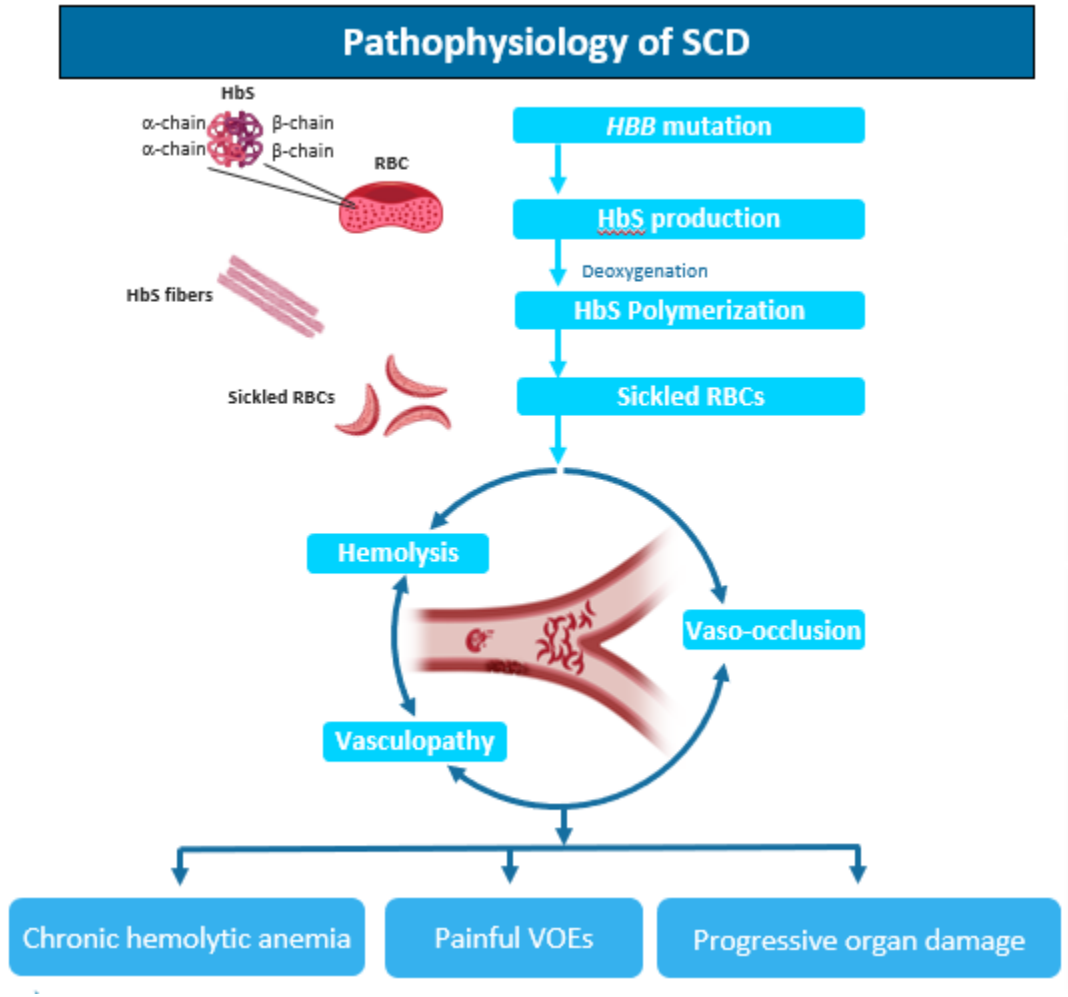
Administration of Lovotibeglogene autotemcel (lovo-cel)

ICD-10 Coordination and Maintenance Committee Meeting

13 – 14 September 2022

Sickle cell disease (SCD) is a severe, progressive and debilitating disease; it begins with a point mutation in the β-globin gene[1,2]

- A point mutation in one or both alleles of the β-globin gene (*HBB*) causes a glutamic acid to valine substitution at the 6th amino acid position forming the β^S allele.[1,2]
- Production of high levels of sickle hemoglobin (HbS) in red blood cells (RBCs) and their subsequent polymerization under low oxygen conditions or other stresses cause RBCs to become sickled, sticky, and rigid with a shorter lifespan, which manifests acutely as hemolytic anemia, vasculopathy, and vaso-occlusion.[1-3]
- SCD is a progressive disease with acute and chronic clinical complications leading to excruciating pain, organ damage and risk of death[1,4,5], requiring lifelong supportive and disease-modifying therapies.
- Allo-HSCT with matched sibling donor remains the sole potentially curative treatment, though use is limited by donor availability and risk of graft-versus-host disease and graft rejection.[1,6]



Allo-HSCT, allogeneic hematopoietic stem cell transplantation ;HbS, sickle hemoglobin; RBCs, red blood cells; SCD, sickle cell disease; VOEs, vaso-occlusive events.

1. Kato, et al. *Nat Rev Dis Primers*. 2018;4:(18010):1-22. 2. Sundd P, et al. *Annu Rev Pathol.* 2019;14:263–292. 3. Ware RE, et al. *Lancet.* 2017;390:311-323. 4. Kanter J and Kruse-Jarres R. *Blood Rev*. 2013;27(6):279- 287.
5. Powars DR, et al. *Medicine.* 2005;84(6):363–376. 6. Shenoy S. *Hematology Am Soc Hematol Educ Program.* 2011;2011:273-279.

lovotibeglogene autotemcel (lovo-cel) is an investigational therapy* not approved for use by the FDA; efficacy and safety have not been established.

*Effective December 20, 2021[1], the FDA has placed the clinical program for lovo-cel gene therapy for sickle cell disease (SCD) on partial clinical hold for patients under the age of 18. The partial, temporary suspension relates to an ongoing investigation by bluebird bio into an adolescent patient with persistent, non-transfusion-dependent anemia following treatment with lovo-cel, now 18 months post-treatment. This patient is clinically well and there is no evidence of malignancy or clonal predominance. Enrollment and dosing for patients 18 and older living with SCD in the HGB-206, HGB-210 and LTF-307 clinical studies, as well as follow up for treated patients of all ages in all studies, are continuing as planned.

1. Bluebird bio press release, December 20, 2021. Accessible at https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-partial-clinical-hold-patients-under-18

Process of *ex vivo* gene therapy with lovo-cel for SCD

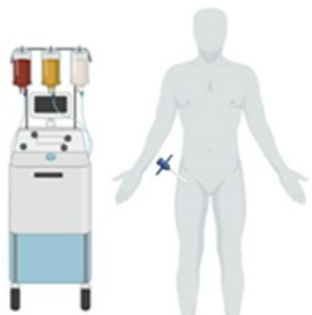
HSPC Collection and Enrichment
Via plerixafor-mobilization and apheresis (HGB-206 Group C) following pre-harvest transfusion*

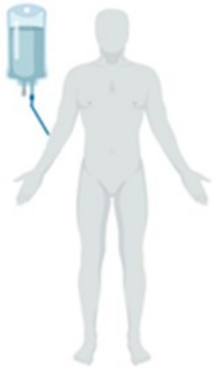
Myeloablative Conditioning
Using busulfan
4 days + washout period

lovo-cel DP Infusion
Hospitalization median ~5 weeks[1] (includes conditioning)

Engraftment of HSPCs and Repopulation

Long-term Monitoring

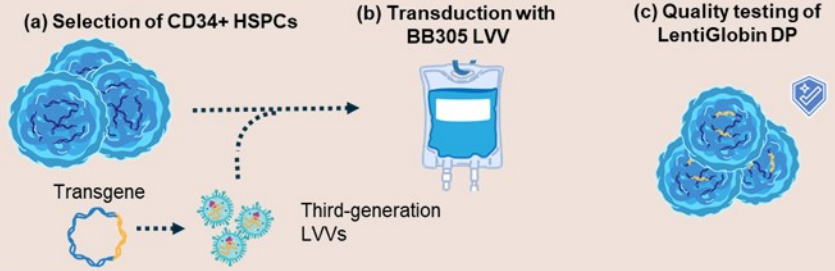




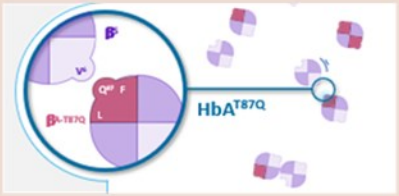
2-yr follow-up

Long-term Follow-up Study (NCT04628585)

lovo-cel DP manufacturing



Modified RBCs express gene therapy-derived HbA^{T87Q}



HbA^{T87Q} is an anti-sickling Hb that prevents interaction with HbS

*Bone marrow harvest (HGB-206 Group A and B).

DP, drug product; HbA^{T87Q}, Hb with modified β-globin gene ($\beta^{A\text{-}T87Q}$); HPLC, high-performance liquid chromatography; HSPC, hematopoietic stem and progenitor cell; LVV, lentiviral vector; RBC, red blood cell; SCD, sickle cell disease.

1. Median lenth of stay from pre-specified interim analysis of Phase 1/2 Study HGB-206 Group C. Kanter J, et al. *N Engl J Med.* 2022;386:617-628.

Figure adapted from Tisdale JF, et al. ASH 2021 Congress, Abstract 561.

Phase 1/2 HGB-206 study of lovo-cel for SCD
(Interim analysis of pivotal cohort, Group C, published in *NEJM*, December 2021)[1]

Ongoing, phase 1/2 , nonrandomized, open-label, single-dose clinical trial being conducted at 11 sites across the US

- **Eligible patients:**
  - Between 12 and 50 years of age
  - A diagnosis of SCD with a $\beta^S\beta^S$, $\beta^S\beta^0$, or $\beta^S\beta^+$ genotype
  - Clinically stable Karnofsky performance status of at least 60 (for patients ≥16 years of age) or a Lansky performance status of at least 60 (for those <16 years of age)
  - Also required to have had a failure of hydroxyurea treatment (standard of care), a 24-month history of SCD before enrollment, and no opportunity for matched HLA-identical hematopoietic-cell donation

- **Pivotal Group C:**
  - Protocol was amended to require a minimum of 4 severe VOEs in the 24 months before enrollment
  - 35 patients received lovo-cel infusion, with a median follow-up of 17.3 months (range, 3.7 to 37.6) as of February 2021 data cut-off; engraftment occurred in all 35 patients

- **Primary efficacy end point** is severe VOE-CR, defined as the complete resolution of severe VOEs between 6 and 18 months after lovo-cel infusion; severe VOEs are defined per protocol,[†] and severe VOE-CR is assessed in Group C patients with ≥4 severe VOEs in the 24 months prior to informed consent and with 6 months follow-up after lovo-cel infusion
- **Key secondary efficacy endpoint** is globin response [††]

[†]Defined per protocol as an event with no medically determined cause other than a vaso-occlusion requiring hospitalization or emergency room visit for ≥24 hours; or ≥2 visits to day unit or emergency room during a 72-hour period (with both visits requiring IV treatment for acute episodes of pain, ACS, acute hepatic sequestration, or acute splenic sequestration; or an episode of priapism lasting more than 2 hours and resulting in a visit to a medical facility.
[††]Weighted average HbA^{T87Q} percentage of non-transfused total Hb ≥30% **AND** weighted average non-transfused total Hb increase of ≥3 g/dL compared with baseline total Hb **OR** weighted average non-transfused total Hb ≥ 10 g/dL.
ACS, acute chest syndrome; CR, complete resolution; Hb, hemoglobin; HbAT87Q, IV, intravenous; SCD, sickle cell disease; VOE, vaso-occlusive event.
1. Kanter J, et al. *N Engl J Med.* 2022;386:617-628.

Phase 1/2 HGB-206 Group C: patient characteristics (TP)
(Interim analysis published in *NEJM*, December 2021)[1]

Transplant population (TP), including all the patients in Group C that received a lovo-cel infusion*

Parameter, n (%)	N=35
Age at consent, years, median (min–max)	24 (12–38)
Age category	
18–50 years	27 (77.1)
12–<18 years	8 (22.9)
Female sex	13 (37.1)
Race	
Black or African American	34 (97.1)
Not provided	1 (2.9)
Genotype	
β^S/β^S	35 (100)
SCD history	
Annualized severe VOEs (24 months before enrollment), median (min–max)*	3.0 (0.0–13.5)
Any history of stroke†	5 (14.3)
Any history of TRJV >2.5 m/s‡	6 (17.1)
HU usage 3 months before enrollment	23 (65.7)

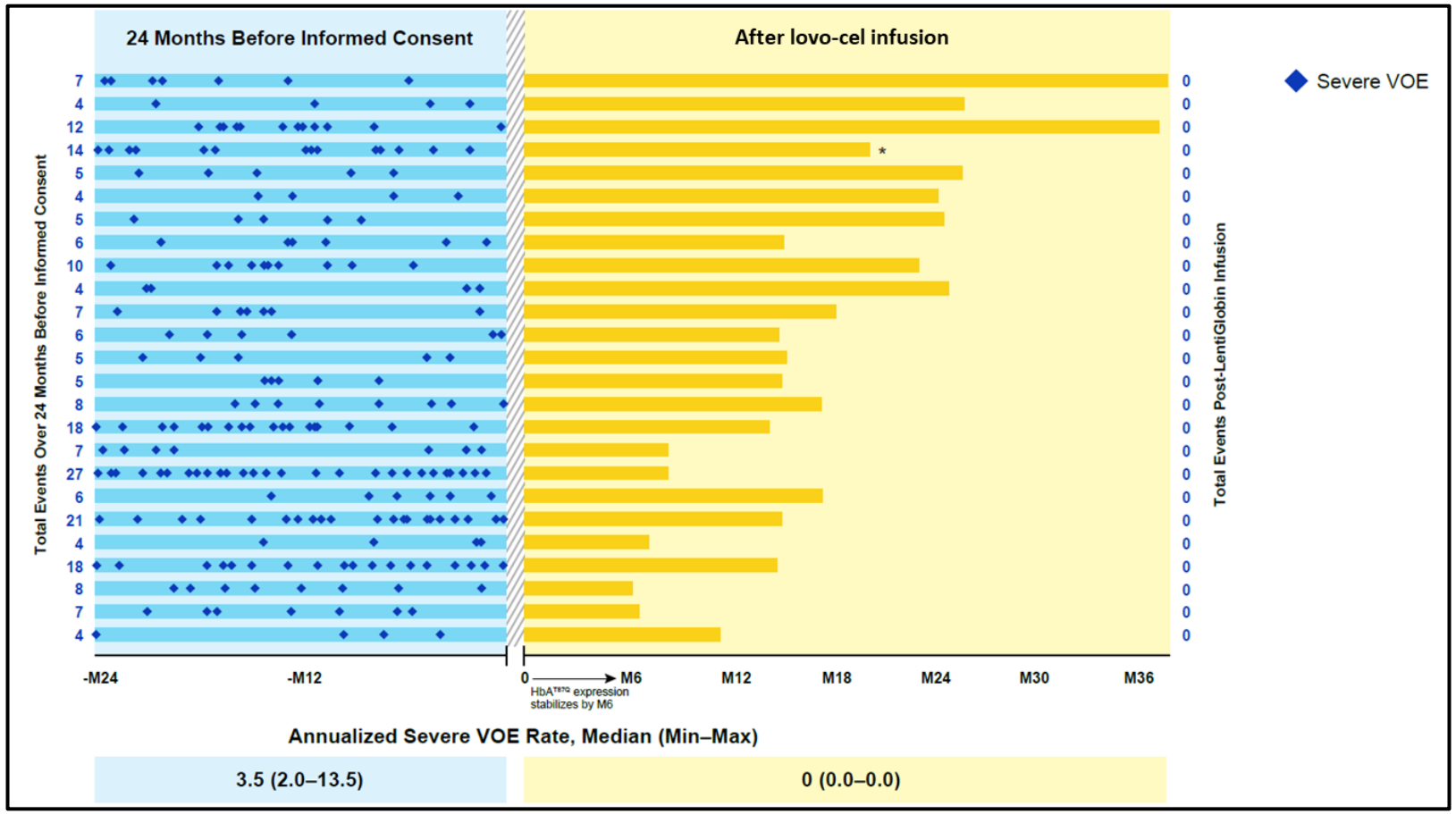
HU, hydroxyurea; SCD, sickle cell disease; TP, transplant population; TRJV, tricuspid regurgitant jet velocity; VOE; vaso-occlusive event.

*Included 6 patients who were enrolled prior to and did not meet the updated eligibility criterion for the minimum severe VOE requirement, which was introduced to evaluate VOEs as key efficacy endpoints; †During the enrollment period, the inclusion criteria were updated to remove history of overt stroke, at which point 6 patients with a history of overt stroke had already been enrolled, of whom 5 received lovo-cel infusion and were assessed as part of the transplant population; ‡TRJV ≥2.5 m/s confers an increased risk for mortality.

*A second study population within Group C was the transplant population with vaso-occlusive events (TPVOE) which included patients who had met the updated inclusion requirement of 4 severe VOEs in the 2 months before enrolment. Six patients in the transplant population did not meet the TPVOE criterion.

1. Kanter J, et al. *N Engl J Med.* 2022;386:617-628.

Severe VOE occurrence before and after lovo-cel infusion in HGB-206 Group C (Interim analysis published in *NEJM*, December 2021)[1]



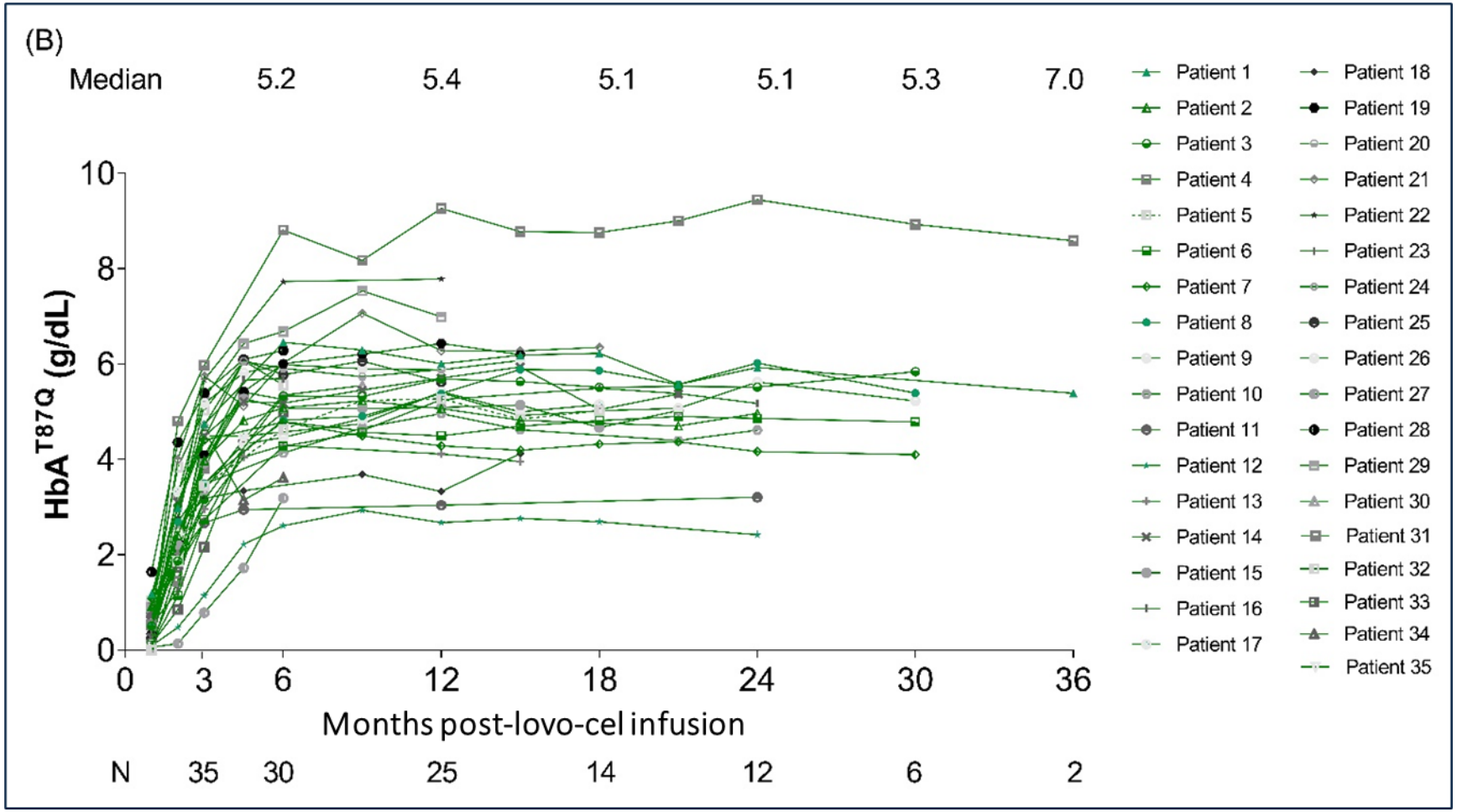
VOEs and severe VOEs were assessed in 25 patients who met the TPVOE population criterion of ≥4 severe VOEs in the 24 months before informed consent, and also met the minimum follow-up of 6 months post-lovo-cel infusion required for VOE analysis. The hatched area represents the time between informed consent and lovo-cel infusion, during which VOE and severe VOE data are not reported because patients received pre-harvest transfusions. VOEs and severe VOEs were defined per the study protocol. A VOE was defined as an episode of acute pain with no medically determined cause other than a vaso-occlusion, including acute episodes of pain, ACS, acute hepatic sequestration, acute splenic sequestration, and acute priapism. A severe VOE is a subset of VOEs requiring a ≥24-hour hospital or emergency room observation unit visit or ≥2 visits to a day unit or emergency room over 72 hours with both visits requiring IV treatment, or priapism episodes lasting >2 hours and requiring a medical facility visit. Adjudication of VOEs and severe VOEs is pending.

*One death, unlikely related to lovo-cel, 20 months post-infusion in a patient with significant baseline sickle cell disease-related cardiopulmonary disease.

ACS, acute chest syndrome; HbA^{T87Q}, Hb with modified β-globin gene ($\beta^{A\text{-}T87Q}$); IV, intravenous; SCD, sickle cell disease; TVPOE, transplant VOE population; VOE, vaso-occlusive event.

1. Kanter J, et al. *N Engl J Med.* 2022;386:617-628.

HGB-206 Group C: HbA^{T87Q} over time
(Interim analysis published in *NEJM*, December 2021)[1]



HbA^{T87Q}, Hb with modified β-globin gene ($\beta^{A\text{-}T87Q}$).

Data are reported for the transplant population (N=35) and missing at some timepoints for patients who have not completed 24-month follow-up and omitted for one patient at Month 36 due to sample being taken within three days of receiving exchange transfusion for gallstone-induced pancreatitis.

1. Kanter J, et al. *N Engl J Med.* 2022;386:617-628.

Interim safety overview for Study HGB-206 Group C
(Interim analysis published in *NEJM*, December 2021)[1]

≥Grade 3 AEs post-lovo-cel infusion *Reported in ≥2 patients*	N=35[†] n (%)
Stomatitis	24 (68.6)
Thrombocytopenia	23 (65.7)
Neutropenia	19 (54.3)
Febrile neutropenia	15 (42.9)
Anemia	13 (37.1)
Leukopenia	11 (31.4)
Aspartate aminotransferase increased	6 (17.1)
Gamma-glutamyl transferase increased	5 (14.3)
Nausea	4 (11.4)
Alanine aminotransferase increased	3 (8.6)
Decreased appetite	3 (8.6)
Abdominal pain	2 (5.7)
Abdominal pain upper	2 (5.7)
Increased blood bilirubin	2 (5.7)
Lymphopenia	2 (5.7)
Pharyngeal inflammation	2 (5.7)
Premature menopause	2 (5.7)

- After lovo-cel infusion, 12 patients (34%) had at least one serious AE
  - Most frequently reported were abdominal pain, drug withdrawal syndrome (opiate), nausea, and vomiting (6% each)
- Overall, 3 patients had AEs attributed by the investigator to lovo-cel infusion, including
  - 2 events deemed possibly related (grade 2 leukopenia and grade 1 decreased diastolic blood pressure) and 1 event deemed definitely related (grade 2 febrile neutropenia); all 3 AEs resolved within 1 week after onset
- One death occurred 20 months after infusion in a patient with cardiopulmonary disease related to SCD at baseline
- No cases of veno-occlusive liver disease, graft failure, circulating replication-competent lentivirus, or vector-mediated insertional oncogenesis were observed in Group C

In the initial cohort (Group A) of study HGB-206, 2 patients treated with lovo-cel developed AML; it has been determined that these were unlikely related to the lovo-cel infusion for SCD.[2,3] The underlying risk of hematologic malignancies in SCD, combined with the transplant procedure and associated proliferative stress, as well as continued hematopoietic stress due to minimal clinical benefit in these two Group A patients (DP manufactured using stem cells collected via BMH and using a previous manufacturing process which has since been discontinued) may have contributed to the development of AML[3-5]

† Reported in the transplant population.

AEs, adverse events; AML, acute myeloid leukemia; SCD, sickle cell disease; DP = drug product; BMH = bone marrow harvest

1. Kanter J, et al. *N Engl J Med.* 2022;386:617-628. 2.Hsieh MM, et al. Blood Adv. 2020;4:2058-2063. 3. Goyal S, et al. N Engl J Med. 2022;386:138-147.
4. Tisdale JF, et al. ASH 2021 Congress, Abstract 561 5. Tisdale JF, et al. 2021 ASGCT Abstract # 196.

lovo-cel treatment regimen, information record, and current coding

- Treatment Regimen: The treatment regimen for patients with lovo-cel comprises mobilization/apheresis to collect the patient's own stem cells, myeloablative conditioning, and intravenous infusion of lovo-cel into a vein
  - The myeloablative conditioning and lovo-cel infusion must occur in the inpatient setting
  - In most cases, the mobilization and apheresis procedures take place in the inpatient setting
- Information Record: Information regarding the comprehensive process by which lovo-cel is administered will be documented in the medical record and traceable (e.g., use of a deidentified patient number on physician orders, pharmacy notes, treatment summary)
- Current ICD-10-PCS codes do not adequately describe the intravenous administration of lovo-cel
  - Without the creation of a specific lovo-cel code, providers and coding professionals will resort to reporting other non-specific ICD-10-PCS codes, which can obscure the use of this therapy within Medicare claims, making it more difficult to efficiently track cases for safety and health economic purposes
  - Long-term follow up is critical, particularly in the case of single administration, potentially curative gene therapies like lovo-cel given that the safety profile and clinical durability of such therapies are central issues for providers, patients, manufacturers, and researchers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