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 explore 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

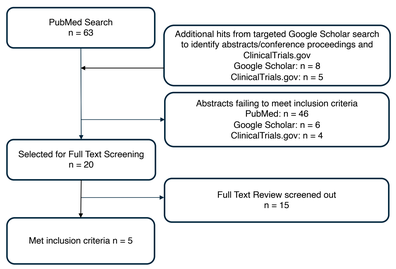
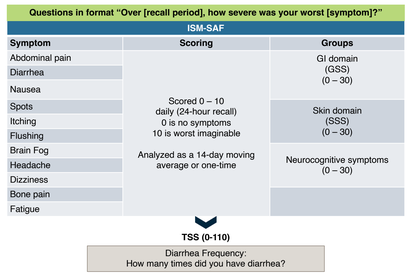


FIGURE 2. ISM-SAF SYMPTOMS ASSESSED, DOMAINS, AND SCORING



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.

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 PRO 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 GI 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	Study (Author Year)			
	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

Abbreviations: RCT: randomized control trial; BSC: best supportive care;; SSM: smoldering systemic mastocytosis; HIPAA: Health Insurance Portability and Accountability Act; TSS: total symptom score, as calculated from ISM-SAF;SF-12 MCS: 12-item Short Form Survey, mental component score; SF-12 PCS: 12-item Short Form Survey, physical component score
‡ ISM-SAF utility validation continuing in PIONEER Part 2 trial with 204 patients.

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 GSS SSS	54.2 10.9 16.2			Not reported		
Reliability: Internal Consistency (Cronbach's Alpha)						
Population	Baseline (n=38)			CS-AP (n=103)		
TSS GSS SSS	0.86 0.83 0.82			0.88 0.78 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 GSS SSS	0.956 0.858 0.981			0.962 (0.936-0.977) 0.936 (0.894-0.962) 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 SF-12 MCS MC-QoL PGIS	-0.226 -0.536 0.695 0.656	-0.275 -0.368 0.538 0.401	-0.179 -0.218 0.550 0.618	-0.631 -0.483 0.849 0.618	-0.493 -0.465 0.679 0.454	-0.308 -0.346 0.587 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)
PGIS: 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)
PGIS: Moderate	11	50.4 (12.1)	9.5 (2.9)	12.6 (6.0)	43	32.4 (13.0)	5.8 (3.7)	10.3 (5.3)
PGIS: 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)
MC-QoL: 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)
MC-QoL: 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)
SF-12: 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)
SF-12: 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 GSS SSS	-12.70 (14.93) -3.83 (5.98) -4.07 (5.64)			Not feasible; one round of 14-day use of tool		

Abbreviations CS-AP: cross-sectional analysis population; ICC: interclass correlation coefficient; CI: confidence interval ; C1D15: cycle 1, day 15; SD: standard deviation; PGIS: Patient global impression of severity; C4D1: cycle 4, day 1; MC-QoL: Mastocytosis Quality of Life survey, total score; * Scores shown in green indicate strong (≥0.6) relationships between ISM-SAF scores and measures of other instruments, conversely, scores shown in red indicate weak (<0.3)relationships between ISM-SAF scores and measures of other instruments

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§

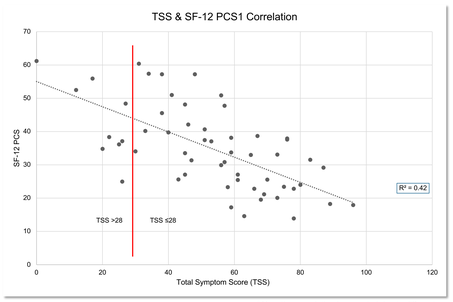
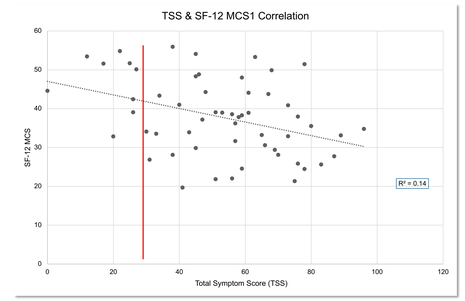


FIGURE 3. CORRELATION BETWEEN TSS AND SF-12 MCS AMONG TOUCHSTONE SM PATIENTS §



§ Negative correlation is expected due to different scoring systems for SF-12 and ISM-SAF.

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