Utility of a Validated Disease-Specific Measure to Assess Symptomology in Patients with Indolent Systemic Mastocytosis (ISM)

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Background

- Systemic mastocytosis (SM) is a rare condition characterized by accumulation of neoplastic mast cells of more than one organ driven by the *KIT* D816V mutation.[1]
- SM manifests as indolent systemic mastocytosis (ISM), smoldering SM (SSM), and advanced SM (AdvSM).[2]
- Non-advanced SM, including ISM and SSM, comprise 90-95% of total cases.[3]
- ISM is associated with long diagnostic delays, decreases quality of life, and causes debilitating and unpredictable symptoms for patients, including life threatening anaphylaxis.[4]
- The ISM symptom assessment form (ISM-SAF) was developed to measure disease symptomology.[5]
- This research assesses and describes the development and validation of the ISM-SAF, a symptom assessment tool developed specifically for ISM patient populations and explores its potential utility.

Methods

- A targeted review of peer-reviewed literature between 2015 and 2021 was conducted to systematically assess and summarize the development and validation of the ISM-SAF and explore its potential utility (Figure 1).
- The primary objective was to identify and synthesize data from publications reporting patient-level results using the ISM-SAF.
- The search was primarily conducted in PubMed and supplemented through Google Scholar and Clinicaltrials.gov.
  - Search terms in PubMed included: "systemic mastocytosis," "symptom assessment," "patient reported outcomes," and "quality of life."
  - A targeted Google Scholar search aimed to capture abstracts, posters, and conference proceedings that were not captured in PubMed. Results from "ISM-SAF" were hand screened for inclusion criteria. Abstracts and clinical trials that include data that were later published in full-text articles were excluded.
    - ClinicalTrials.gov was queried for ISM trials that are "active, not recruiting," "enrolling by invitation," "recruiting," or "not yet recruiting" and hand screened for those utilizing ISM-SAF.
- Records that utilized the ISM-SAF and reported patient-level outcomes met inclusion criteria. Records that used different symptom assessment tools or did not report patient-level outcomes were excluded from the final review.
- Prioritized outcomes were abstracted from the final sources including study characteristics and psychometric properties.

FIGURE 1. SEARCH FLOW DIAGRAM FOR REVIEW OF ISM-SAF

FIGURE 2. ISM-SAF SYMPTOMS ASSESSED, DOMAINS, AND SCORING
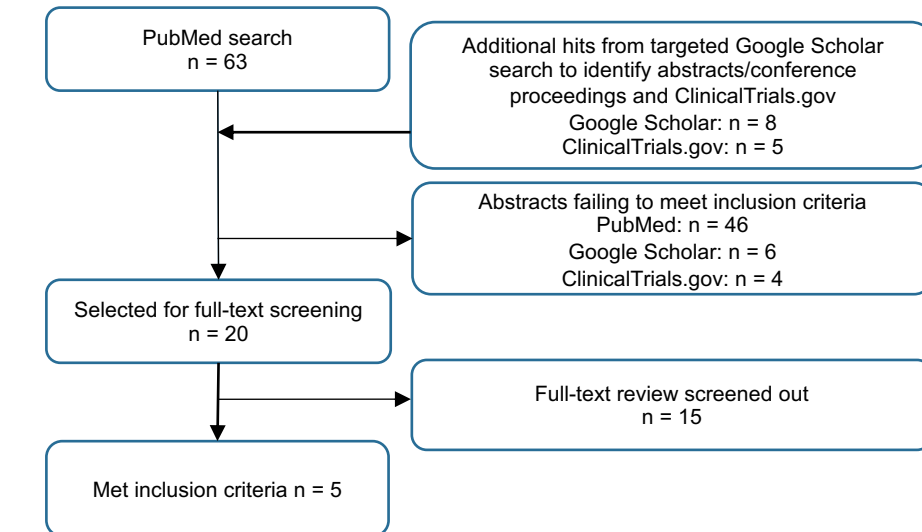
Conclusions

- The development and validation of the ISM-SAF as a 'fit for purpose' tool to assess disease-related symptom severity in ISM patients in both clinical trial and observational research settings has been documented by peer-reviewed publications.
  - Use of a reliable and valid symptom assessment tool that evaluates concepts relevant and important to individuals with a condition is important for determining clinical benefit of new treatments.
- The findings from this review highlight the utility of the ISM-SAF as a valuable tool to assess symptom burden and change in ISM symptoms over time.
- As part of the validation, TSS scores have been shown to correlate well with commonly used measures of health status, quality of life (i.e., SF-12, PGIS).
- Research has shown that a 30% individual percentage decrease in TSS is clinically meaningful improvement in ISM symptoms at the individual level.
- The ISM-SAF may offer clinicians a valuable tool to assess symptom severity and potential treatment benefits in clinical practice.

References
1. Jara-Acevedo M, et al. *Mod Pathol.* 2015;28(8):1138-1149.; 2. Pardanani A. *Am J Hematol.* 2019;94(3):363-377; 3. Cohen SS, et al. *Br J Haematol.* 2014;166(4):521-528; 4. Padilla B, et al. *Orphanet J Rare Dis.* 2021;16(1):434; 5. Taylor F, et al. *Orphanet J Rare Dis.* 2021;16(1):414; 6. Shields A.L., et al. Poster presented at: ISPOR Europe; December 2019; 7. Mesa R.A., et al. Poster presented at: American Society of Hematology; 5 December 2020.; 8. (HARBOR) Study to evaluate efficacy and safety of BLU-263 versus placebo in patients with indolent systemic mastocytosis. Clinicaltrials.gov identifier: NCT04910685. Updated 22 December 2021. Accessed 28 December 2021.

Results

ISM-SAF Literature Review Results

- One full-text article on the development of the ISM-SAF, three presentations/publications on the application and validation of the ISM-SAF, and one ongoing clinical trial met the inclusion criteria (Table 1).
- The ISM-SAF was developed using best practices for patient-reported outcome development, including clinician and patient input on symptoms, cognitive debriefing interviews with patients, and regulatory feedback.[5]
- The ISM-SAF assesses 11 relevant symptoms: abdominal pain, nausea, diarrhea, spots, itching, flushing, bone pain, fatigue, dizziness, brain fog, and headache (Figure 2) and has been validated in multiple languages.[4]
- In addition to a total symptom score (TSS), reflective of overall disease burden, the ISM-SAF tool allows for an evaluation of gastrointestinal and skin-specific SM domain scores.

ISM-SAF Utility Results

- The ISM-SAF has been used in multiple research settings – randomized controlled trial,[4,8] prospective observational study,[6] and a cross-sectional patient survey.[7]
- Psychometric analyses have demonstrated the reliability, validity, and responsiveness of the ISM-SAF (Tables 1 & 2, Figures 3 and 4), and confirmed it is a 'fit for purpose' tool to assess symptom severity in SM patients (Table 2)
- The ISM-SAF has been used to:
  - Assess the overall severity of SM-specific symptoms, calculated as a TSS at a single point in time (Table 3),
  - Measure change (i.e., improvement, increased severity) over time in SM-specific symptoms, with a 30% reduction in TSS considered clinically meaningful, and
  - Differentiate between patients with moderate-severe versus mild SM disease (e.g., moderate-severe SM patients have TSS ≥ 28).
- The ISM-SAF is being used in the ongoing HARBOR clinical trial to assess the effects of a new ISM treatment on SM symptoms.[8]

TABLE 1. STUDY CHARACTERISTICS

Study Characteristics	PIONEER Part 1 (Padilla 2021)	Prospective Observational (Shields 2019)	TouchStone (Mesa 2020)	HARBOR (ongoing P2/3 study)
NCT Number	NCT03731260	n/a	n/a	NCT04910685
Study Design	RCT	Prospective Observational	Cross-Sectional	RCT
Patients	38	103	30	403 (estimated)
Study Duration	Up to 5 years	15 days	1 day	Up to 5 years
Intervention	Randomized to avapritinib or placebo + BSC	n/a	n/a	Randomized to BLU-263 or placebo + BSC
SM Subtype	ISM	ISM or SSM	SM	ISM
Use of Instrument	14-day rolling average	14-day	1-time	Not reported in ClinicalTrials.gov
Administration Methods	Daily administration in eDiary	Web-based HIPAA-compliant platform (Survey Monkey)	Online survey	Not reported in ClinicalTrials.gov
Scoring Details	24-hour recall	24-hour recall	Not reported	Not reported in ClinicalTrials.gov
Utility of ISM-SAF	Symptom Improvement	Symptom Burden	Symptom Burden	Symptom Improvement
Key Outcomes Reported	Mean Baseline TSS Scores, Reliability (Internal Consistency and Test-Retest) Validity (Construct-Related Validity, Known-Groups Analysis), Sensitivity to change	Reliability (internal consistency, test-retest validity), Validity (Construct-Related Validity, Known-Groups Analysis)	Mean TSS scores, Mean SF-12 MCS, Mean SF-12 PCS	n/a
Conclusion/ Findings	The ISM-SAF produced reliable, construct valid, and sensitive scores among ISM patients in a randomized clinical trial setting.	These psychometric results support the conclusion that the ISM-SAF can produce trustworthy scores when administered to patients in the target population in that the domain and item scores are reliable, construct-valid, and able to distinguish among clinically unique groups.	This study is the first time the ISM-SAF has been used in a real-world setting and with one-time administration. The TSS scores were correlated with the symptoms assessed; however, further validation work is necessary.	n/a

TABLE 2. COMPARISON OF RELIABILITY, VALIDITY, AND SENSITIVITY RESULTS FROM PIONEER PART 1 AND PROSPECTIVE OBSERVATIONAL STUDY

| Study	PIONEER Part 1[†] (Padilla 2021)	Observational Study (Shields 2019)
Mean Baseline Scores on ISM-SAF		
TSS	54.2	Not reported
GSS	10.9	
SSS	16.2	
Reliability: Internal Consistency (Cronbach's Alpha)		
Population	Baseline (n=38)	CS-AP (n=103)
TSS	0.86	0.88
GSS	0.83	0.78
SSS	0.82	0.67
Reliability: Test-Retest Reliability, ICC (95% CI)		
Population	Between baseline and C1D15 (n=16 for TSS and GSS, n=17 for SSS)	PGIS Stable Participants (n=61)
TSS	0.956	0.962 (0.936-0.977)
GSS	0.858	0.936 (0.894-0.962)
SSS	0.981	0.962 (0.937-0.977)

Validity: Spearman correlations of ISM-SAF total and domain scores with other measures (≥0.6=green, <0.3=red)*

Population	At time C4D1 (n=34)			CS-AP (n=103)		
Concurrent Measure	TSS	GSS	SSS	TSS	GSS	SSS
SF-12 PCS	-0.226	-0.275	-0.179	-0.631	-0.493	-0.308
SF-12 MCS	-0.536	-0.368	-0.218	-0.483	-0.465	-0.346
MC-QoL	0.695	0.538	0.550	0.849	0.679	0.587
PGIS	0.656	0.401	0.618	0.618	0.454	0.446

Validity: Known-Groups analysis of ISM-SAF total and domain scores based on PGIS, MC-QoL, and SF-12 scores

Population		At time C4D1 (n=34)				CS-AP (n=103)			
	Group	n	TSS mean (SD)	GSS mean (SD)	SSS mean (SD)	n	TSS mean (SD)	GSS mean (SD)	SSS mean (SD)
	Absent/Minimal	12	27.1 (10.2)	4.3 (3.3)	8.1 (4.0)	41	18.5 (14.1)	3.9 (5.1)	4.7(3.9)
	Severe/Very Severe	11	55.2 (15.1)	9.7 (6.5)	18.3 (6.5)	18	50.4 (20.7)	9.3 (7.7)	11.8 (5.7)
MC-QoL	Mild	10	29.5 (10.6)	4.7 (3.6)	9.7 (7.1)	37	16.6 (9.9)	3.4 (3.0)	5.4 (4.7)
	Moderate	12	43.4 (16.4)	7.3 (3.7)	12.5 (6.3)	32	29.5 (9.3)	5.1 (3.3)	9.5 (5.4)
	Severe	12	55.8 (14.8)	10.7 (5.8)	15.9 (6.5)	33	42.0 (12.0)	8.3 (3.6)	11.0 (3.3)
SF-12	Mild	11	53.4 (10.8)	10.6 (3.2)	13.8 (7.1)	34	17.2 (11.5)	3.1 (2.6)	5.6 (4.4)
	Moderate	12	47.8 (19.6)	7.6 (6.5)	14.2 (5.7)	33	24.8 (8.7)	4.7 (3.5)	8.1 (5.3)
	Severe	11	29.4 (11.4)	5.0 (3.3)	10.4 (7.7)	34	43.9 (13.4)	8.8 (4.2)	11.7 (3.9)

Sensitivity to Change: Mean change (SD) in biweekly scores from baseline to C4D1

TSS	-12.70 (14.93)	Not feasible; one round of 14-day use of tool
GSS	-3.83 (5.98)	
SSS	-4.07 (5.64)	

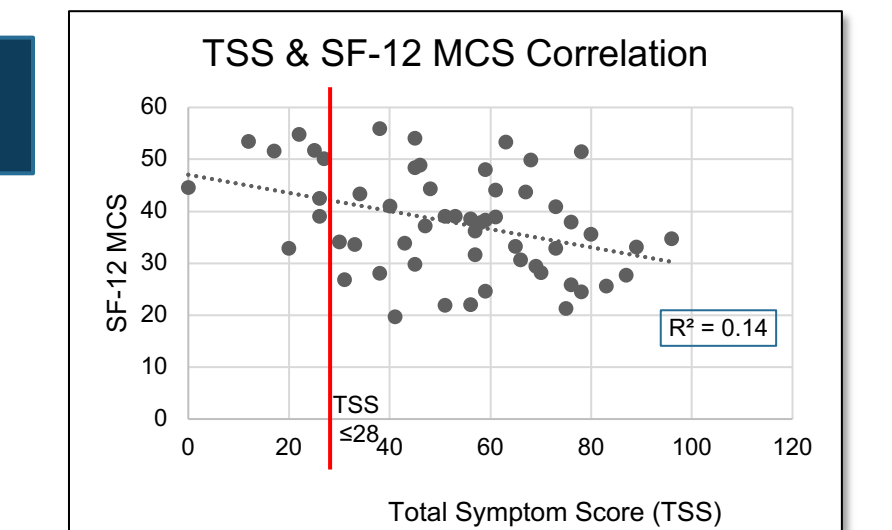### TABLE 3. RESULTS FROM TOUCHSTONE SM PATIENT SURVEY (MESA 2020)

Methods	Online cross-sectional survey of patients self-reporting SM diagnosis. The 100-item questionnaire, which included the full ISM-SAF, evaluated disease and healthcare system burden of SM patients in real-world settings.		
Key Outcomes Reported	Mean TSS	Mean (SD) SF-12 MCS	Mean (SD) SF-12 PCS
	50	44 (1.8)	43 (2.5)

FIGURE 3. CORRELATION BETWEEN TSS AND SF-12 PCS AMONG TOUCHSTONE SM PATIENTS[§]
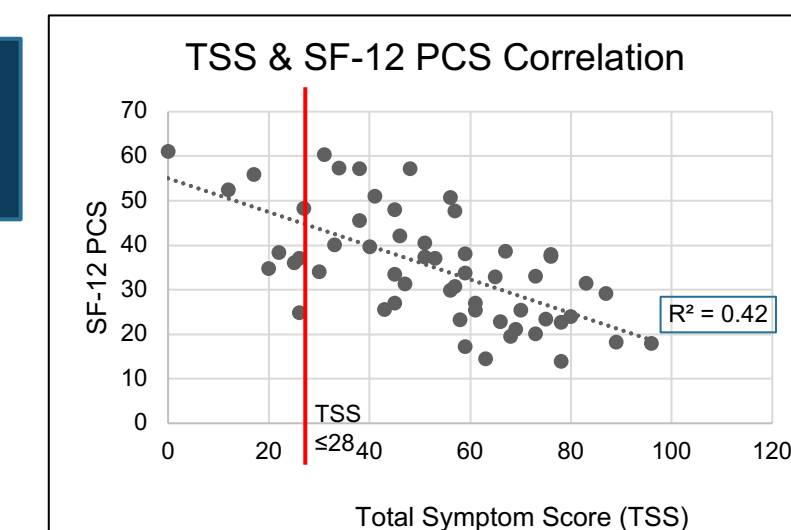
§ Negative correlation is expected due to different scoring systems for SF-12 and ISM-SAF.

FIGURE 3. CORRELATION BETWEEN TSS AND SF-12 MCS AMONG TOUCHSTONE SM PATIENTS[§]

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