Sustained Improvements in Patient-Reported Quality of Life up to 24 Months Post-Treatment with LentiGlobin for Sickle Cell Disease (bb1111) Gene Therapy

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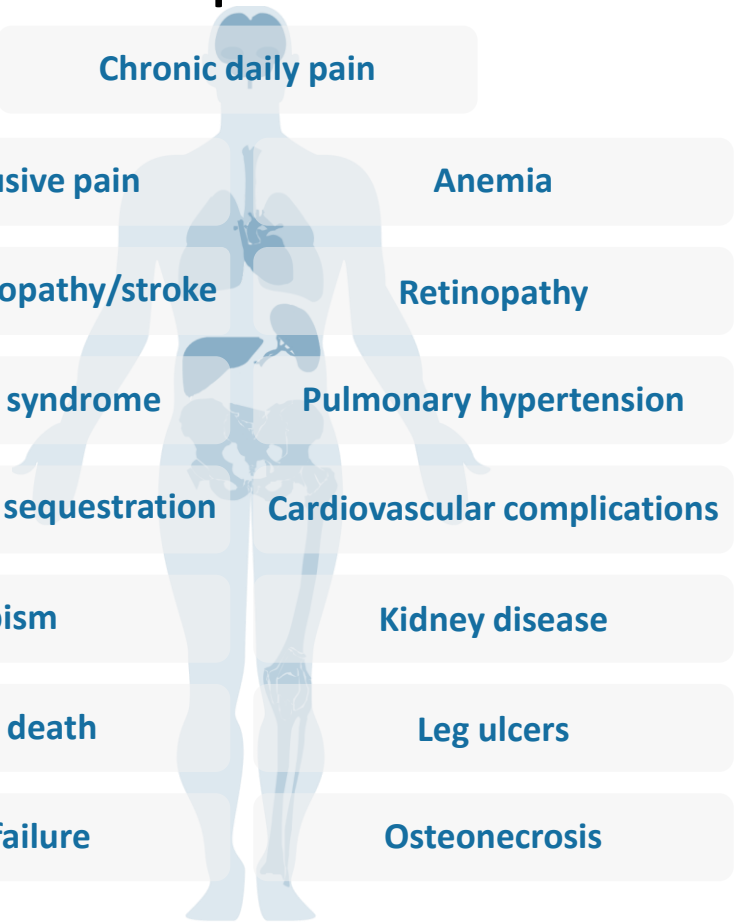
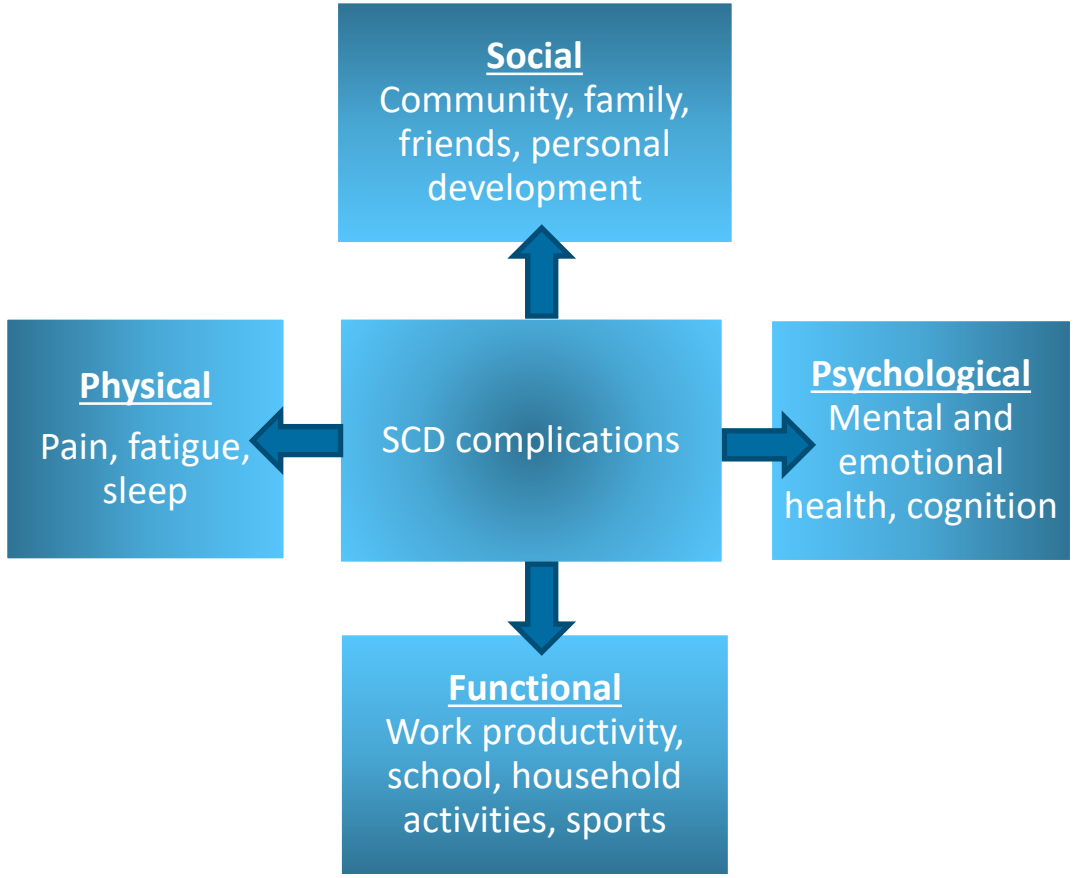
Sickle cell disease is characterized by extensive morbidity and early mortality, with negative impact on quality of life

SCD Complications[1,2]



- Chronic daily pain
- Vaso-occlusive pain
- Anemia
- Cerebral vasculopathy/stroke
- Retinopathy
- Acute chest syndrome
- Pulmonary hypertension
- Hepato-splenic sequestration
- Cardiovascular complications
- Priapism
- Kidney disease
- Sudden death
- Leg ulcers
- Organ failure
- Osteonecrosis

SCD complications affect all aspects of QoL[3–5]



1. Kanter, et al. *Blood Rev.* 2013;27(6):279-287; 2. Hassell K. et al. *Am J Prev Med.* 2010; 38:S512-21 3. Melo, et al. *PLoS One.* 2018;13:e0208916; 4. Treadwell et al. *Clin J Pain.* 2014;30(10):902-9144; 5. Holdford et al. *Value Health.* 2021; 24(8):1095–1101.
SCD, sickle cell disease; QoL, quality of life.

Phase 1/2 HGB-206 study of LentiGlobin for SCD (bb1111) GT measures both clinical and PRO endpoints

- Open-label, multicenter, registrational study has up to 37.6 months follow-up in Group C per Feb 2021 datacut
- Enrollment Criteria for Group C: (1) ≥12–≤ 50 years, (2) $\beta^S\beta^S$, $\beta^S\beta^0$, $\beta^S\beta^+$ genotype, (3) history of severe VOEs*, (4) failure of or intolerance to hydroxyurea; study ongoing and enrollment is complete

Clinical Outcomes

- Complete resolution of severe VOEs*
- Near-normalization of key hemolysis markers
- Normalization of total Hb
- Near-pancellular HbA^{T87Q} distribution across RBCs

Patient-reported outcomes

- HRQoL using PROMIS-57 (secondary endpoint)
- Work productivity using the WPAI questionnaire
- Overall health status using the EuroQoL 5 dimension instrument (EQ-5D-3L)

Treatment with LentiGlobin has previously demonstrated clinically-meaningful improvements in patient HRQoL[1]. Updated PROMIS-57 findings with up to 24 months follow up are shown.

*Defined per protocol as ≥4 severe VOEs in 2 years before informed consent; patients were also required to have ≥6 months follow up post-LentiGlobin infusion to be included in the data analysis. 1. Kanter, et al. *Blood.* 136 (S1);10-10. GT, gene therapy; Hb, hemoglobin; HbA^{T87Q}, anti-sickling Hb; HRQoL, Health-related quality of life; PROMIS, Patient Reported Outcomes Measurement Information System; RBC, red blood cell; WPAI, Work Productivity and Activity Impairment; VOE, vaso-occlusive event.

PROMIS-57 system for the measurement of health-related quality of life

- PROMIS-57 (v2.1) is a 57-question tool that measures HRQoL across 7 domains and has been validated for use in SCD[1–3]

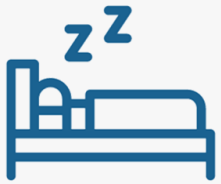
Physical Health

Pain Intensity[a]

Pain Interference

Fatigue

Physical Function



Sleep Disturbance

Mental Health

Anxiety

Depression

Socioemotional Health

Ability to participate in social roles

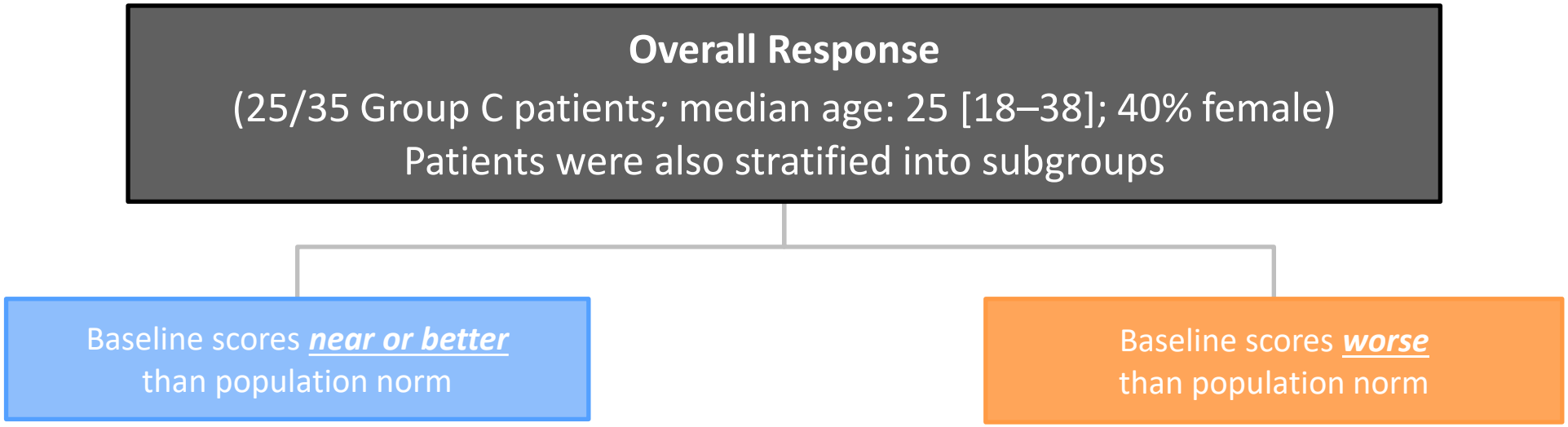
Sample questions and responses

Physical function: Are you able to go for a walk of at least 15 minutes?	Without any difficulty 5	With a little difficulty 4	With some difficulty 3	With much difficulty 2	Unable to do 1
Pain Interference: How much did pain interfere with your enjoyment of life?	Not at all 1	A little bit 2	Somewhat 3	Quite a bit 4	Very much 5

*7-day recall period for all domains except the "social roles" and "physical functioning" domains, which have no recall period.
†Average pain (0–10) over the past 7 days.

1. Esham KS et al. *Blood Adv*. 2020;4(1):19–27; 2. Keller S et al. *Health Qual Life Outcomes*. 2017;15:117; 3. PROMIS Cooperative Group. 2020. PROMIS Adult profile instruments. Available at www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Adult_Profile_Scoring_Manual.pdf. Accessed November 6, 2020. HRQoL; Health-related quality of life; NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; SCD, sickle cell disease.

HGB-206 Group C: Methods for PROMIS-57 data analysis

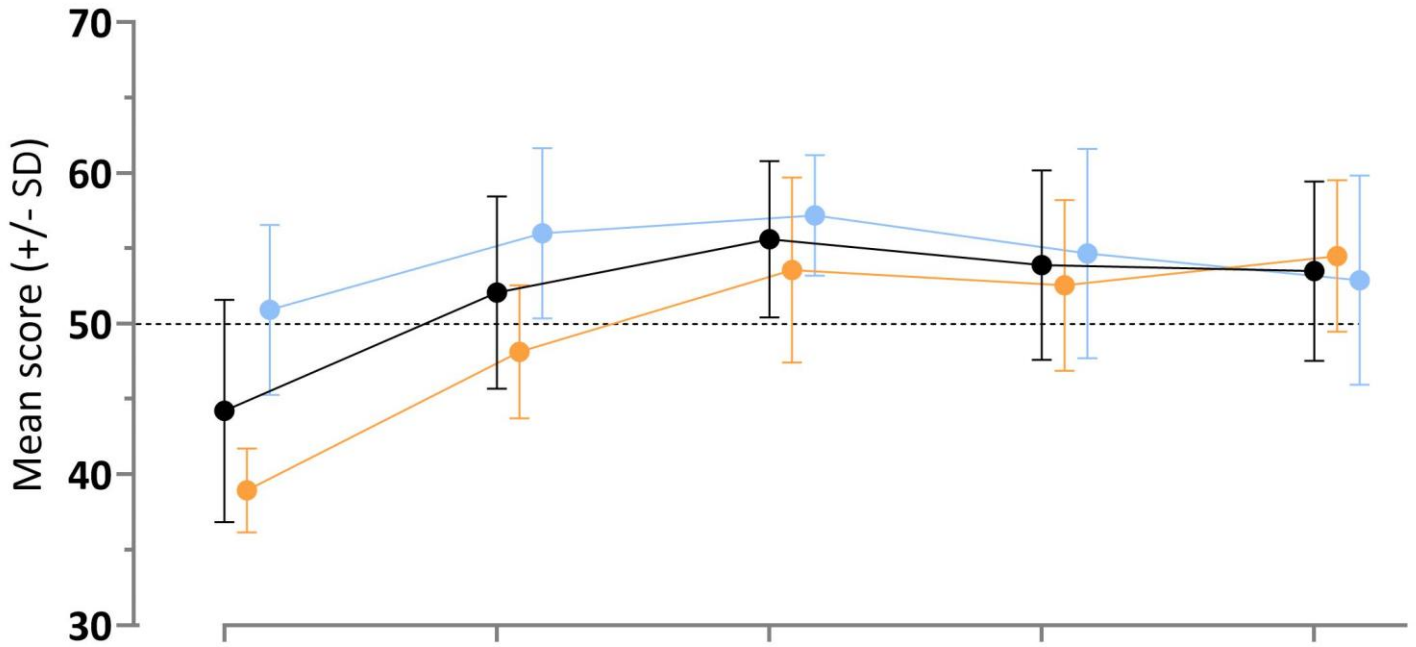


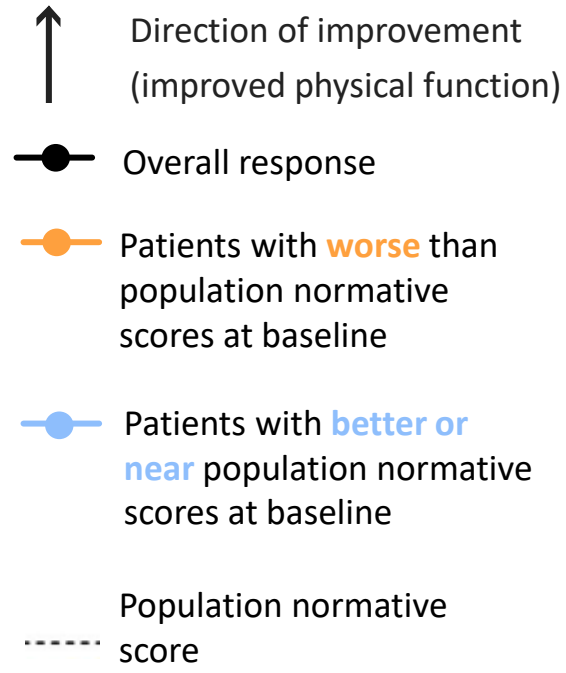
- Stratification depended on whether a patient's baseline score was "**near or better**" or "**worse**" than the population norm
- US general population norm standardized T-score is 50 for all domains and 2.6 for Pain Intensity NRS[1]
- Meaningful within-patient change was ≥5-point change for all domains and ≥2-point change for pain NRS[2–4]
- PROMIS-57 may not account for environmental and contextual factors that also influence a patients' overall QOL

1. PROMIS Cooperative Group. 2020. PROMIS Reference Populations. Available at https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/reference-populations. Accessed November 17, 2020; 2. Norman GR et al. *Med Care*. 2003;41:582-592; 3. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516;
4. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making. Available at: https://www.fda.gov/media/132505/download. Accessed November 16, 2020. NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System.

HGB-206 Group C PROMIS-57: Physical function

Physical Function





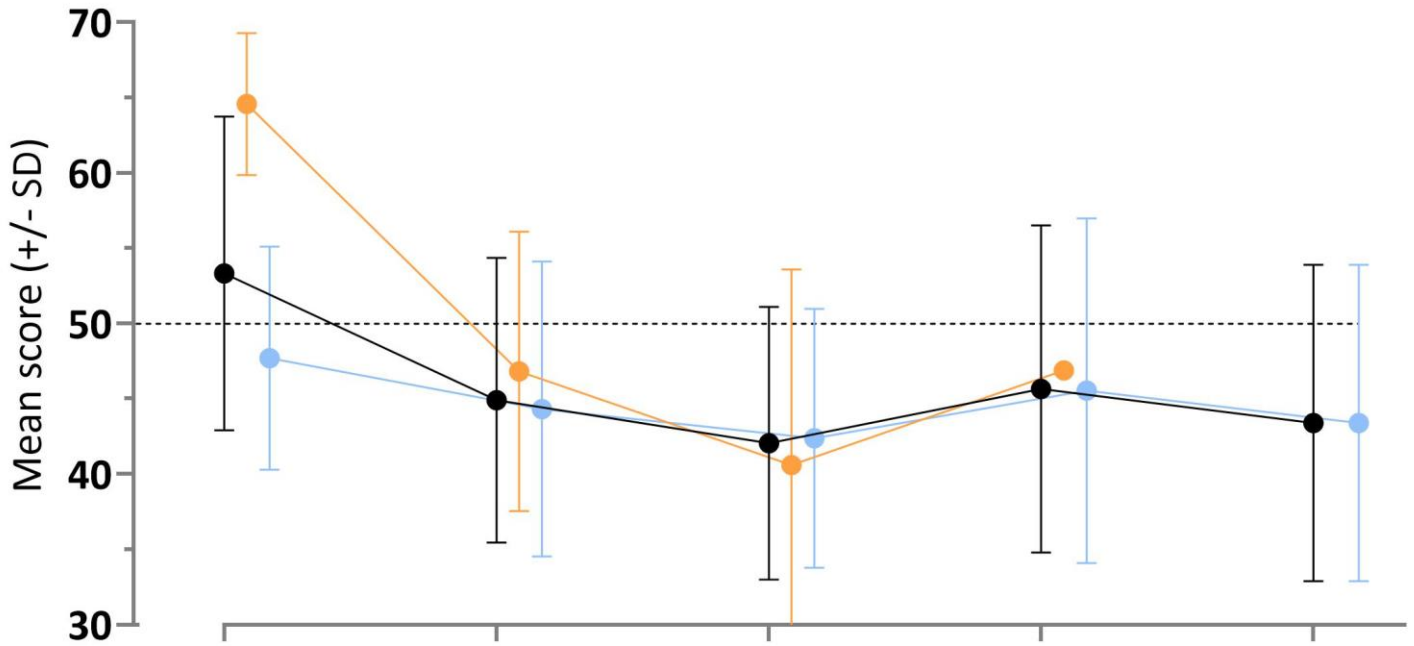
11/16 (69%) patients reported clinically meaningful improvements in physical function at Month 12, and 5/8 (63%) patients at Month 24

Clinically-meaningful change for PROMIS-57 is generally regarded as at least a 2-point change for the pain NRS and a 5-point change for the other domains[1-3].

1. Norman GR et al. *Med Care*. 2003;41:582-592; 2. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516; 3. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making.
NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation.

HGB-206 Group C PROMIS-57: Fatigue

Fatigue



Sample size (**overall** worse/better or near at baseline)

Direction of improvement (less fatigue)

Overall response

Patients with worse than population normative scores at baseline

Patients with better or near population normative scores at baseline

Population normative score

8/16 (50%) patients reported clinically meaningful reductions in fatigue at Month 12, and 5/9 (56%) patients at Month 24

Clinically-meaningful change for PROMIS-57 is generally regarded as at least a 2-point change for the pain NRS and a 5-point change for the other domains[1-3].

1. Norman GR et al. *Med Care*. 2003;41:582-592; 2. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516; 3. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making.
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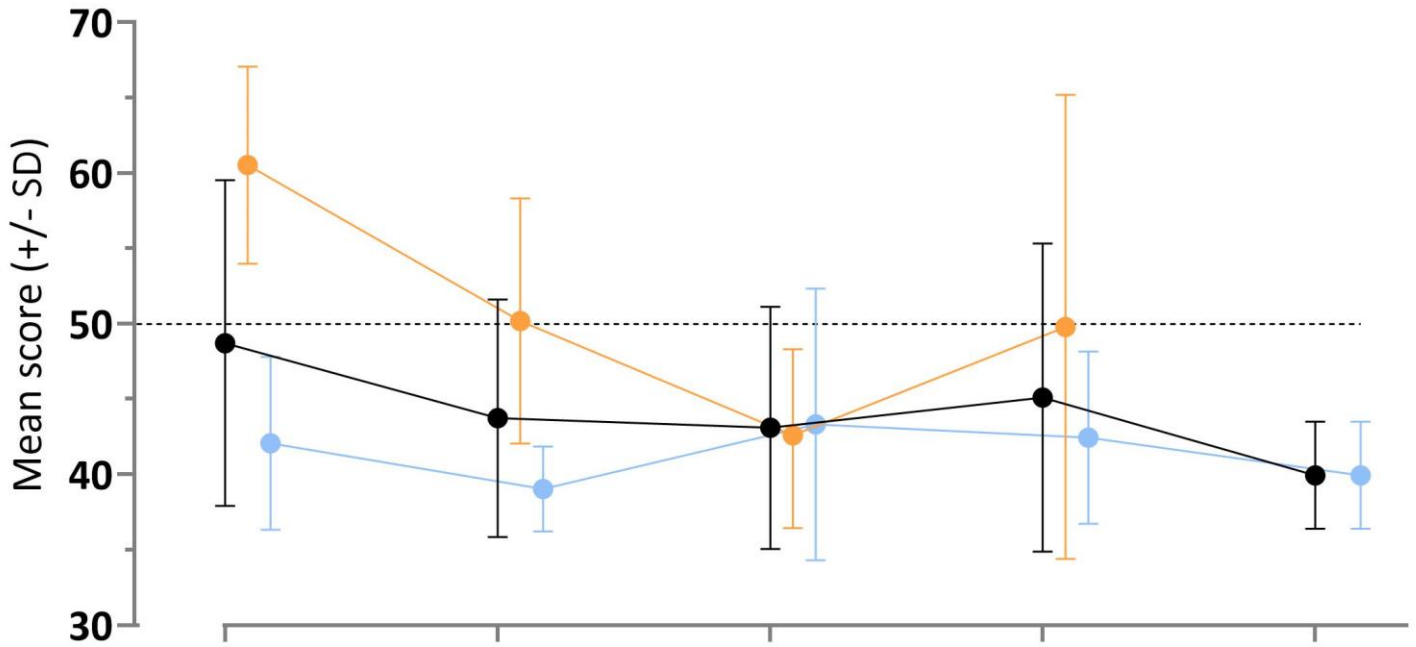
HGB-206 Group C PROMIS-57: Depression

Depression



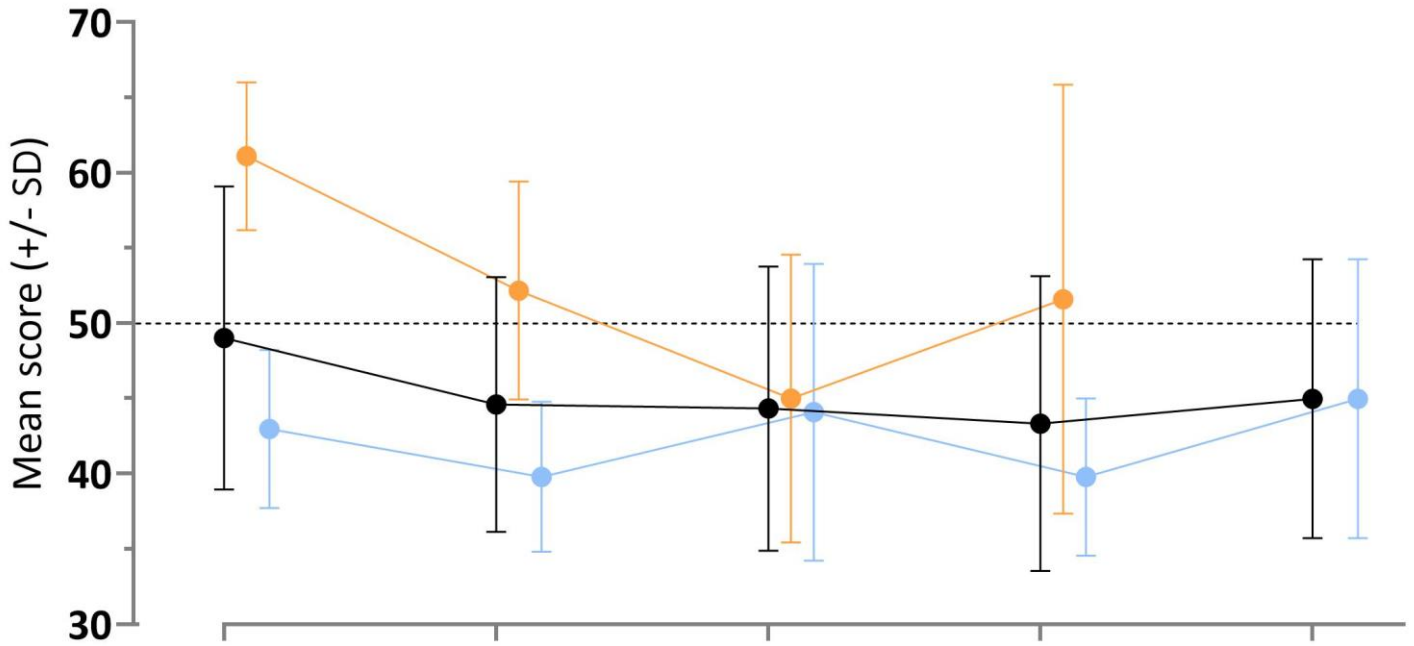
7/16 (44%) patients reported clinically meaningful reductions in depression at Month 12, and the overall trend is sustained at Month 24*

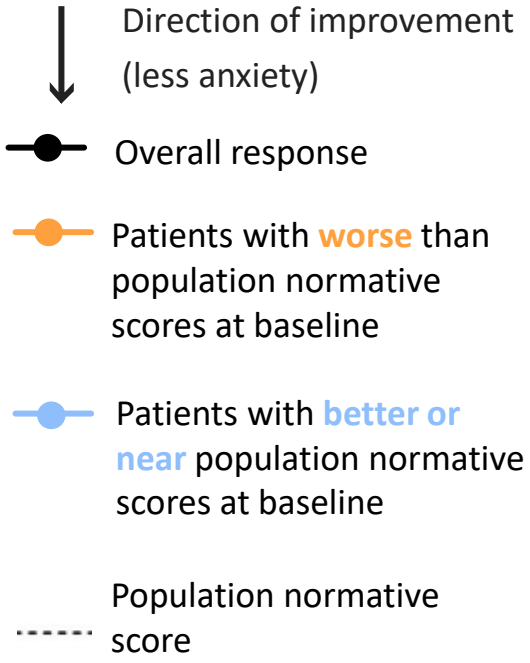
Clinically-meaningful change for PROMIS-57 is generally regarded as at least a 2-point change for the pain NRS and a 5-point change for the other domains[1-3]. *Analysis at Month 24 is limited by data availability so far.

1. Norman GR et al. *Med Care*. 2003;41:582-592; 2. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516; 3. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making.
NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation.

HGB-206 Group C PROMIS-57: Anxiety

Anxiety





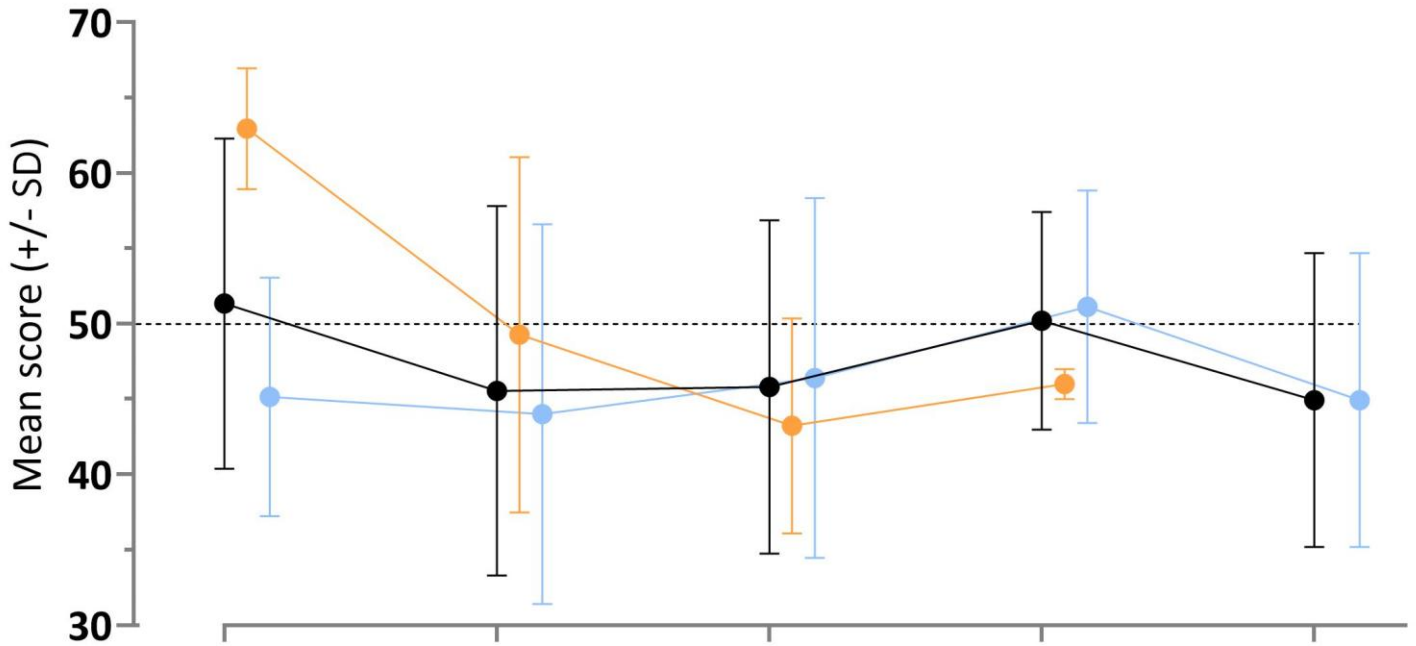
7/15 (47%) patients reported clinically meaningful reductions in anxiety at Month 12, and the overall trend is sustained at Month 24*

Clinically-meaningful change for PROMIS-57 is generally regarded as at least a 2-point change for the pain NRS and a 5-point change for the other domains[1-3].*Analysis at month 24 is limited by data availability so far.

1. Norman GR et al. *Med Care*. 2003;41:582-592; 2. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516; 3. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making.
NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation.

HGB-206 Group C PROMIS-57: Sleep disturbance

Sleep Disturbance



Direction of improvement (less sleep disturbance)

Overall response

Patients with worse than population normative scores at baseline

Patients with better or near population normative scores at baseline

Population normative score

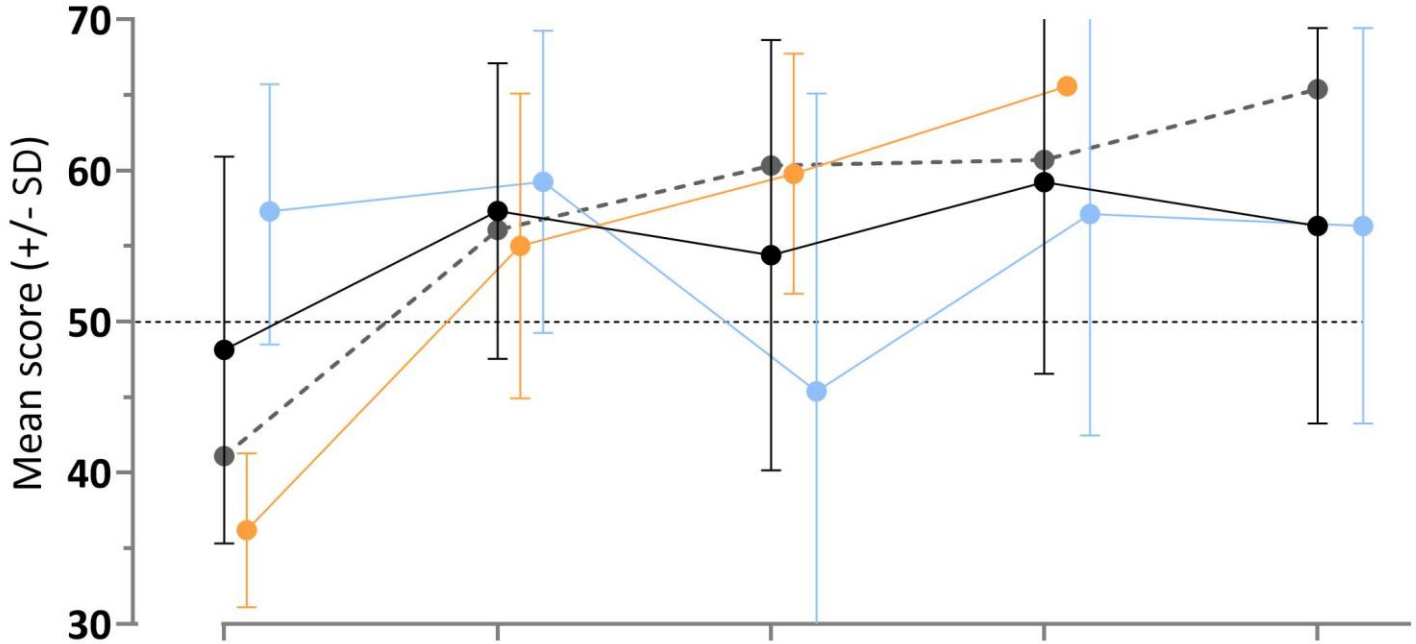
Baseline overall sleep disturbance level is consistent with that of the general population and trends to improvement at Month 24

Clinically-meaningful change for PROMIS-57 is generally regarded as at least a 2-point change for the pain NRS and a 5-point change for the other domains[1-3].

1. Norman GR et al. *Med Care*. 2003;41:582-592; 2. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516; 3. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making.
NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation.

HGB-206 Group C PROMIS-57:
Satisfaction with participation in social roles/activities

Satisfaction with Participation in Social Roles and Activities



Sample size (**overall** worse/better or near at baseline)	Baseline	Month 6	Month 12	Month 18	Month 24
	N=23	11	8	4	2
	(10, 13)	(5, 6)	(5, 3)	(1 ,3)	(2)
	N=1	5	10	5	7

Direction of improvement (improved ability to participate)

Overall response

Patients with worse than population normative scores at baseline

Patients with better or near population normative scores at baseline

Population normative score

'Ability to participate in social roles and activities' using updated V2.1 of PROMIS-57*

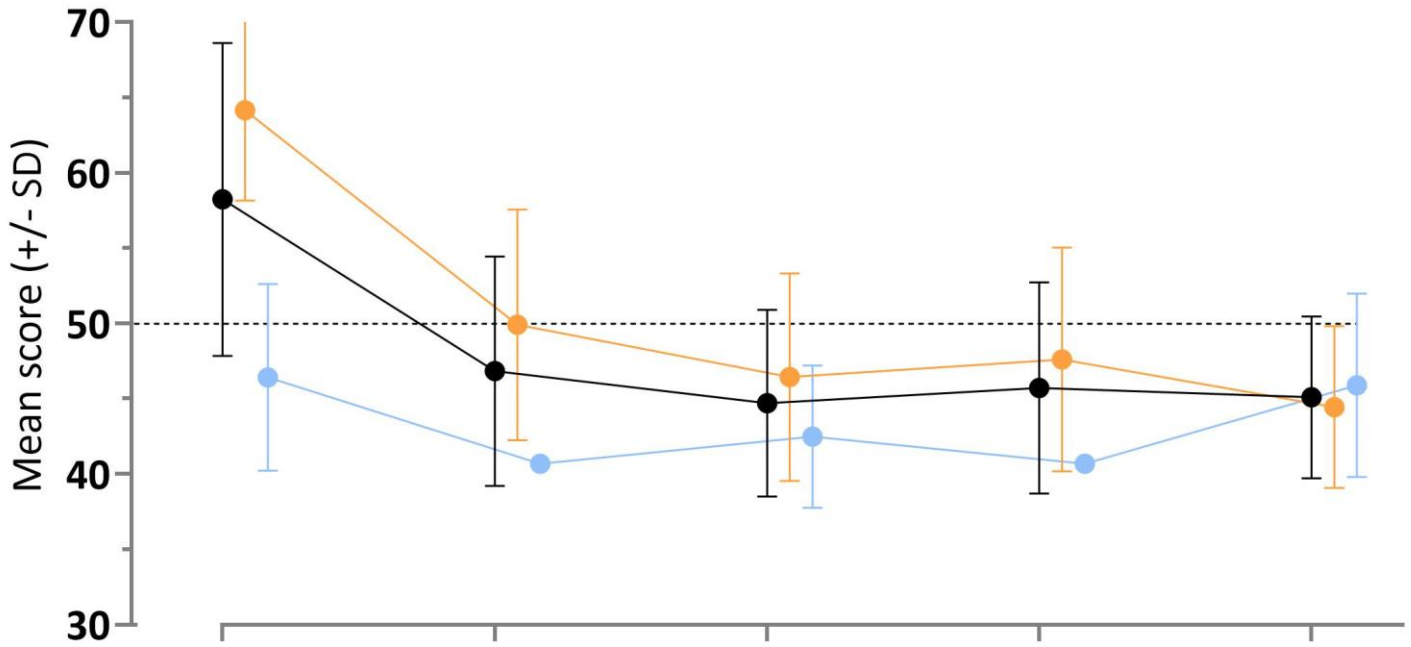
Overall trends reflect an improvement in patient social activities, but statistical interpretation from baseline is limited by Instrument version change for this domain

Clinically-meaningful change for PROMIS-57 is generally regarded as at least a 2-point change for the pain NRS and a 5-point change for the other domains[1-3].
*Analysis of clinically meaningful changes from baseline was not possible owing to changes to in PROMIS-57 (2.0 to 2.1).

1. Norman GR et al. *Med Care*. 2003;41:582-592; 2. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516; 3. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making.
NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation.

HGB-206 Group C PROMIS-57: Pain interference

Pain Interference



Direction of improvement (less pain)

Overall response

Patients with worse than population normative scores at baseline

Patients with better or near population normative scores at baseline

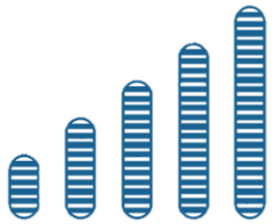
Population normative score

9/16 (56%) patients reported clinically meaningful reductions in pain interference at Month 12, and 5/9 (56%) patients at Month 24

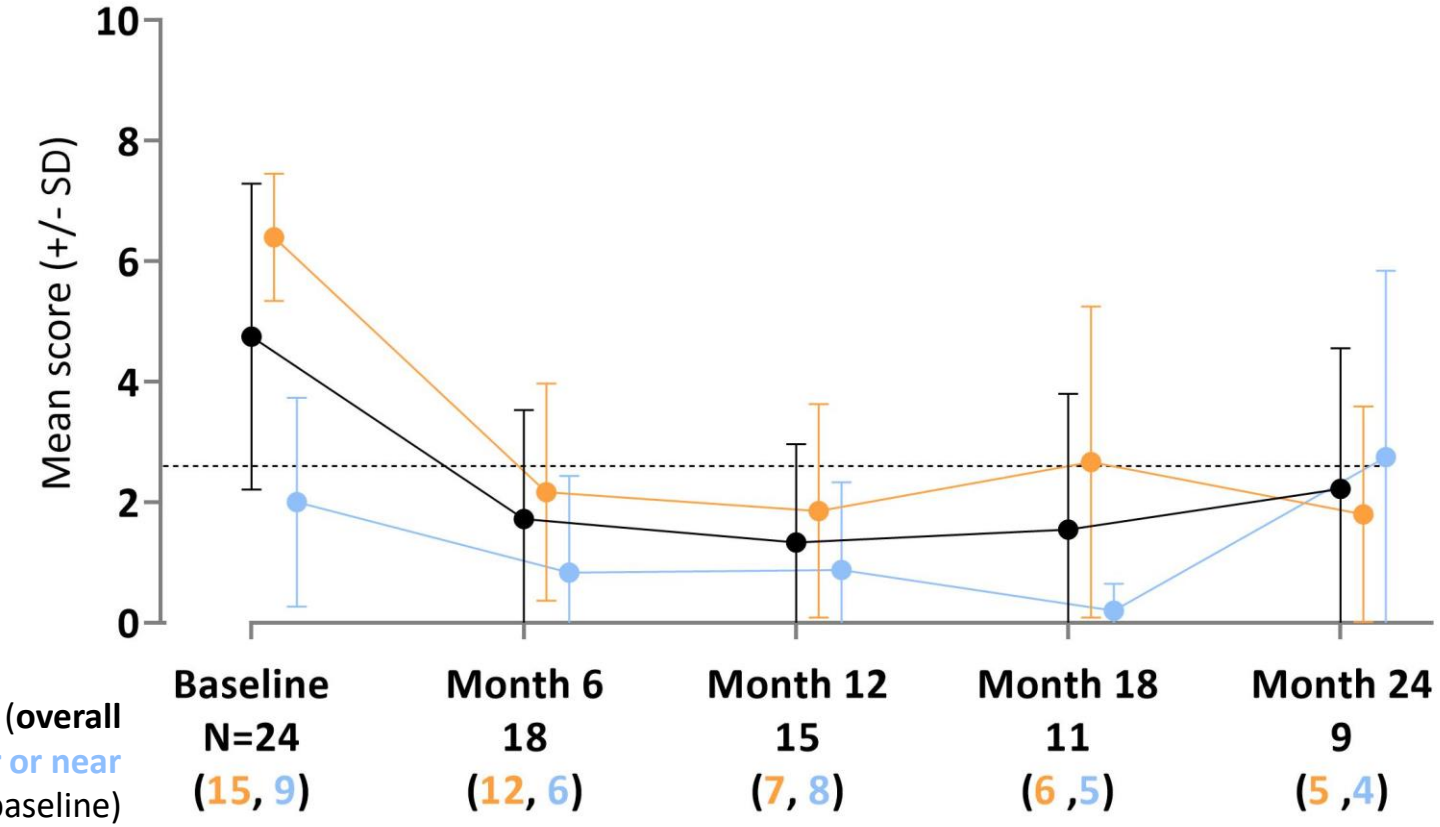
Clinically-meaningful change for PROMIS-57 is generally regarded as at least a 2-point change for the pain NRS and a 5-point change for the other domains[1-3].

1. Norman GR et al. *Med Care*. 2003;41:582-592; 2. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516; 3. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making.
NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation.

HGB-206 Group C PROMIS-57: Pain intensity NRS



Pain Intensity



Sample size (**overall worse/better or near** at baseline)

Direction of improvement (less pain)

Overall response

Patients with **worse** than population normative scores at baseline

Patients with **better or near** population normative scores at baseline

Population normative score

10/15 (67%) patients reported clinically meaningful reductions in pain intensity at Month 12, and 5/9 (56%) patients at Month 24

Clinically-meaningful change for PROMIS-57 is generally regarded as at least a 2-point change for the pain NRS and a 5-point change for the other domains[1-3].

1. Norman GR et al. *Med Care*. 2003;41:582-592; 2. Yost KJ et al. *J Clin Epidemiol*. 2011;64:507-516; 3. FDA. 2020. Incorporating clinical outcome assessments into endpoints for regulatory decision-making.
NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation.

HGB-206 Group C PROMIS-57: Summary

- HRQoL data helps to define the therapeutic effect in patients beyond established clinical endpoints
- Previously reported clinically-meaningful HRQoL improvements for patients at Month 12 were sustained across all domains at Month 24 post-LentiGlobin infusion
  - The pain, fatigue and physical functioning domains continue to demonstrate the greatest improvements for patients overall
  - Patients with worse scores at baseline reported better QoL response compared with those with baseline near/better normative scores who maintained their QoL level over time
- These findings complement our clinical results of complete resolution of severe VOEs in all patients up to and beyond 24 months[1], with improvements to patient QoL not yet observed in the SCD treatment landscape to-date
- Additional follow-up will continue to evaluate QoL improvements post-LentiGlobin infusion

1. Kwiatkowski J et al. EHA 2021:324669; S261. HRQoL; Health-related quality of life; NRS, numeric rating scale; PROMIS, Patient Reported Outcomes Measurement Information System; QoL, quality of life; SCD, sickle cell disease; VOE, vaso-occlusive event.

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