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)

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BACKGROUND AND OBJECTIVE

- Niemann-Pick disease Type C (NPC) is a rare, progressive neurodegenerative disease
- The 5DNPCCSS is a validated clinician reported outcome tool for assessing clinical severity of and disease progression across 5 domains (ambulation, fine motor skills, speech, swallow and cognition)
- The 5DNPCCSS was the primary endpoint in the arimoclomol phase 2/3 study in NPC (NCT02612129)
- During the initial new drug application review of arimoclomol, the FDA raised concerns about the linearity and scoring options within the 5DNPCCSS swallow domain
- This study was conducted in response to those concerns, working with swallow experts to develop and validate a revised version of the swallow scale score

METHODS

- Qualitative semi-structured interviews were conducted by an independent research organization with 12 NPC and swallow experts
- Interview questions were designed to capture insights on swallow domain assessments and structure
- Interviews were followed by cognitive debriefing to evaluate swallow domain content validity
- Clinical experts included 3 groups of 4 experts from the United States (n=5) and Europe (n=7) (Table 1)
- The revised swallow scoring domain was applied to the results of the NTC02612129 study in NPC, with results presented using both the original swallow scoring and updated swallow scoring

RESULTS

- The experts engaged in the research project represented NPC clinical experts, NPC-002 clinical experts, and swallow experts (Table 1)
- There was equal distribution among experts with and without experience using the 5DNPCCSS/NPCCSS (Table 2)
- All NPC clinical experts (n=8/8) felt that the response category descriptions and anchoring examples provided would allow for consistent interpretation of clinical presentation
- All clinical experts (n=12/12) found the response categories clinically relevant for assessing dysphagia in NPC patients, although some (n=3/12) described the information they would want added to the response category descriptions
- All clinical experts (n=12/12) felt the swallow domain could be assessed across the age spectrum from 2 years to adulthood. Most clinical experts (n=9/12) found the additional guidance for patients under 4 years provided in the Rater's Manual useful
- Considering the response category combinations and scoring, most clinical experts (n=11/12) felt the categories were correctly ordered by severity and would allow for assessment of progressive deterioration of swallow function
- Clinical expert feedback yielded a more linear scoring algorithm of the swallow domain (Figure 1)
- The revised scoring reranked dysphagia by frequency (intermittent=2 or consistent=3), applied a supplemental tube-feeding score of 4, and a tube-feeding-only score of 5 (Figure 1)
- Applying the rescored algorithm to NTC02612129 outcomes (N=50), to the rescored 4-Domain NPCCSS, omitting cognition, yielded a treatment difference of -1.51 (*P*=0.0413)

RESULTS

Figure 1: Rescoring of the Swallow Domain

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

Figure 1: A) The original swallow domain scoring methodology for the 5DNPCCSS. Scores with + are additive to the category score (cough while eating). B) Updated swallow domain scoring methodology. The updated scoring reflects distinct categorization with a more linear scoring pattern.

Figure 2: Outcomes of NCT02612129

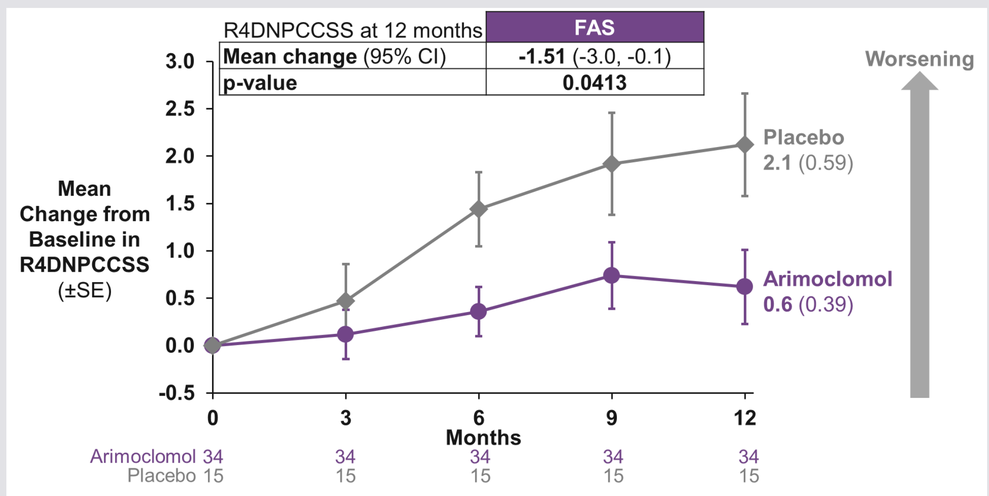

Figure 2: The R4DNPCCSS endpoint showed a statistically significant estimated treatment difference between arimoclomol and placebo of -1.51 ([-3.0, -0.16]$_{95\%\ CI}$; p=0.0413) from baseline to last visit, reflecting a meaningful reduction in NPC disease progression with arimoclomol. FAS- full analysis set

Table 1: Population Background Data

		Clinical Specialty		
	Total (n=12)	NPC Clinical Experts (n=4)	NPC-002 Clinical Experts (n=4)	Swallow Experts (n=4)
Area of clinical expertise				
Child neurologist	2 (16.7%)	1 (25.0%)	1 (25.0%)	0
Clinical or biochemical genetics	1 (8.3%)	1 (25.0%)	0	0
Speech language, swallow pathologist	2 (16.7%)	0	0	2 (50.0%)
Speech therapist	1 (8.3%)			1 (25.0%)
Other*	6 (50.0%)	2 (50.0%)	3 (75.0%)	1 (25.0%)
NPC patients seen per typical year				
Mean (SD)	18.2 (14.60)	19.3 (15.09)	9.0 (5.48)	26.3 (17.97)
NPC patients seen over career				
Mean (SD)	65.2 (108.74)	51.5 (38.41)	20.3 (15.50)	123.8 (184.72)
Do you have experience assessing swallow dysfunction				
Yes	8 (100.0%)	4 (100.0%)	4 (100.0%)	n/a

*- Other areas of clinical expertise included: metabolic pediatrics, pediatric lysosomal storage disorders/NPC, and pediatric gastroenterology.

Table 2: Experience with the 5DNPCCSS/NPCCSS

		Clinical Specialty		
	Total (n=8)	NPC Clinical Experts (n=4)	NPC-002 Clinical Experts (n=4)	Swallow Experts (n=4)
Experience using measure				
Yes	4 (50.0%)	4 (100%)	n/a	0
No	4 (50.0%)	0	n/a	4 (100%)

CONCLUSIONS

- **Data from a qualitative swallow study indicates that the rescored 5DNPCCSS swallow domain reflects the patient's level of swallow function and progressive deterioration in NPC patients aged 2 years to adulthood**
- **A change in score reflects actual improvements or worsening in a patient's swallowing function**
- **The rescored swallow domain data in the 5DNPCCSS yields consistent results with the original swallow domain scoring methodology, as well as for the R4DNPCCSS**

Disclosures: Poster was prepared by Zevra Therapeutics