The 9-Item Sickle Cell Disease Severity Measure (SCDSM): A Novel Measure of Daily SCD Symptom Severity 
Developed to Assess Benefit of GBT440, an Experimental Hbs Polymerization Inhibitor

Laurie Burke, MPH1; Jeremy Hobart, PhD, FRPC2; Kathleen M. Fox, MHS, PhD3; Kenneth Bridges, MD4; Martine Kraus, PhD5; Felicia Lipansky1; Joshua Lehrer-Graiver, MD, MPH, FACC6

1LDRA Group, LLC, Royal Oak, MI USA; 2Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK, 3HealthiVibe, LLC, Arlington, VA USA; 4Global Blood Therapeutics, South San Francisco, CA USA

INTRODUCTION
- Patients with sickle cell disease (SCD) have a high and variable burden of daily symptoms.
- Patients have frequent, severe exacerbations of symptoms that are acute and chronic.
- There is an unmet need for disease-modifying therapies in SCD, but the VOD endpoint is an impediment to new drug development.
- Developing SCD-specific patient reported outcome (PRO) measures focus on clinical impact, not on the daily core signs and symptoms.
- Accelerating the development of new therapies for SCD, which is a global and unmet need, is needed to measure daily SCD symptoms and detect all crises events.

OBJECTIVES
- The objectives of this study are to develop a PRO measure of daily SCD symptoms severity and
  - Meets scientific criteria as reliable, valid, sensitive to change in SCD severity (both improvement and worsening).
  - Generates scores that are interpretable and clinically meaningful.
  - Can be administered in a daily electronic diary format.
  - Meets regulatory requirements as a well-defined and reliable COA for use in adequate and well-controlled studies.

Methods: establishing content validity
- The PRO's content was derived from 1-on-1, open-ended, concept elicitation interviews in patients with SCD (see Table 1).
- Patients (n = 50) and adolescents aged 12 to 17 years (n = 10) from the US and UK.
- Interviews were recorded, transcribed, and coded using Atlas.ti to identify the most bothersome and frequently mentioned symptoms related to both “good” and “bad” days, as defined by the patients with SCD.
- Interviews continued in sequential groups of n = 10 until “saturation” was demonstrated (ie, no new themes emerged).
- The candidate items and response options proposed in the initial conceptual framework were examined during the interviews – qualitatively and quantitatively – and revised accordingly after each round of interviews.
- A multidomain structure was replaced with a single domain total score after patients reported, and psychometric analyses confirmed, that all items retained as SCDSM items contributed to their perception of “SCD severity.”
- A draft final version of the SCDSM was examined in formal cognitive debriefing studies (see Table 2).
- Additional interviews with adolescents (n = 10) and adults (n = 6) in both the US and the UK were conducted.
- These interviews revealed the need to add an additional item that was not useful.
- The interviews also supported the final 9-item content as appropriate, understandable, and complete to represent SCD symptoms.

SCD Severity Measure (SCDSM) developed to be fit-for-purpose for planned Phase 3 clinical study
- Concept of interest: daily measure of core signs and symptoms of disease
  - Literature review and expert interviews guided development
  - Meets regulatory requirements as a well-defined and reliable COA for use in adequate and well-controlled studies.
  - Meets scientific criteria as reliable, valid, sensitive to change in SCD severity (both improvement and worsening).
  - Generates scores that are interpretable and clinically meaningful.
  - Can be administered in a daily electronic diary format.
  - Meets regulatory requirements as a well-defined and reliable COA for use in adequate and well-controlled studies.

SCDSM measurement properties support use as a single total symptom score (TSS) of SCD symptom severity
- The draft item set was administered to 50 patients with SCD.
- We derived 2 algorithms for generating estimates of SCD symptoms from individual responses.
  - An ordinal-level total SCDSM score, computed by summing item scores.
  - A new interval-level (linear) SCDSM measure, derived from item responses using RMT analysis.
- SCDSM properties include
  - Good and bad days vary widely in their range of SCDSM measurements
  - The SCDSM is compared to 70 questions focusing on all aspects of SCD symptoms.
  - Each item has 6 response options, grading either severity or frequency of an event
  - The SCDSM distributions for patients who have “good” and “bad” days are different.
  - Differences are numerically and statistically large.

Next steps for SCDSM utilization in Phase 3 study
- Longitudinal testing of SCDSM measurement properties and the development of interpretation guidelines will occur using the final 9-item content in the Phase 3 HTE study.
- Translation and cultural adaptation will allow the SCDSM to be used in all languages, languages, and countries in which the clinical trial is planned.

SUMMARY
- The 9-item SCDSM is a promising new PRO measure of daily SCD symptom severity.
- Quantitative and qualitative research supports the use of a single TSS using these 9 items to measure the daily severity of symptoms in SCDSM.
- The SCDSM has been designed to address a full range of symptom to distinguish acute exacerbations from chronic pain to measure all crises events, regardless of health care utilization.
- Quantitative research, including psychometric analysis and RMT support that the SCDSM is reliable, valid, and interpretable.
- The SCDSM will be used as a clinical endpoint in the Phase 3 HTE study of GBT440.
- During the Phase 3 HTE study, longitudinal measurement properties and guidelines for measure interpretability will be defined.
- SCDSM has the potential to accelerate the development of urgently needed new therapies in SCD as compared with the use of the traditional VOD endpoint.

Table 1. SCDSM-conceptual framework/item content

<table>
<thead>
<tr>
<th>Item</th>
<th>Response Options</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy level (today)</td>
<td>Extremely low, low, good, excellent</td>
<td></td>
</tr>
<tr>
<td>Feeling physically weak (today)</td>
<td>All of the time, a little of the time, I did not have trouble breathing all day</td>
<td></td>
</tr>
<tr>
<td>Feeling physically weak (yesterday)</td>
<td>All of the time, a little of the time, I did not have trouble breathing all day</td>
<td></td>
</tr>
<tr>
<td>Feeling weak (today)</td>
<td>All of the time, a little of the time, I did not have trouble breathing all day</td>
<td></td>
</tr>
<tr>
<td>Feeling weak (yesterday)</td>
<td>All of the time, a little of the time, I did not have trouble breathing all day</td>
<td></td>
</tr>
<tr>
<td>Feeling physically weak (today)</td>
<td>All of the time, a little of the time, I did not have trouble breathing all day</td>
<td></td>
</tr>
<tr>
<td>Feeling physically weak (yesterday)</td>
<td>All of the time, a little of the time, I did not have trouble breathing all day</td>
<td></td>
</tr>
<tr>
<td>Feeling weak (today)</td>
<td>All of the time, a little of the time, I did not have trouble breathing all day</td>
<td></td>
</tr>
<tr>
<td>Feeling weak (yesterday)</td>
<td>All of the time, a little of the time, I did not have trouble breathing all day</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. SCDSM conceptual framework/item content

<table>
<thead>
<tr>
<th>Grouping Variable</th>
<th>Group</th>
<th>ANOVA F (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCDSM baseline</td>
<td>0.832</td>
<td>0.656</td>
</tr>
<tr>
<td>SCDSM change</td>
<td>0.832</td>
<td>0.656</td>
</tr>
</tbody>
</table>

Figure 1. FDA recommendations for COA development

Figure 2. Person-item threshold analysis: the SCDSM “rule” is well-tailed to measure the full range of daily symptoms.

Figure 3. SCDSM items work together to separate patients on the continuum of symptom severity

Figure 4. Conceptual illustration of SCDSM clinical endpoints designed to be more sensitive than VOD.

<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
</table>

©2016 Global Blood Therapeutics

Disclosure
Laurie Burke is employed by Global Blood Therapeutics and is a co-inventor on one pending and two granted U.S. patents for the SCDSM. Kenneth Bridges is the lead author on the SCDSM; the content was derived from 1-on-1, open-ended, concept elicitation interviews. Joshua Lehrer-Graiver is an employee of Global Blood Therapeutics. The other authors have indicated no financial relationships. This study was supported by a grant from Global Blood Therapeutics, South San Francisco, CA USA.

To access the poster digitally, please use the following QR code.