Durable Efficacy and Safety With Lovotibeglogene Autotemcel for Sickle Cell Disease

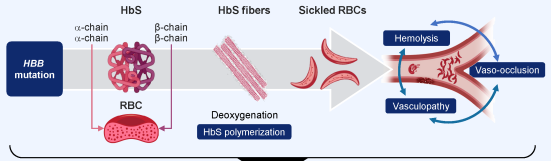
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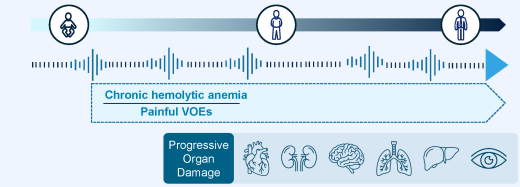
SICKLE CELL DISEASE

- Sickle cell disease (SCD) is a genetic disease caused by a single point mutation in one or both alleles of the β-globin gene (*HBB*) that results in production of sickle hemoglobin (HbS) in place of healthy adult hemoglobin (HbA)[1,2]
- Production of high levels of HbS and subsequent polymerization impair the structure and function of red blood cells (RBCs). RBCs become sickled and prone to hemolysis, leading to vaso-occlusion, chronic hemolytic anemia, and vasculopathy[1,2]
- SCD causes frequent acute pain crises (APCs) and chronic progressive complications[3,4]
  - Acute and chronic complications impact health-related quality of life (QoL) across age groups

Pathophysiology of SCD



Morbidity and disease progression across age groups



HbS, sickle hemoglobin; RBCs, red blood cells; SCD, sickle cell disease; VOEs, vaso-occlusive events.

Broad health-related quality of life impacts

- The burden of SCD impacts nearly all aspects of a person's life[1]
  - Patients and caregivers often report worse health-related QoL impacts than those of other chronic conditions



Current treatment options for SCD include disease-modifying therapies, allogeneic transplant, and gene therapy[5-8]

Disease-modifying therapies: hydroxyurea and RBC transfusion

Hydroxyurea reduces APC and acute chest syndrome (ACS) by increasing intracellular fetal hemoglobin (HbF); the number HbSS cells (two copies of the HbS gene) is reduced[5]

Requires ongoing treatment and adherence

Allogeneic transplant

Potentially curative, one-time therapy that can eliminate APC/ACS in many patients by replacing HbSS stem cells with donor-derived stem cells[6,7]

Use limited by donor availability and risks that include graft-versus-host disease (GVHD), graft failure, infection, and conditioning-related toxicity

Gene therapy

One-time gene editing and gene addition therapies are available. Lovotibeglogene autotemcel (lovo-cel), consisting of autologous hematopoietic stem and progenitor cells (HSPCs) transduced with lentiviral vector encoding functional copies of the β-globin gene ($\beta^{A\text{-}T87Q}$), is approved for patients aged ≥12 years. Modified HSPCs express antisickling adult hemoglobin (HbA^{T87Q}) with near-identical oxygen affinity as wild-type adult hemoglobin[8]

Although there is no risk of GVHD, conditioning-related toxicity risks remain

OBJECTIVE

To report vaso-occlusive event (VOE)-related efficacy, durability of response, and health-related quality of life (QoL) outcomes among participants treated with lovotibeglogene autotemcel (lovo-cel) in clinical trials using the current commercial manufacturing process

METHODS

- Data as of July 2025 were pooled from 2 prospective trials
  - HGB-206 (Group C; aged ≥12 to ≤50 years; NCT02140554) and
  - HGB-210 (aged ≥2 to ≤50 years; NCT04293185)
- Follow-up of participants treated with lovo-cel is ongoing in LTF-307 (NCT04628585)

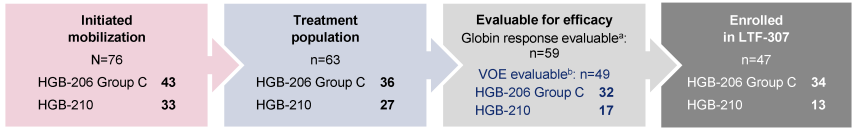
Endpoints

- VOE-related endpoints were complete resolution of VOEs (VOE-CR) and severe VOEs (sVOE-CR), assessed during months 6-18 post lovo-cel infusion among participants with ≥4 VOEs at baseline and ≥18 months of follow-up
  - A VOE was defined as any acute episode of pain with no medically determined cause other than vaso-occlusion lasting >2 hours and requiring care at a medical facility
- Participants evaluable for globin response are those who achieved globin response or have ≥18 months of follow-up
  - Globin response was defined as achieving weighted average HbA^{T87Q} percentage of non-transfused total hemoglobin (Hb) ≥30% and either (1) weighted average nontransfused total Hb increase of ≥3 g/dL compared with baseline total Hb or (2) weighted average nontransfused total Hb ≥10 g/dL for a continuous period of ≥6 months
- Treatment durability (VOEs, HbA^{T87Q} expression, red cell indices, biologic markers of hemolysis) and safety were assessed
- PROMIS QoL outcomes as of July 2024 were evaluated among HGB-206 Group C participants with data available up to 60 months post lovo-cel

RESULTS

Participant disposition

- A total of 76 participants initiated mobilization and 63 received lovo-cel; 49/63 were VOE evaluable
  - Following completion of a parent trial, 47 participants enrolled in the long-term follow-up trial, LTF-307



All data as of July 2025; 5 participants are currently pending infusion in HGB-210; 8 participants discontinued after cell collection and prior to infusion: 1 failed to mobilize, 2 discontinued due to physician decision, and 5 withdrew. Of the 63 participants in the treatment population, 10 were recently infused and not evaluable for VOE-CR at data cutoff and 4 were not evaluable due to stroke history and no VOEs at baseline.

[a]Participants who achieved globin response or have ≥18 months of follow-up. [b]Participants who had ≥1 adjudicated VOE between 6 and 18 months after drug product infusion or have ≥18 months of follow-up. Includes participants with ≥4 VOEs at baseline.
VOE, vaso-occlusive event; VOE-CR, complete resolution of vaso-occlusive event.

Demographics and baseline characteristics

- Median (range) age at enrollment was 23 (12-38) years
  - 75.5% were adults (aged ≥18 years) and 24.5% were adolescents (aged ≥12 to <18 years)

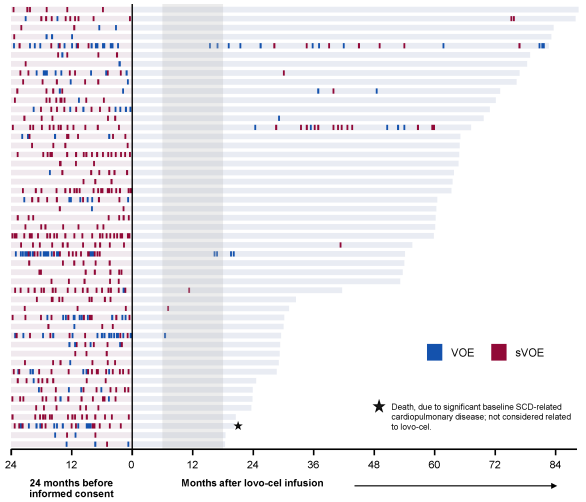
Demographics and participant characteristics	Total N=49
Age at enrollment, median (min, max), y	23 (12, 38)
Adult, ≥18 y, n (%)	37 (75.5)
Adolescent, ≥12 to <18 y, n (%)	12 (24.5)
Sex, n (%)	
Male	31 (63.3)
Female	18 (36.7)
Follow-up post infusion, median (min, max), mo	60.1 (18.4, 88.5)
Genotype for β-globin, n (%)	
β^S/β^S	46 (93.9)
β^S/β^0	3 (6.1)
Genotype for α-globin, n (%)	
αα/αα	34 (69.4)
αα/-$\alpha^{3.7}$	13 (26.5)
-$\alpha^{3.7}$/-$\alpha^{3.7}$	2 (4.1)
Baseline clinical characteristics	**Median (min, max)**
Annualized number of adjudicated VOEs[a,b]	4.0 (1.5, 16.5)
Annualized number of adjudicated sVOEs[a,b]	3.5 (0.5, 13.0)
Annualized number of packed RBC transfusions[a]	3.0 (0.0, 17.0)
Total Hb,[c] g/dL	8.7 (6.1, 12.5)
HbF, nontransfused, %	6.7 (0, 33.7)
Prior HU, n (%)	46 (93.9)

[a]In the 24 months prior to consent. [b]As confirmed by the Independent Event Adjudication Committee after participant enrollment. [c]Baseline total Hb is defined as average of 2 most recent qualifying Hb assessments made prior to or during screening that met the following criteria: assessments were separated by ≥1 month, assessments were drawn no earlier than 24 months prior to informed consent and could include the Hb result from screening, and the participant did not receive a packed RBC transfusion within 3 months prior to each Hb assessment (n=34).
Hb, hemoglobin; HbF, fetal hemoglobin; HU, hydroxyurea; RBC, red blood cell; sVOE, severe vaso-occlusive event; VOE, vaso-occlusive event.

Complete and long-term VOE resolution

- 89.8% (44/49) achieved VOE-CR and 95.9% (47/49) achieved sVOE-CR. At last follow-up (median 60.1 [min, max: 18.4, 88.5] months), 77.6% (38/49) remained VOE free

Participant-level VOEs



Complete and long-term VOE resolution

Trial endpoints, n/N (%)	
VOE-CR[a] (6-18 mo)	44/49 (89.8)
sVOE-CR[a] (6-18 mo)	47/49 (95.9)
Ad hoc endpoints, n/N (%)	
VF12[b]	48/50 (96.0)
VOE free to last follow-up, n/N (%)	
All participants	38/49 (77.6)
Baseline VOEs	
<10 VOE/y at baseline	33/40 (82.5)
≥10 VOE/y at baseline	5/9 (55.6)
Age	
Pediatric, <18 y	10/12 (83.3)
VOE free, median (range)	
Duration,[b] mo	48.6 (15.1-86.3)
Change from baseline, median (range)	
VOE hospital days	-100 (-100 to -31.7)

An Independent Event Adjudication Committee confirmed VOEs met protocol criteria. Single VOEs for 2 participants shown here were retracted after adjudication.
[a]In the 6-18 months after infusion; participants with ≥18 months of follow-up and ≥4 VOEs ≤2 years before enrollment. [b]VOE-free duration is calculated for participants with ≥16 months of follow-up (n=50). VOE-free duration starts 60 days after last pRBC transfusion for posttransplant support or SCD management during the parent studies. Participants who experienced a VOE after 60 days following the last pRBC transfusion may have >1 VOE-free period; the longest VOE-free period was used in the summary.
Lovo-cel, lovotibeglogene autotemcel; pRBC, packed red blood cell; SCD, sickle cell disease; sVOE, severe vaso-occlusive event; sVOE-CR, complete resolution of severe vaso-occlusive event; VF12, vaso-occlusive event free for 12 consecutive months; VOE, vaso-occlusive event; VOE-CR, complete resolution of vaso-occlusive event.

Pharmacodynamic and hematologic endpoints

- HbA^{T87Q} expression and improvements in hematologic parameters (red cell indices and biologic markers of hemolysis) were robust and sustained at last follow-up

100% (63/63) of treated participants had **successful engraftment**

91.5% (54/59) of evaluable participants achieved **globin response**

- **VCN ≈2 copies/cell** confirms consistent gene transfer and durable engraftment
- **HbA^{T87Q} ≈50%** of nontransfused Hb regardless of VOE status = robust antisickling protection
- **Mean total Hb 12.9 g/dL** at last follow-up

Hb, hemoglobin; VCN, vector copy number.

Quality of life

- Clinically meaningful improvements in pain intensity, pain interference, and fatigue were observed early and sustained through month 60

Safety

- The long-term safety profile remains favorable; no lovo-cel–related insertional oncogenesis has been observed, and the overall safety profile is consistent with that of myeloablative conditioning and underlying SCD[9]
  - One myelodysplasia case was reported (diagnosis disputed) with α-globin chain imbalance (now a limitation of use for lovo-cel treatment), identified as a possible contributing factor

KEY TAKEAWAYS

- Lovo-cel is durable, safe, and effective for SCD. After treatment, patients experienced a reduction in VOEs and improvements in QoL. Benefits were sustained through last follow-up (≥5 years)
- Lovo-cel's safety profile is generally consistent with myeloablative conditioning and underlying SCD. No lovo-cel–related insertional oncogenesis was observed
- Real-world implementation of lovo-cel treatment requires evaluation by an SCD specialist and referral to a qualified treatment center for long-term multidisciplinary follow-up, including hematologists/oncologists, pharmacists, advanced practice providers, and trained nurses
- For optimal outcomes, treatment teams must be familiar with lovo-cel's treatment pathway and postinfusion requirements

References

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