Psychometric Evaluation of the C-Path PRO Consortium's Asthma Daytime and Nighttime Symptoms Diaries (ADSD and ANSD) in the 54-Week, Randomized, Placebo-Controlled, Double-Blinded Phase IIb Study of MSTT1041A in Patients with Uncontrolled Severe Asthma (NCT02918019)

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BACKGROUND

- Despite asthma therapies demonstrating efficacy in exacerbation reduction, measurable symptom control remains elusive.
- Under-controlled symptoms further impact patients' quality of life and drive increased health care resource utilization.[1-5]
- The PRO Consortium's Asthma Working Group at C-Path developed the Asthma Daytime Symptom Diary (ADSD) and the Asthma Nighttime Symptom Diary (ANSD) to assess severity of core asthma symptoms among adults and adolescents (ages ≥12).
- The measures were developed in accordance with the FDA PRO Guidance and are qualified via the FDA's Drug Development Tools program pathway for inclusion in clinical research to support assessment of asthma treatment benefit.[6]
- Both measures include 6 items (Difficulty breathing, Wheezing, Shortness of breath, Chest tightness, Chest pain, and Cough) that allow patients to rate symptom severity on an 11-point scale, with scores calculated as the average.

METHODS

Objective

- Evaluate the psychometric properties of the ADSD and ANSD and establish thresholds for meaningful change/responder definition.

Study Design

- Data for psychometric validation of the ADSD/ANSD measures were collected via a Phase IIb study of MSTT1041A compared with placebo as add-on therapy in patients with severe, uncontrolled asthma.
- The study included a 2-4-week screening period, a 2-week run-in period, and a 52-week treatment period. The ADSD and ANSD were administered as daily diaries; other PROs were assessed at randomization, Week 26, and Week 54.
- Analyses were conducted to evaluate item-level response and score distributions, domain/factor structure), reliability (internal consistency and test-retest reliability), construct validity (convergent/divergent, known-groups), and ability to detect change.
- Meaningful change estimates were derived using anchor- and distribution-based approaches alongside cumulative distribution curves based on selected anchors.

RESULTS

Demography and Clinical Variables

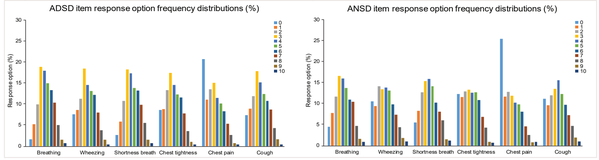
Table 1. Patient demographics.

Characteristic	ADSD (n=428)	ANSD (n=309)
Age (years)		
Range	18-75	18-75
Average (SD)	52.1 (12.0)	51.4 (12.5)
Sex		
Male	161 (33%)	108 (35%)
Female	321 (67%)	201 (65%)
Race		
American Indian/Alaska Native	20 (4%)	18 (6%)
Asian	23 (5%)	18 (6%)
Black or African-American	28 (6%)	23 (7%)
Multiple	6 (1%)	3 (1%)
White	405 (84%)	247 (80%)

Item Response and Score Distributions

- All response categories for daytime/nighttime asthma symptoms were scored by the participants at screening. Options 3 and 4 were most represented.
- Floor effects for ADSD and ANSD Chest pain items (respectively 20.78% and 25.68%) were indicated by percentages above 9.09% (i.e. 100%/11 response options) on the lowest possible scores. No ceiling effects were observed.

Figure 1. ADSD/ANSD response option frequency distribution at screening.



- The lowest average scores among the six ADSD and ANSD items at randomization for Chest pain were 3.0 and 2.8, respectively.
- Similarly, the highest average scores were 4.4 and 4.2 points, respectively, for Difficulty breathing.

Factor Analyses

- Confirmatory Factor Analysis conducted on randomization data using various goodness-of-fit indices supported the use of summary scores for the ADSD and ANSD.

Table 2. ADSD/ANSD confirmatory factor analysis model fit.

		Fit Summary			
		Stringent Criteria	Loose Criteria	ADSD Value	ANSD Value
Absolute Index	Standardized RMR (SRMR)	<0.05	<0.10	0.0317	0.0280
	Goodness of Fit Index (GFI)	>0.90	>0.80	0.8665	0.8937
Parsimony Index	Adjusted GFI (AGFI)	>0.90	>0.80	0.6886	0.7521
	RMSEA Estimate	<0.05	<0.10	0.2126	0.1877
Incremental Index	Bentler Comparative Fit Index	>0.95	>0.80	0.9379	0.9530
	Bentler-Bonett NFI	>0.95	>0.80	0.9378	0.9517
	Bentler-Bonett Non-normed Index	>0.95	>0.80	0.8966	0.9217

- Both ADSD and ANSD sets of items produced high standardized factor loadings (all >0.78) for their respective designated factors showing that constituent items contribute significantly to overall latent traits of daytime and nighttime symptom severity.

Table 3. ADSD/ANSD confirmatory factor analysis standardized estimates.

	ADSD				ANSD			
Variable	Estimate	Standard Error	T-Value	Pr > |t|	Estimate	Standard Error	T-Value	Pr > |t|
Breathing	0.93023	0.00205	453.6	<0.0001	0.93826	0.00481	195.0	<0.0001
Wheezing	0.90131	0.00266	338.3	<0.0001	0.89509	0.00725	123.4	<0.0001
Shortness breath	0.93356	0.00198	471.0	<0.0001	0.94930	0.00422	224.8	<0.0001
Chest tightness	0.90437	0.00260	348.0	<0.0001	0.90640	0.00661	137.2	<0.0001
Chest pain	0.79668	0.00484	164.6	<0.0001	0.81638	0.01161	70.29	<0.0001
Cough	0.79171	0.00494	160.3	<0.0001	0.78469	0.01327	59.12	<0.0001

Reliability

- ADSD score reproducibility was observed among subjects stable on PGIS-Daytime between screening and Week 26 (ICC=0.89). The number of ANSD assessments for stable patients according to the PGIS-Nighttime was insufficient to assess the ANSD.
- ADSD and ANSD scores demonstrated a high internal consistency with Cronbach's alpha coefficients of 0.95 and 0.96, respectively, based on screening data. Test-retest ICC for ADSD was also high (0.89), though there were an insufficient number of assessments for stable patients based on PGIS-Nighttime to assess for the ANSD.
- ADSD averaged item-to-item spearman correlations were high, ranging from 0.65 (Breathing and Chest pain) to 0.91 (Breathing and Shortness of breath), showing potential redundancy. ANSD showed a similar pattern with correlations ranging from 0.67 (Cough and Chest pain) to 0.91 (Shortness of breath and Breathing).

Construct Validity

- Convergent/divergent validity was demonstrated by moderate to high correlations (Spearman's) with other measures at randomization. Further hypotheses specifying greater correlation with disease-proximal measures (i.e. ACQ-5 and AQLQ symptoms) were also confirmed.

Table 4. ADSD/ANSD confirmatory factor analysis standardized estimates.

	PGIS	EQ5D_ VAS	AQLQ_ ALL	AQLQ_ Activity	AQLQ_ Symptom	AQLQ_ Emotion	AQLQ_ Environ	ACQ-5
ADSD	0.85	-0.36	-0.47	-0.39	0.48	-0.40	-0.37	0.50
ANSD	0.87	-0.39	-0.49	-0.43	-0.48	-0.43	-0.37	0.48

- Known-groups (discriminant) validity was demonstrated as mean ADSD and ANSD scores at randomization were significantly lower (all p<0.0001) among subgroups categorized (via median splits) as healthier on external anchors (PGIS- Daytime/Nighttime, ACQ-5, EQ-5D-5L VAS).

Responsiveness/Ability to Detect Change

- ADSD scores showed statistically significant differences (p<0.05) between mean change scores based on groups defined as "improved", "unchanged/stable" or "worsened" according to the PGIS-Daytime, PGIC, CGIC and ACQ-5 at Weeks 26 and 54.
- ANSD scores detected change in disease status with statistically significant differences (p<0.05) found between mean change scores based on groups defined as "improved", "unchanged/stable" or "worsened" according to the PGIS-Nighttime at Weeks 26 and 54.

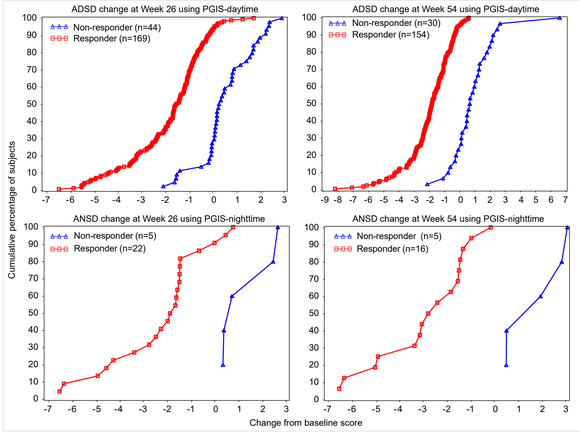
Responder Definition/Meaningful Change Threshold

- Anchor-based estimates corresponding to mean ADSD score change at Week 54 using PGIS-Daytime 1-point and 2-point decrease, PGIC, CGIC, and ACQ-5 measures were -2.01, -2.61, -1.69, -1.52 and -1.70, respectively. Estimates for the ANSD were -2.87, -3.74, -1.88, -1.80 and -2.07, respectively. Week 26 scores produced similar estimates.
- Distribution-based ADSD average score thresholds were calculated using a variety of methods (Table 5). Results based on effect size i.e 0.8 x SD (1.51) and MDC90 (1.47) support employing within-patient change exceeding 1 point. Similar estimates were found for the ANSD - apart from the SEM and MDC90, which were discounted given reliability coefficient (r=0.5) below the threshold of acceptability (≥0.70).
- Cumulative distribution function (CDF) curves were generated to compare the change at weeks 26 and 54, plotted by responder/non-responder defined by the PGIS-Daytime anchor. Separation of CDF curves show approximately 2-point magnitudes of change around the medians (cumulative percentages of 50%). See Figure 2.
- Triangulation across these methods, with most consideration given to estimates generated from PGIS and PGIC anchor-based analyses tied to the patient perspective via easily-interpretable measures, support selection of a 2-point responder threshold.

Table 5. ADSD/ANSD distribution-based thresholds at baseline.

Methods	ADSD averaged total score thresholds	ANSD averaged total score thresholds
0.2 x SD_{BL}	0.38	0.42
0.5 x SD_{BL}	0.94	1.06
0.8 x SD_{BL}	1.51	1.70
SEM_1 = SD_{BL} x SQRT(1-alpha)	0.41	0.44
SEM_2 = SD_{BL} SQRT(1-ICC)	0.63	1.50
MDC90_1= 1.65 x SEM_1 x SQRT(2)	0.96	1.02
MDC90_2= 1.65 x SEM_2 x SQRT(2)	1.47	3.51

Figure 2. ADSD/ANSD score changes from baseline.



CONCLUSIONS

- Findings support for the validity and reliability of ADSD and ANSD scores as respective measures of asthma daytime and nighttime symptom severity, although additional data to confirm ANSD reliability are warranted.
- Analyses demonstrate the measures' responsiveness/ability to detect change, and confirmatory factor analyses reinforce use of single domain structures via overall daytime/nighttime symptom scores.
- A 2-point responder threshold is robustly defined for both ADSD and ANSD measures, allowing for the interpretation of scores when employed in clinical research alongside physiologic and clinician-reported endpoints to support the assessment of asthma treatment benefit.

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