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 No. 228

Eugen Mengel [1], Marc Patterson [2], Sven Guenther [3], Christine í Dali [4]

[1] SphinCS, Clinical Science for LSD, Hochheim, Germany, [2] Neurology, Pediatrics and Medical Genetics, Mayo Clinic, Rochester, MN, USA, [3] Zevra Therapeutics, Inc, Celebration, FL, USA, [4] Zevra Denmark A/S, Frederiksberg, Denmark

BACKGROUND

- Niemann-Pick disease type C (NPC) is an ultra-rare, progressive neurodegenerative lysosomal disease. Clinical presentation is heterogeneous with declining neurological functions.
- The NPC Clinical Severity Scale (NPCCSS)[1] is a disease-specific, clinician-reported outcome measure used to quantify disease progression.
- A validated 5-domain version (5DNPCCSS)[2] including the Swallow, Fine Motor Skills, Speech, Ambulation, and Cognition domains was used in a 12-month, double-blind, randomized, placebo-controlled trial investigating the efficacy and safety arimoclomol (NPC-002, NCT02612129).
- Arimoclomol, an orally available small molecule, is the first FDA-approved treatment for NPC when used in combination with miglustat.
- Treatment effect is also presented with a rescored 4-domain NPCCSS (R4DNPCCSS) omitting the Cognition domain, which is more appropriate for a 12-month clinical trial in patients with a wide age range.
- The Swallow domain was rescored and simplified to improve linearity of the response categories with disease severity (See also poster no. 032).
- This poster presents efficacy data from the NPC-002 trial obtained with both the prespecified 5DNPCCSS endpoint and the R4DNPCCSS.

METHODS

- The 5 domains of the 5DNPCCSS were originally selected to capture key symptoms regarded as the most important disease manifestations by patients, caregivers, and clinicians.
- The scale was adapted based on regulatory recommendations, by omitting the Cognition domain, to address concerns that a single item would be unable to fully evaluate a broad concept like cognition in a 12-month trial (**Figure 1**).
- Further, the original scoring methodology for the Swallow domain could yield incorrect equivalencies in disease severity (**Figure 2A**).
- A questionnaire administered to swallow experts and clinical NPC experts informed a new scoring algorithm for the Swallow domain.
- Importantly, these experts only reviewed the Swallow scoring methodology, and did not make recommendations based on study data.
- With this updated methodology, the scores are clearly delineated, each step-wise increase in a patient's level of swallow dysfunction is matched with a numeric point increase in score (**Figure 2B**).
- The revised scoring methodology was applied to the original source data captured in the clinical trial.
- Validation work completed for the domains of the 5DNPCCSS also apply to the R4DNPCCSS (**Table 1**).
- Additional correlations were performed between the R4DNPCCSS, and the NPC Clinical Database (NPC-cdb)[3] and Clinical Global Impression Scale of Severity (CGI-S).
- The NPC-002 included 50 children with NPC aged 2-18 years.
- The prespecified primary analysis of the difference in change assessed with 5DNPCCSS was based on an MMRM (mixed model for repeated measures) model.
- For the subgroup of patients who also received miglustat, the difference in change of disease progression between treatments was evaluated using an analysis of covariance (ANCOVA) model.

Figure 1. 5DNPCCSS vs R4DNPCCSS

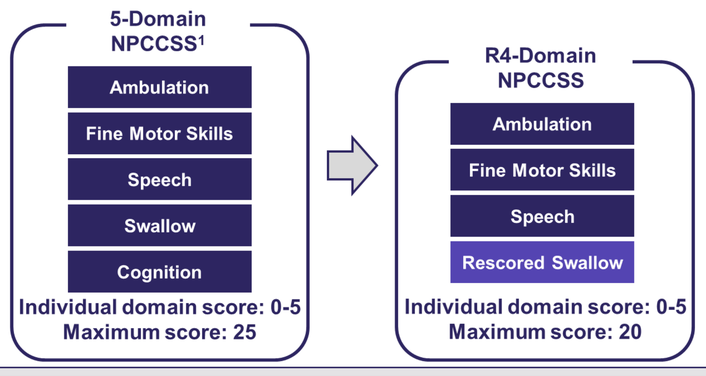


Figure 2. Original and Updated Swallow Domain Scoring

A

Original Swallow Domain Scoring Methodology	Score
Normal, no dysphagia	0
Cough while eating	1
Intermittent dysphagia with liquids	+ 1
Intermittent dysphagia with solids	+ 1
Dysphagia with liquids	+ 2
Dysphagia with solids	+ 2
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5

B

Updated Swallow Domain Scoring Methodology	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**

RESULTS

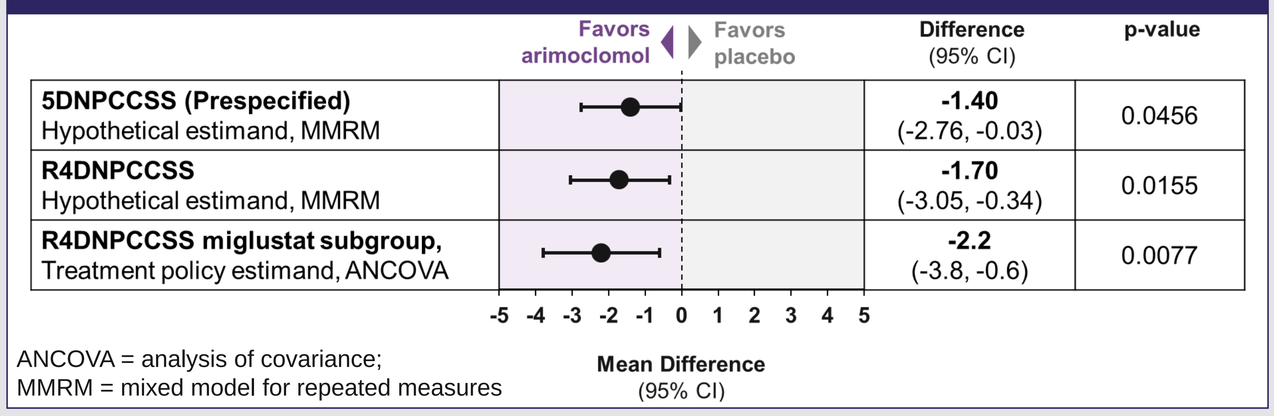
- Moderate to strong correlations were found between the individual domains and corresponding items on performance-based tests (**Table 1**). The rescoring of the Swallow domain did not negate the validation results.
- Analyses using the R4DNPCCS scale reiterated the significant treatment difference between the arimoclomol and placebo groups as shown for the prespecified primary analysis of 5DNPCCSS (**Figures 3** and **4**).

Table 1. Convergent Validity

NPCCSS Domain (score range)	Performance Test Item	Polychoric and Spearman Correlation at 0, 6 and 12 months
Ambulation (0-5, score of 3 is not an option)	SARA GAIT (0-8)	0.85-0.97
Fine motor skills (0-5, 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, score of 4 is not an option)	SARA Speech disturbance	0.89-0.99

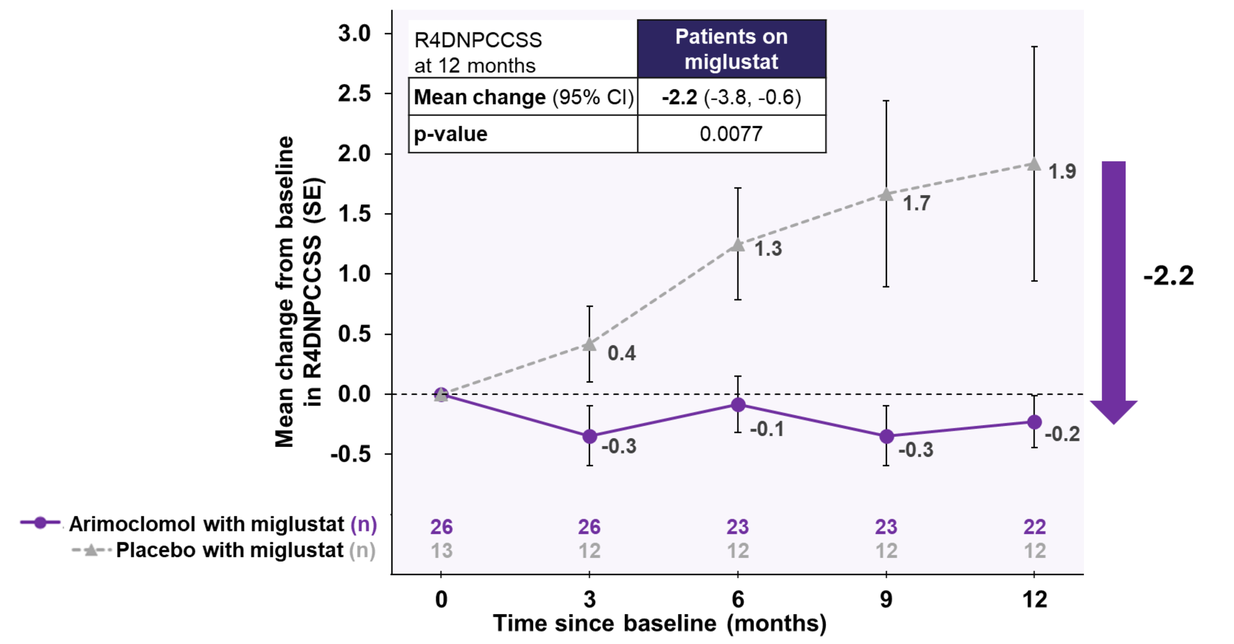
NPCCSS: NPC Clinical Severity Scale; SARA: Scale for the Assessment and Rating of Ataxia; 9-HPT: 9-Hole Peg Test

Figure 3. Analyses of Treatment Differences at 12 Months



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

Figure 4. Change in 4DNPCCSS Over 12 Months in Patients Who Also Received Miglustat



CONCLUSIONS

- The R4DNPCCSS is a valid and reliable endpoint that demonstrated consistent outcomes with the 5DNPCCSS.
- Similar to the statistically significant treatment difference obtained with the prespecified 5DNPCCSS endpoint, arimoclomol slowed disease progression through 12 months compared with placebo as measured by the R4DNPCCSS.
- When used in combination with miglustat, a statistically significant estimated treatment difference in R4DNPCCSS of -2.2 ($[-3.8, -0.6]_{95\%\ CI}$; p=0.0077) between arimoclomol and placebo was shown, reflecting a clinically meaningful reduction in NPC disease progression with arimoclomol.

REFERENCES

1. Yanjanin NM, Vélez JI, Gropman A, et al. Linear clinical progression, independent of age of onset, in Niemann-Pick disease, type C. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(1):132-140. doi:10.1002/ajmg.b.30969
2. Patterson MC, Lloyd-Price L, Guldberg C, et al. Validation of the 5-domain Niemann-Pick type C Clinical Severity Scale. Orphanet J Rare Dis. 2021;16(1):79. Published 2021 Feb 12. doi:10.1186/s13023-021-01719-2
3. Stampfer M, Theiss S, Amraoui Y, et al. Niemann-Pick disease type C clinical database: cognitive and coordination deficits are early disease indicators. Orphanet J Rare Dis. 2013;8:35. Published 2013 Feb 22. doi:10.1186/1750-1172-8-35