# Efficacy Results from a 12-month Double-blind Randomized Trial of Arimoclomol for Treatment of Niemann Pick Disease Type C – Presenting an Improved 4-Domain NPC Clinical Severity Scale

Poster ID
21260

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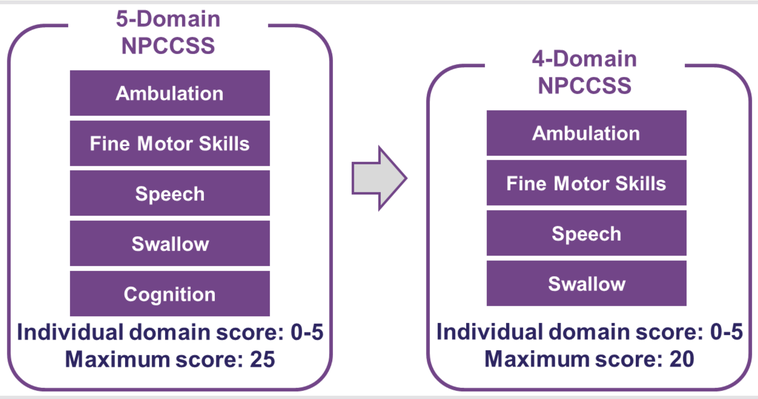
## BACKGROUND

- 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 of the investigational drug, arimoclomol, in 50 NPC patients aged 2-18 years (NPC-002) (EudraCT 2015-004438-93, NCT02612129).
- Treatment effect was also assessed with a new 4-domain endpoint (4DNPCCSS) which omitted the Cognition domain and may be more appropriate for a 12-month clinical trial in patients with a wide age range.
- To improve the linearity of the 4DNPCCSS swallow domain, the scoring was updated and simplified as described below (**Figure 2**).
- This poster presents efficacy data from the NPC-002 trial obtained with both the original 5DNPCCSS and modified 4DNPCCSS.

## 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 FDA 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 2 A**).
- A qualitative study including questionnaires and interviews with swallow- and clinical NPC experts was therefore used to inform 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 2 B**).
- 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 4DNPCCSS.
- Additional correlations were performed between the 4DNPCCSS, and the NPC-cdb[3] and CGI-S.
- The difference in change of disease progression between treatments was evaluated with a while-on treatment-estimand.

## Figure 1. 5DNPCCSS vs 4DNPCCSS




## 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**

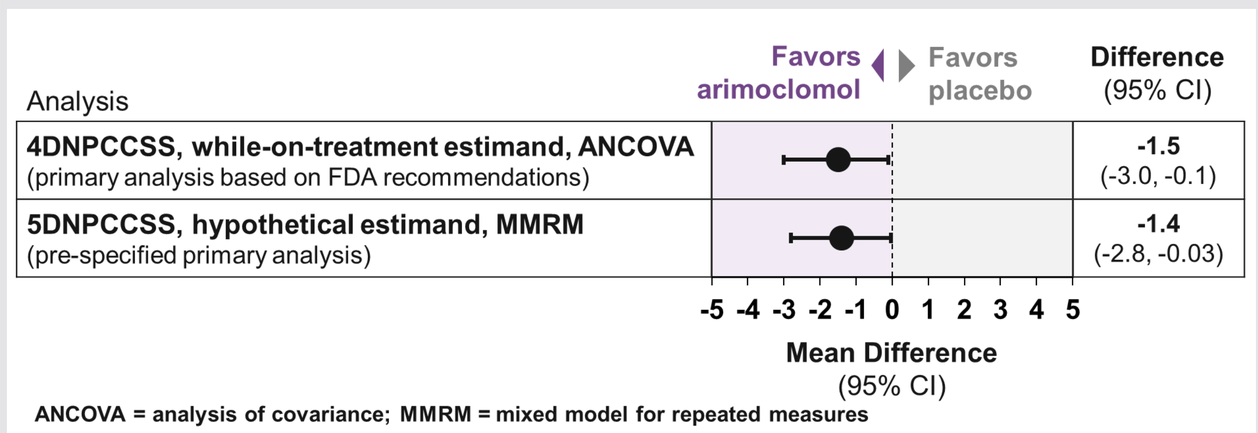
## RESULTS

- Moderate to strong correlations were found between the individual 4 domains and corresponding items on performance-based tests (**Table 1**).
- The results of the 4DNPCCS scale reiterated the significant treatment difference between the arimoclomol-treated and placebo groups (**Figures 3** and **4**).

## Table 1. Convergent Validity

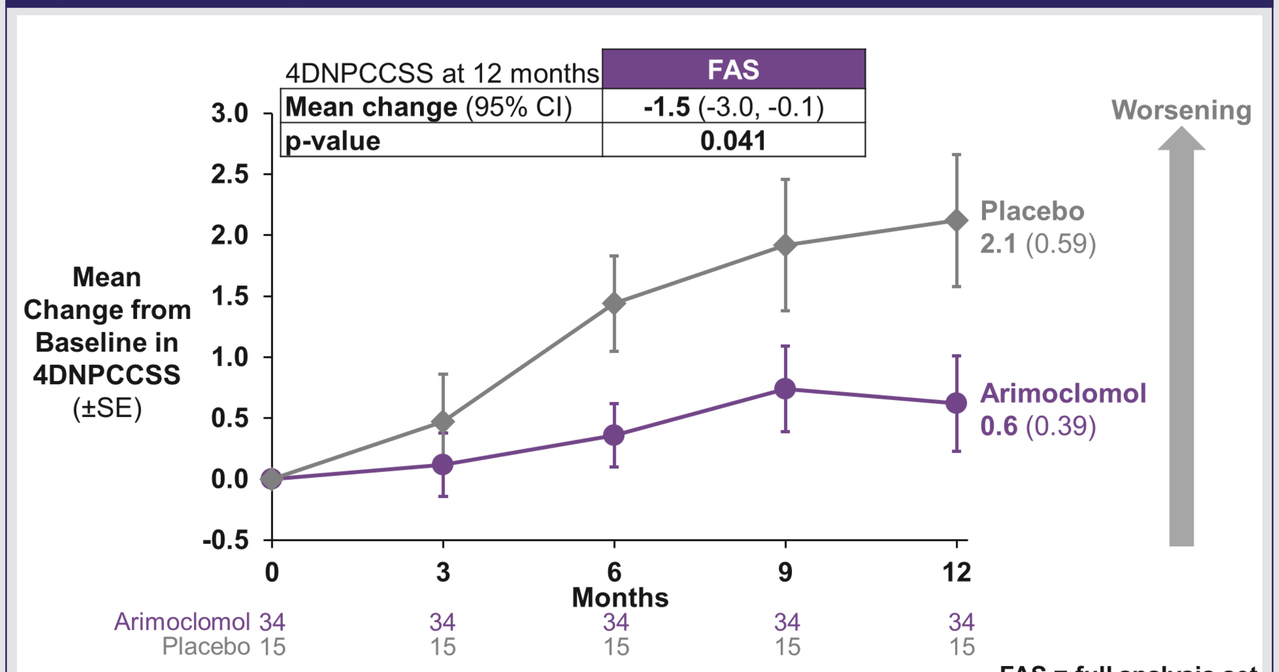
| NPCCSS Domain (score range) | Performance Test Item | Polychoric and Spearman Correlation at 0, 6 and 12 months |
|---|---|---|
| Ambulation (0-5, score of 3 is not an option) | SARA GAIT (0-8) | 0.85-0.97 |
| Fine motor skills (0-5, score of 3 is not an option) | SARA Finger chase (0-4) | 0.58-0.93 |
| | 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 |

## Figure 3. Analyses of Treatment Differences – 4DNPCCSS and 5DNPCCSS




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

## Figure 4. Change in 4DNPCCSS over 12 Months




FAS = full analysis set

## CONCLUSIONS

- A statistically significant treatment effect was shown with the prespecified 5DNPCCSS primary endpoint.
- The revised scoring methodology for the Swallow domain did not negate the validation results.
- The 4DNPCCSS is a valid and reliable endpoint for which a statistically significant estimated treatment difference between arimoclomol and placebo of -1.5 ($[-3.0, -0.16]_{95\%\ CI}$; p=0.041) from baseline to last visit was shown, reflecting a meaningful reduction in NPC disease progression with arimoclomol.

## REFERENCES

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SSIEM 2024
03-06 September, Porto, Portugal

MP has worked under consultancy agreements for Zevra Therapeutics.
CD and SG are employees of Zevra Therapeutics.