Prospective Validation of the Scleroderma Skin Patient-reported Outcome (SSPRO) in a Phase 2 Trial of Anabasum (JBT-101) in Diffuse Cutaneous Systemic Sclerosis (dcSSc)

Poster # 738

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ABSTRACT

Background/Purpose: Skin thickening is the defining manifestation of dcSSc. A dcSSc patient's assessment of their skin involvement can provide information about how that patient feels and functions in response to treatment. No skin-specific patient-reported outcome (PRO) measure has been prospectively validated in dcSSc in a clinical trial.

Methods: SSPRO is a validated PRO measure that assesses health-related quality of life (HRQOL) related to skin involvement in SSc. It has 18 items representing 4 HRQOL scales: physical effects, emotional effects, physical function, and social effects. All items are scored from 0 (better) to 6 (worse). Anabasum is a preferential cannabinoid receptor type 2 agonist that was tested for safety and efficacy in dcSSc in a double-blind randomized placebo-controlled Phase 2 trial (JBT101-SSc-001). Efficacy outcomes included the SSPRO, Patient Global Assessment (PtGA), HAQ-DI, Physician Global Assessment (MDGA), modified Rodnan Skin Score (mRSS), and FVC % predicted. SSPRO baseline scores were correlated with other baseline outcome scores using Pearson's Correlation Coefficient. Internal consistency was estimated using Cronbach's α. Effect size (ES, ratio of mean change in SSPRO total score from baseline to 12 weeks, to the standard deviation of the total score at baseline) was calculated to assess the SSPRO's responsiveness to change.

Methods: SSPRO was administered to 41 subjects with dcSSc. Internal consistency was high for the total (0.87) and for all scale scores (0.92). The SSPRO total and scale scores correlated strongly with PtGA, and moderately with HAQ-DI (except for the emotion scale) showing convergent validity. SSPRO also correlated moderately with MDGA and weakly with mRSS. As expected, SSPRO total and scale scores did not correlate with FVC % predicted, showing divergent validity. The SSPRO total mean score showed a significant difference in anabasum-treated (N = 26) compared to placebo-treated subjects (N = 15) at 12 weeks, LS means difference (SE) = -16.9 (6.0), P = 0.004 ANCOVA. The ES (n = 41) was moderate at -0.51, also demonstrating the SSPRO's responsiveness to change.

Conclusion: In this clinical trial dcSSc population, SSPRO showed high internal consistency, construct validity, and responsiveness to change. Moderate and significant correlations of SSPRO scores with PtGA and HAQ-DI scores validate the usefulness of SSPRO as an outcome measure of how the patient with dcSSc feels and functions. Its weaker but still significant and directionally concordant correlations with mRSS shows that the SSPRO may provide additional information on the patient's experience of their skin involvement that the mRSS does not assess. This is the first prospective validation of the SSPRO in a clinical trial

BACKGROUND

- It is important to measure health-related quality of life (HRQOL) when determining the effectiveness of therapies for systemic sclerosis (SSc)
- Skin thickening, the hallmark disease manifestation of SSc, affects the patient's physical and social function and emotional well-being
- The modified Rodnan skin score (mRSS) does not correlate well with patients' illness perception in SSc[1]. The Health Assessment Questionnaire-Disability Index HAQ (HAQ-DI) does not address emotional or social health status of the patient and does not specifically address skin involvement
- Scleroderma Skin Patient Reported Outcome (SSPRO) is the first validated patient questionnaire that assesses skin HRQOL specific to SSc.
- SSPRO has been previously shown to be reliable and valid (high internal consistency, construct, content and face validity).[2] SSc patient input was central to all phases of its development.
- SSPRO has 18 items that represent 4 HRQOL scales: physical symptoms, social effects, emotional effects and physical function. Each item is scored on a 7 point Likert scale (Figure 1)
- In this study, SSPRO was prospectively validated in a double-blind randomized placebo-controlled Phase 2 trial of safety and efficacy of anabasum in diffuse cutaneous SSc (JBT101-SSc-001)

METHODS

- Anabasum is a preferential cannabinoid receptor type 2 agonist that was tested for safety and efficacy in dcSSc in a 12-week double-blind randomized placebo-controlled Phase 2 trial.
- Efficacy outcomes included the SSPRO, Patient Global Assessment (PtGA), HAQ-DI, Physician Global Assessment (MDGA), mRSS, ACR Combined Response Index in Diffuse Cutaneous Systemic Sclerosis (CRISS), and FVC % predicted.
- SSPRO scores were transformed to a 0-100 scale.
- SSPRO baseline scores were correlated with other baseline outcome scores using Pearson's Correlation Coefficient to test construct validity. Internal consistency was estimated using Cronbach's α.
- Responsiveness to change was assessed by comparing the change in SSPRO scores between placebo and active groups. Effect size (ES, ratio of mean change in outcome total score from baseline to 12 weeks, to the standard deviation of the total score at baseline) was calculated for efficacy outcomes.
- SSPRO scores were compared between participants who improved vs not improved, as defined by PtGA change ≥ 1/10, CRISS, MDGA change ≥ 1/10, and HAQ change ≥ 0.25 at 12 weeks.

SSPRO

Figure 1. Scleroderma Skin PRO (SSPRO) items and scales

Question	Scale
1. How tight has your skin felt?	PS
2. How dry has your skin been?	PS
3. How painful has your skin been?	PS
4. How discolored has your skin been?	PS
5. How itchy has your skin felt?	PS
6. How self-conscious have you been because of your skin?	EE
7. How worried have you been about your skin?	EE
8. How depressed have you been about your skin?	EE
9. How much have you not felt like your true self because of the way your skin is?	EE
10. How frustrated have you been about your skin?	EE
11. How much have you felt like you lack control over your skin's condition?	EE
12. How much difficulty have you had doing things with your hands because of skin tightness?	PF
13. How much difficulty have you had with opening or closing your mouth because of skin tightness?	PF
14. How much difficulty have you had with moving parts of your body because of skin tightness?	PF
15. How much has your skin's condition interfered with your daily activities (examples: work, study, leisure activities)?	PF
16. How much has your skin prevented you from going out to socialize?	SE
17. How much has your skin interfered with your interactions with people?	SE
18. How much has your skin affected the clothes you wear?	SE
PS = Physical Symptoms, EE = Emotional Effects, PF = Physical Function, SE = Social Effects	

BASELINE CHARACTERISTICS OF STUDY SUBJECTS

- SSPRO was administered to 42 participants with dcSSc in study JBT101-SSc-001 (anabasum-treated N = 27, placebo N=15)
- 41 participants had at least one post-baseline efficacy assessment and are the sample used
- Mean age was 47.9 years, disease duration was 33.9 months, and mRSS was 24.5 **(Table 1)**

Table 1. Baseline characteristics of the 42 SSc subjects in study JBT101-SSc-001

Characteristic	Anabasum (N = 27)	Placebo (N = 15)
Age in years, mean (SD) Range	48.7 (10.42) 24 - 69	46.5 (11.05) 18 - 63
Female sex, n (%)	23 (85.2)	9 (60.0)
White, n (%)	22 (81.5)	12 (80.0)
mRSS, mean (SD)	23.5 (10.4)	26.2 (11.1)
Disease duration in months, mean (SD)	34.0 (16.6)	33.0 (17.9)
Patient Global Assessment, mean (SD)	4.9 (2.3)	4.9 (2.8)
Physician Global Assessment, mean (SD)	4.6 (1.8)	5.2 (2.1)
Health Assessment Questionnaire-Disability Index, mean (SD)	1.51 (0.8)	1.26 (0.8)
Concomitant immunosuppressive drugs (%)	92.9%	80.0%

RESULTS

Internal Consistency of SSPRO was high for both total (0.87) and for all scale sores (0.92) **(Table 2)**

Table 2. Descriptive statistics and internal consistency of the SSPRO

Scale	Score, mean (SD)	Floor Effect, %	Ceiling Effect, %	Cronbach's α
Total	58.5 (24.10)	0	2.4%	0.87
Physical Symptoms	60.2 (22.46)	0	2.4%	0.92
Emotional Effects	62.9 (30.67)	2.4%	2.4%	0.92
Physical Function	60.0 (26.10)	0	2.4%	0.92
Social Effects	45.0 (34.15)	19.5%	2.4%	0.92

SSPRO **correlated strongly with PtGA and HAQ-DI**, **moderately with MDGA and mRSS** and not at all with forced vital capacity (FVC) % predicted, as expected **(Table 3)**

Table 3. Correlations of SSPRO total and scale scores with other efficacy outcomes at baseline in a Phase 2 trial of anabasum in SSc

Efficacy Outcome	Total SSPRO Score	Physical Symptoms	Emotional Effects	Physical Function	Social Effects
PtGA	**0.626[4]**	**0.506[3]**	**0.482[3]**	**0.646[3]**	**0.573[4]**
HAQ-DI	**0.521[3]**	**0.500[3]**	0.264	**0.592[4]**	**0.581[4]**
MDGA	**0.514[3]**	**0.371[1]**	**0.372[1]**	**0.543[3]**	**0.551[3]**
mRSS	**0.445[3]**	**0.378[1]**	**0.387[1]**	**0.338[1]**	**0.433[3]**
FVC % predicted	-0.315	-0.115	-0.242	-0.165	-0.211

[1]P ≤ 0.05; [2]P ≤ 0.01; [3]P ≤ 0.005; [4]P ≤ 0.0001

SSPRO was **responsive to change:**

- SSPRO showed a **significant improvement in anabasum-treated participants compared to placebo-treated subjects** at 12 weeks, LS means difference (SE) = -16.9 (6.0), P = 0.004
- SSPRO **scores of participants who improved at 12 weeks were numerically greater than for participants who did not improve, which was statistically significant for MDGA (p = 0.0146**; 2-sample t-test**)**, although not significant for CRISS (p = 0.1856), HAQ-DI (p = 0.4331), or PtGA (p = 0.4639), possibly due to the small sample size (Figure 2).
- The **Effect Size (ES) for change in SSPRO total score for anabasum-treated patients was 0.51** This was higher than SSPRO emotional effects scale score, the SSPRO social effects scale score, the mRSS, PtGA and HAQ-DI. It was lower than the SSPRO physical symptom scale, the SSPRO physical function scale, and the MDGA **(Table 4).** (ES 0.2-0.49 small, 0.5-0.79 moderate, ≥ 0.80 large)

RESULTS

Figure 2 Change in SSPRO total scores for patients who improved vs. not improved

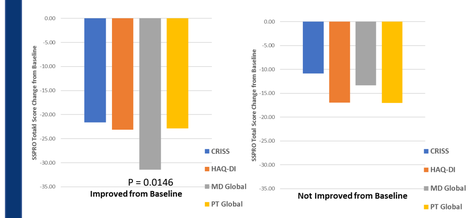

Figure 2. *Improvement was defined by PtGA change by ≥ 1/10, CRISS-improvement, MDGA change by ≥ 1/10, and HAQ change by ≥ 0.25, from baseline to week 12.*

Table 4. Effect sizes of efficacy outcomes in anabasum-treated subjects at 12 weeks

Efficacy Outcome	Effect Size
SSPRO	
Total	0.51
Physical Symptoms	0.57
Emotional Effects	0.39
Physical Function	0.57
Social Effects	0.42
mRSS	0.38
PtGA	0.35
MDGA	0.57
HAQ-DI	0.25

REFERENCES

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2. Man A, Correa JK, Ziemek J, Simms RW, Felson DT, Lafyatis R. Development and validation of a patient-reported outcome instrument for skin involvement in patients with systemic sclerosis. Ann Rheum Dis. 2017 Aug;76(8):1374–80.

SUMMARY AND CONCLUSIONS

- SSPRO is a multidimensional instrument that assesses the skin-specific health-related quality of life in SSc patients
- In this clinical trial SSc population, SSPRO showed high internal consistency, construct validity and responsiveness to change
- SSPRO would be useful in both future clinical trial and practice settings, providing additional information about how the SSc patient feels and functions in response to therapy

THANK YOU

❖ **To the people with SSc who participated in this study**

❖ **To the investigators and study staff who successfully executed this trial**

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For related clinical data from the trial, please see the following posters and presentation:
Spiera et al., Poster # 725, Safety and Efficacy of Anabasum (JBT-101) in Diffuse Cutaneous Systemic Sclerosis (dcSSc) Subjects Treated in an Open-Label Extension of Trial JBT101-SSc-001; 11/5, 9 – 11am
Spiera et al, Oral Presentation, Abstract # 2884, A Phase 2 Study of Safety and Efficacy of Anabasum (JBT-101), a Cannabinoid Receptor Type 2 Agonist, in Diffuse Cutaneous Systemic Sclerosis; 11/7, 4:30 – 6pm
Martyanov et al., Poster # 1707, Effect of Anabasum (JBT-101) on Gene Expression in Skin Biopsies from Subjcts with Diffuse Cutaneous Systemic Sclerosis (dcSSc) and the Relationship of Baseline Molecular Subsets to Clinical Benefit in the Phase 2 Trial.