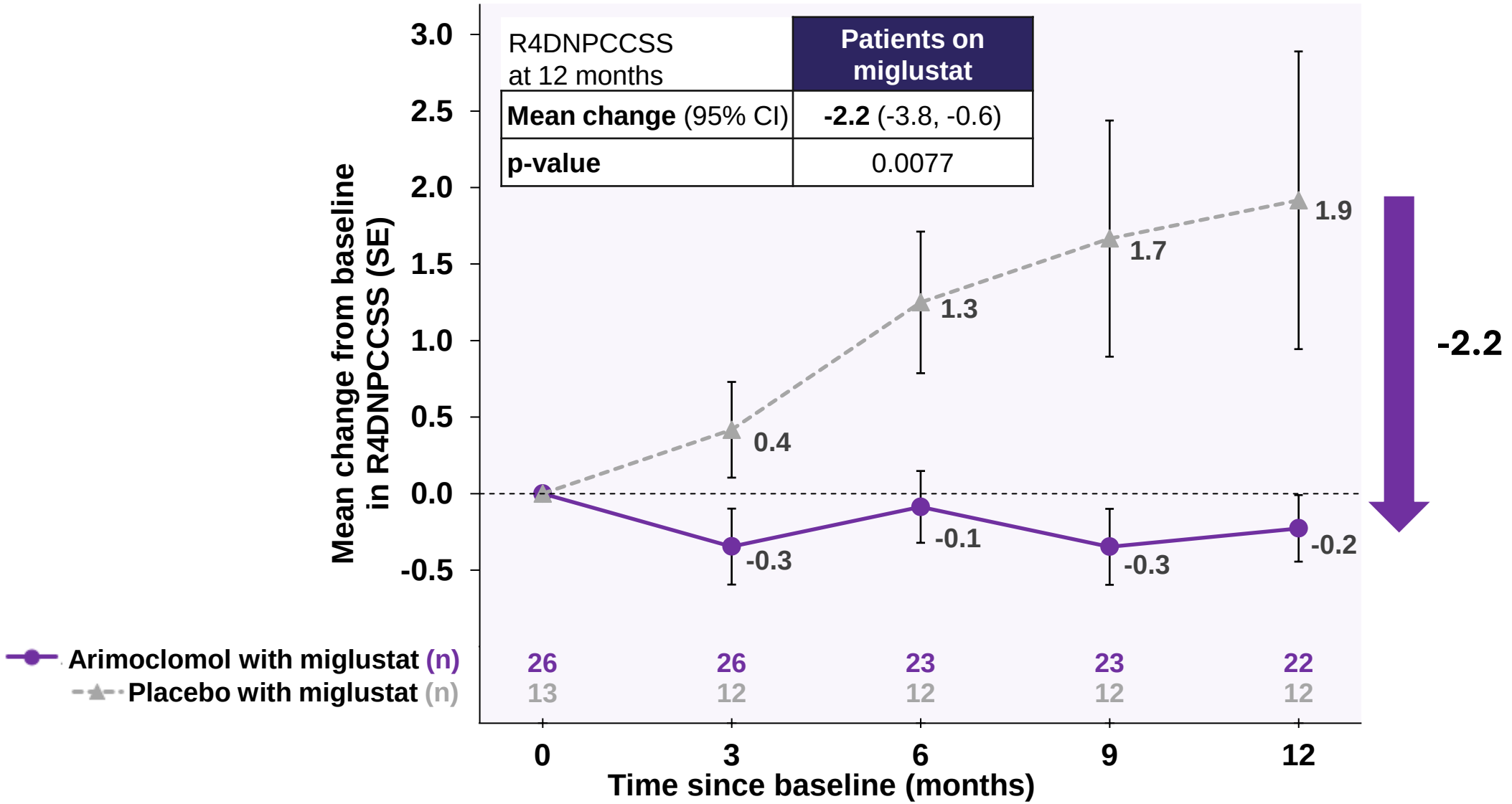
Treatment difference at 12 months



ANCOVA = analysis of covariance; MMRM = mixed model for repeated measures

1. Mengel E, Patterson MC, Da Riol RM, et al. *J Inherit Metab Dis*. 2021;44(6):1463-1480. doi:10.1002/jimd.12428

Change in R4DNPCCSS over 12 months in patients who also received miglustat



Safety

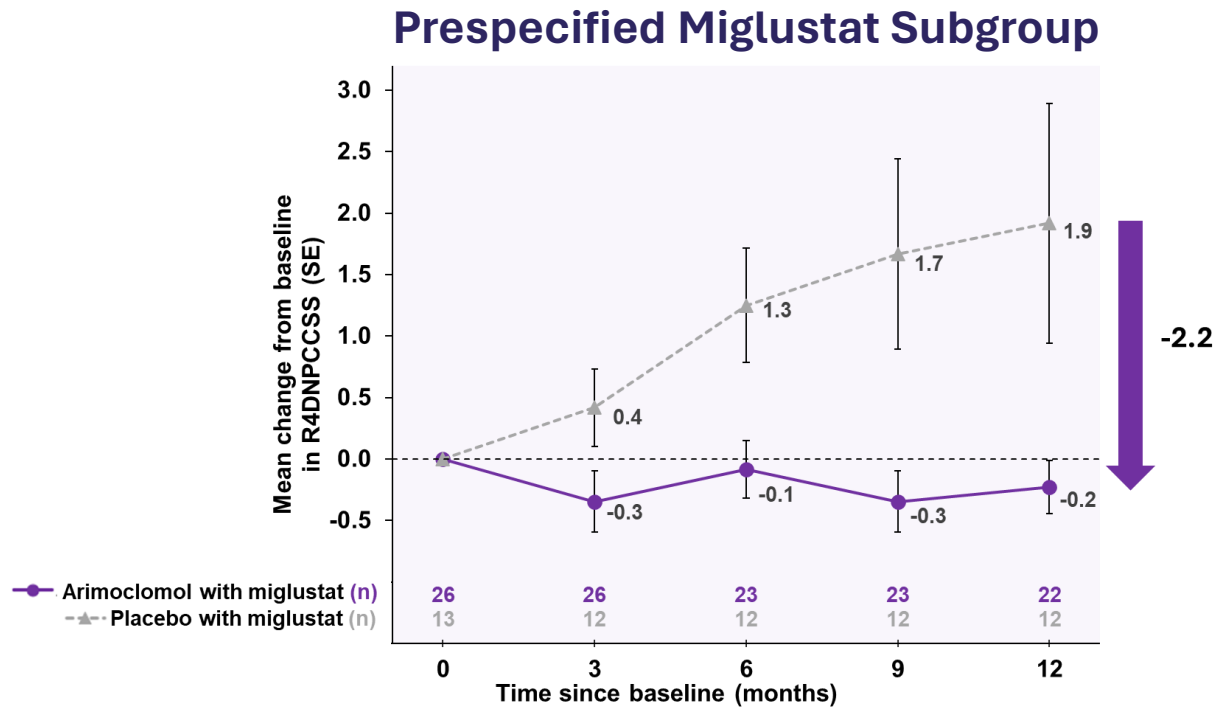
Preferred terms reported in > 10% patients, **n (%)**	Arimoclomol N = 34	Placebo N = 16
Any AE	**30 (88%)**	**12 (75%)**
Vomiting	**8 (24%)**	**4 (25%)**
Diarrhea	**7 (21%)**	**3 (19%)**
Constipation	**7 (21%)**	**3 (19%)**
Pyrexia	**6 (18%)**	**3 (19%)**
Upper respiratory tract infection	**6 (18%)**	**1 (6%)**
Rhinitis	**5 (15%)**	**2 (13%)**
Weight decreased	**5 (15%)**	**-**
Bronchitis	**4 (12%)**	**2 (13%)**
Nasopharyngitis	**2 (6%)**	**4 (25%)**
Gastroenteritis	**2 (6%)**	**2 (13%)**
Epilepsy	**1 (3%)**	**2 (13%)**
Ear infection	**-**	**2 (13%)**
Eye infection	**-**	**2 (13%)**
Pneumonia	**-**	**2 (13%)**

N = number of patients in safety population; n = number of patients with at least 1 event; % = percentage of patients

1. Mengel E, Patterson MC, Da Riol RM, et al. *J Inherit Metab Dis*. 2021;44(6):1463-1480. doi:10.1002/jimd.12428

Conclusions

- R4DNPCCSS is a valid and reliable endpoint
- Consistent outcomes with the 5DNPCCSS were demonstrated
- Arimoclomol in combination with miglustat slowed disease progression through 12 months



Thank you to NPC patients and their families!

Further Information:

- Poster **228** “Efficacy Results From a 12-month Double-blind Randomized Trial of Arimoclomol for the Treatment of Niemann-Pick Disease Type C - Presenting a Rescored 4-Domain NPC Clinical Severity Scale”
- Poster **229** “Long-Term Efficacy and Safety Evaluation of Arimoclomol Treatment in Patients With Niemann-Pick Disease Type C – Data From a 48-Month Open Label Trial”
- Poster **065** “Safety of Arimoclomol in a Pediatric Substudy of Niemann-Pick Disease Type C Patients Aged 6 to <24 Months at Study Enrollment”
- Poster **153** “Arimoclomol Upregulates Expression of Genes Belonging to the Coordinated Lysosomal Expression and Regulation (CLEAR) Network”
- Poster **031** “Arimoclomol for the Treatment of Niemann-Pick disease type C in a Real-World Setting: Long-Term Outcomes From an Expanded Access Program in the United States”
- Poster **032** “Qualitative Assessment of the Validity and Standardization of the Swallow Domain in the 5-Domain Niemann-Pick Disease Type C (NPC) Clinical Severity Scale (5DNPCCSS) and Analysis in an NPC Clinical Trial Data Set”
- Poster **094** “Arimoclomol Safety Profile in the Treatment of NPC in a Real-World Setting: Long-Term Data From an Expanded Access Program in the USA”

Co-authors:

- **Marc Patterson**
  Neurology, Pediatrics and Medical Genetics
  Mayo Clinic
  Rochester, MN, USA
- **Sven Guenther**
  Zevra Therapeutics, Inc
  Celebration, FL, USA
- **Christine í Dali**
  Zevra Denmark A/S
  Frederiksberg, Denmark