Confirmatory Psychometric Evaluation of the Axillary Sweating Daily Diary: A Validated Patient-Reported Outcome Measure to Assess Axillary Hyperhidrosis Sweating Severity

Dee Anna Glaser,[1] Adelaide A. Hebert,[2] Sheri Fehnel,[3] Dana DiBenedetti,[3] Lauren Nelson,[3] Janice Drew,[4] David M. Pariser[5]

[1]Saint Louis University, St. Louis, MO; [2]UTHealth McGovern Medical School at Houston, Houston, TX; [3]RTI Health Solutions, Research Triangle Park, NC; [4]Dermira, Inc., Menlo Park, CA; [5]Eastern Virginia Medical School and Virginia Clinical Research, Inc., Norfolk, VA

INTRODUCTION

- Hyperhidrosis affects an estimated 4.8% of the US population[1]; approximately three-quarters of patients experience negative psychological effects, with anxiety and depression occurring over 3.5-times more frequently in people with hyperhidrosis than in people without it[1,2]
- Despite high prevalence and burden of disease, few disease-specific outcome measures are available
  - The Hyperhidrosis Disease Severity Scale (HDSS) is widely used in clinical studies and well understood in clinical practice; however, it does not conform to current regulatory standards for patient-reported outcome (PRO) measures used to support product approvals and labeling
- The 4-item Axillary Sweating Daily Diary (ASDD; **Table 1**) and a child-specific 2-item version (ASDD-C for use in patients ≥9 to <16 years of age; **Table 1**) were developed according to current regulatory standards[3]
  - The ASDD/ASDD-C axillary sweating severity item (Item 2) was specifically developed for use as an endpoint in clinical trials in support of approval and labeling (and also as a useful clinical parameter)
- In addition to the ASDD, patients ≥16 years of age were asked to complete 6 Weekly Impact Items designed to assess the impact and bother of hyperhidrosis on daily activities and a single-item Patient Global Impression of Change (PGIC) to assess overall change in sweating severity (**Table 1**)
- Initial psychometric evaluation of the ASDD was conducted using data from a phase 2 study of topical glycopyrronium tosylate (GT; formerly DRM04), an investigational treatment for primary axillary hyperhidrosis in patients ≥9 years of age; results have been previously reported and provide preliminary support for the use of this measure to evaluate the efficacy of axillary hyperhidrosis treatment in clinical trials[4]

OBJECTIVE

- To confirm and extend the psychometric evidence supporting ASDD/ASDD-C axillary sweating severity item (Item 2) based on pooled data from two phase 3 clinical trials of GT: ATMOS-1 (DRM04-HH04; NCT02530281) and ATMOS-2 (DRM04-HH05; NCT02530294)

METHODS

Study Design

- ATMOS-1 and ATMOS-2 were phase 3, multicenter (ATMOS-1: sites in US and Germany; ATMOS-2: sites in US), parallel-group, 4-week, double-blind clinical trials in which patients with primary axillary hyperhidrosis were randomized (2:1) to GT or vehicle
- Eligible patients were ≥9 years of age (patients <16 years were only recruited at US sites) and had primary axillary hyperhidrosis for ≥6 months, with gravimetrically-measured sweat production of ≥50 mg/5 min in each axilla, ASDD/ASDD-C axillary sweating severity item (Item 2) score ≥4, and Hyperhidrosis Disease Severity Scale (HDSS) grade 3 or 4

Assessments

- Axillary Hyperhidrosis Patient Measures (AHPM)
  - ASDD/ASDD-C Item 2 responses and sweat production were assessed in two age groups (≥9 years and ≥16 years)
  - ASDD/ASDD-C items were scored as a weekly average of daily responses; at least 4 days of daily data were required for analysis
  - Weekly Impact Items and PGIC were included to evaluate construct validity

Psychometric Evaluation

- Potential floor and ceiling effects and nonresponse bias were evaluated based on both summary statistics and graphical techniques
- Test-retest reliability was evaluated through the computation of intraclass correlation coefficients (ICCs) between Week 3 and Week 4; a value ≥0.70 was considered acceptable
- Construct validity was evaluated at Week 4 based on correlations between ASDD/ASDD-C Item 2 and ASDD items related to the impact and bother of sweating (Items 3 and 4, respectively), HDSS, sweat production, and other PRO measures as available
- All statistical tests were two-tailed using a type I error rate of 1% (alpha=0.01)

Table 1. Axillary Hyperhidrosis Patient Measures (AHPM)[a]

Axillary Sweating Daily Diary (ASDD)[b]	
Instructions: The questions in the diary are designed to measure the severity and impact of any underarm sweating you have experienced within the previous 24 hour period, including nighttime hours. While you may also experience sweating in other locations on your body, please be sure to think only about your underarm sweating when answering these questions. Please complete the diary each evening before you go to sleep.	
Item 1 [Gatekeeper]	**During the past 24 hours**, did you have **any** underarm sweating? *Yes/No* When Item 1 is answered "no," Item 2 is skipped and scored as zero
Item 2	**During the past 24 hours**, how would you rate your underarm sweating **at its worst**? *0 (no sweating at all) to 10 (worst possible sweating)*
Item 3	**During the past 24 hours**, to what extent did your underarm sweating impact your activities? *0 (not at all), 1 (a little bit), 2 (a moderate amount), 3 (a great deal), 4 (an extreme amount)*
Item 4	**During the past 24 hours**, how bothered were you by your underarm sweating? *0 (not at all bothered), 1 (a little bothered), 2 (moderately bothered), 3 (very bothered), 4 (extremely bothered)*
Axillary Sweating Daily Diary-Children (ASDD-C)[c]	
Instructions: These questions measure how bad your underarm sweating was last night and today. Please think only about your underarm sweating when answering these questions. Please complete these questions each night before you go to sleep.	
Item 1 [Gatekeeper]	Thinking about **last night and today**, did you have any underarm sweating? *Yes/No* When Item 1 is answered "no," Item 2 is skipped and scored as zero
Item 2	Thinking about **last night and today**, how bad was your underarm sweating? *0 (no sweating at all) to 10 (worst possible sweating)*
Weekly Impact Items[b]	
Instructions: Please respond "Yes" or "No" to each of the following questions.	
a. **During the past 7 days**, did you ever have to change your shirt during the day because of your underarm sweating?	*Yes/No*
b. **During the past 7 days**, did you ever have to take more than 1 shower or bath a day because of your underarm sweating?	*Yes/No*
c. **During the past 7 days**, did you ever feel less confident in yourself because of your underarm sweating?	*Yes/No*
d. **During the past 7 days**, did you ever feel embarrassed by your underarm sweating?	*Yes/No*
e. **During the past 7 days**, did you ever avoid interactions with other people because of your underarm sweating?	*Yes/No*
f. **During the past 7 days**, did your underarm sweating ever keep you from doing an activity you wanted or needed to do?	*Yes/No*
Patient Global Impression of Change (PGIC) Item[b]	
Overall, how would you rate your underarm sweating **now** as compared to before starting the study treatment? *1 (much better), 2 (moderately better), 3 (a little better), 4 (no difference), 5 (a little worse), 6 (moderately worse), 7 (much worse)*	

[a]ASDD/ASDD-C Item 2 is a validated PRO measure
[b]For use in patients ≥16 years of age
[c]For use in patients ≥9 to < 16 years of age

RESULTS

- The pooled phase 3 study population (N=697) included 665 patients who were ≥16 years of age and 32 patients who were ≥9 to <16 years of age (**Table 2**)

Table 2. Demographic Characteristics: ATMOS-1 and ATMOS-2 Pooled Population

Characteristic	Age ≥9 Years (N=697)	Age ≥16 Years (N=665)
Age (years), mean ± SD	32.7 ± 11.4	33.6 ± 10.9
Axillary hyperhidrosis history (years), mean ± SD	15.5 ± 10.8	16.1 ± 10.7
Female, n (%)	371 (53.2)	344 (51.7)
White, n (%)	570 (81.8)	544 (81.8)

- The response distribution for the ASDD/ASDD-C axillary sweating severity item (Item 2) demonstrated no floor or ceiling effect, and no nonresponse bias (**Table 3**)
- Construct validity was supported by strong correlations between ASDD Item 2 and the ASDD items addressing the impact and bother of axillary sweating (Items 3 and 4, respectively) (**Table 3**)
- Test-retest reliability was supported by ICCs of 0.93 for both age subgroups (**Table 3**), which is well above the 0.70 criterion, and within the confidence interval of the phase 2 estimate of 0.91 (95% CI: 0.87, 0.94)[4]
- The ASDD/ASDD-C Item 2 responsiveness, or ability to detect change in sweating severity, was demonstrated by large effect sizes and correlations that were within the expected range for the change in ASDD/ASDD-C Item 2 and the change in the gravimetric measures of sweat production (**Table 3**)

Table 3. ASDD/ASDD-C Axillary Sweating Severity Item (Item 2) Measurement Properties

Measurement Property		Age ≥9 Years (N=593[a])	Age ≥16 Years (N=568[a])
Response distribution, mean ± SD [median]	Baseline	7.2 ± 1.6 [7.3]	7.2 ± 1.3 [7.3]
	Week 4	3.3 ± 2.8 [2.5]	3.2 ± 2.7 [2.4]
	Change	-3.9 ± 2.7 [-3.9]	-4.0 ± 2.7 [-4.0]
Construct Validity, Pearson r			
ASDD Item 3 (impact)	Week 4	—[b]	0.89
ASDD Item 4 (bother)		—[b]	0.91
Sweat Production[c]		0.26[d]	0.25[d]
Test-retest reliability, ICC	Week 4-Week 3	0.93	0.93
Responsiveness			
Sweat production,[c] r	Week 4-Baseline	0.23[d,e]	0.22[d,e]
Effect size of change (SD baseline units)		-2.4	-2.4
Standardized response mean		-1.4	-1.5

[a]Subjects with Baseline and Week 4 scores
[b]ASDD-C (for use in patients <16 years of age) does not include items corresponding to ASDD Items 3 and 4
[c]Measured gravimetrically
[d]Spearman correlation coefficient
[e]Based on the change from Baseline to Week 4 in ASDD Item 2 scores and the natural logarithm of sweat production
ASDD, Axillary Sweating Daily Diary; ICC, intraclass correlation; SD, standard deviation

CONCLUSIONS

- The current study confirms and extends the psychometric evidence supporting the ASDD/ASDD-C as a new PRO measure developed according to current regulatory standards
- The psychometric findings presented here continue to support use of the ASDD/ASDD-C axillary sweating severity item (Item 2) as an endpoint in assessing the efficacy of treatments for patients with axillary hyperhidrosis

References

1. Doolittle et al. *Arch Dermatol Res.* 2016;308(10):743-9. **2.** Bahar et al. *J Am Acad Dermatol.* 2016;75(6):1126-33. **3.** Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. FDA; 2009. **4.** Glaser et al. Poster presentation at: 13th Annual Maui Derm for Dermatologists; March 20-24, 2017; Maui, HI.

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