

# An Update on Lovotibeglogene Autotemcel (Lovo-cel) Clinical Trials for Sickle Cell Disease (SCD) and Analysis of Early Predictors of Response to Lovo-cel

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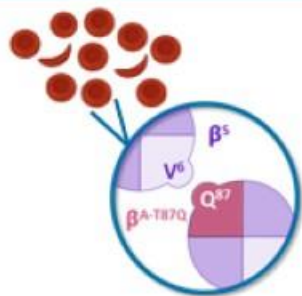
*\*Presenting author. \*\*Former employee of bluebird bio, Inc.*

This presentation includes off-label information

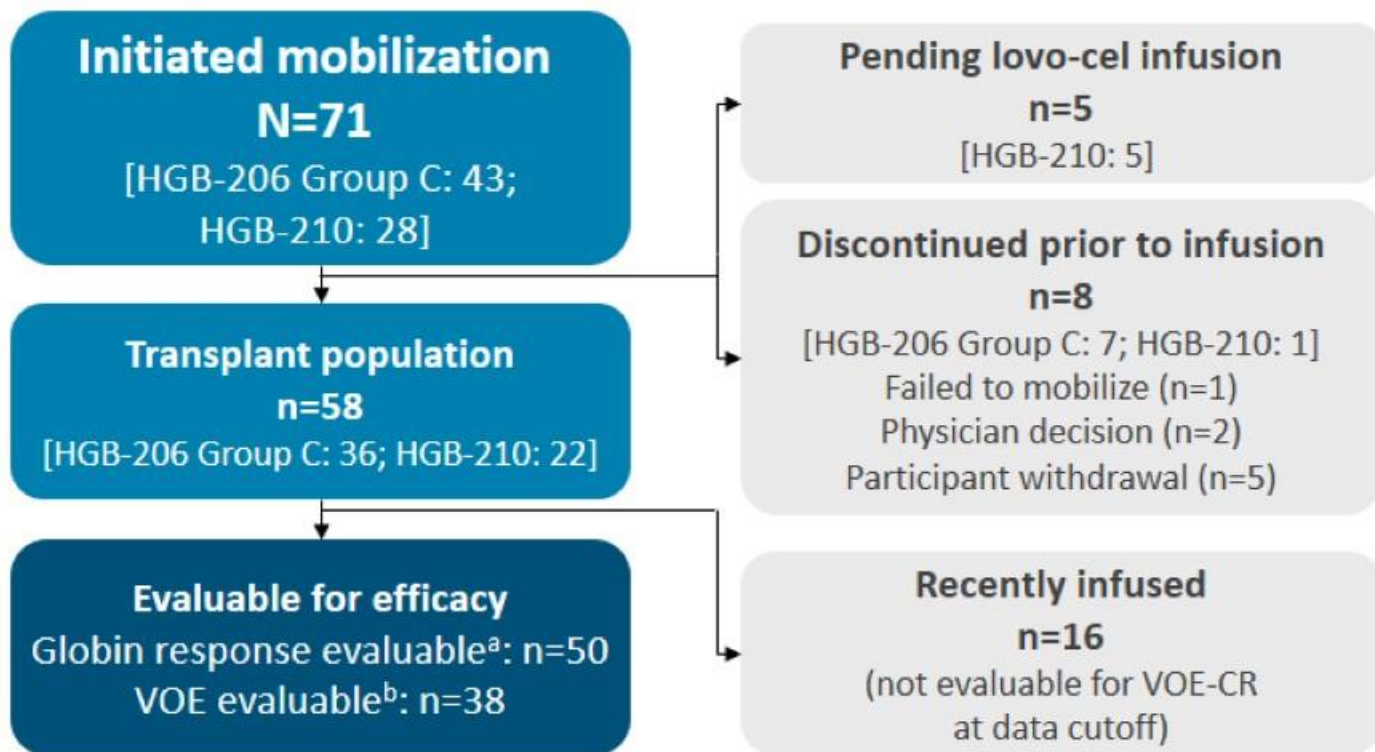
# Disclosures

- **SR-Z:** Has been a member of the board of directors or served on advisory committees for Vertex Pharmaceuticals
- **JK:** Consultancy for Fulcrum, EcoR1, Bausch, Watkins, Lourie, Roll & Chance, Beam Tx, Novartis, GLG Pharma, Guidepoint Global, Optum United Health, BioLine Rx, Novo Nordisk, GSK, Sanofi, Bristol Myers Squibb, and bluebird bio; has been a member of the board of directors or served on advisory committees for Chiesi, GSK, GlycoMimetics, Vifor, Afimmune, and Merck; received research funding from Beam, bluebird bio, NIH/NHLBI, Health Resources and Services Administration, CDC, Novo Nordisk, Vifor, Afimmune, and Takeda; received honoraria from Chiesi, Vifor, GSK, Afimmune, and ETS (Emerging Therapy Solutions)
- **JLK:** Consultancy for and received research funding from Agios, Forma Therapeutics, bluebird bio, CRISPR/Vertex, and Imara; consultancy for Vertex Pharmaceuticals, BioMarin, Chiesi, Bristol Myers Squibb, Silence Therapeutics, and Novartis; received research funding from Editas Medicine, Pfizer, and Apopharma
- **RSN:** Received research funding from Janssen
- **MCW:** Consultancy for Sanofi; has been a member of the board of directors or served on advisory committees for Ensoma; and has been a member of the board of directors or served on steering committees for Vertex Pharmaceuticals
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- **AOG:** Consultancy and has been a member of the board of directors or served on advisory committees for Vertex Pharmaceuticals; served on Speakers Bureaus for Emerging Therapies Solutions; received research funding from Jazz Pharmaceuticals, Beam Therapeutics, bluebird bio, and Orchard Therapeutics
- **MAK, AC, AL, LP, FJP:** Current employees of and equity holders in bluebird bio
- **ES-W:** Former employee of and equity holder in bluebird bio
- **APG, PLM, JFT:** Nothing to disclose

# Lovo-cel for the Treatment of SCD Using the Refined Manufacturing Process (HGB-206 Group C and HGB-210)



Lovo-cel consists of genetically modified autologous stem and progenitor cells to produce RBCs containing HbA<sup>T87Q</sup>, which due to a single amino acid change, has anti-sickling properties and normal adult HbA oxygen affinity<sup>1-3</sup>



## Follow-up time

### Among 58 participants who received lovo-cel:

- Median follow-up time: **47.7** months (4.0 years)
- Overall exposure: **195.6** participant-years
- Longest follow-up: **79.4** months (6.6 years)<sup>c</sup>

<sup>a</sup>Globin response—evaluable participants who achieved globin response or have  $\geq 18$  months of follow-up. <sup>b</sup>Participants who had  $\geq 1$  adjudicated VOE between 6 and 18 months post drug product infusion or have  $\geq 18$  months of follow-up. Includes participants with  $\geq 4$  VOEs at baseline. <sup>c</sup>These data refer to the longest follow-up in participants treated with the current manufacturing process.

# Demographics and Clinical Characteristics: Transplant Population (HGB-206 Group C and HGB-210)

Demographics and participant characteristics	Total N=58
<b>Age at enrollment, median (min, max), years</b>	21 (8, 38)
≥18 years, n (%)	42 (72.4)
<18 years, n (%)	16 (27.6)
<b>Sex, n (%)</b>	
Male	35 (60.3)
<b>Follow-up post infusion, median (min, max), months</b>	47.7 (1.2, 79.4)
<b>Genotype for β-globin, n (%)</b>	
β <sup>S</sup> /β <sup>S</sup>	55 (94.8)
β <sup>S</sup> /β <sup>0</sup>	3 (5.2)
<b>Genotype for α-globin, n (%)</b>	
αα/αα	41 (70.7)
αα/-α <sup>3.7</sup>	15 (25.9)
-α <sup>3.7</sup> /-α <sup>3.7</sup>	2 (3.4)
<b>Baseline clinical characteristics</b>	
<b>Annualized number of adjudicated VOs<sup>a,b,c</sup> median (min, max)</b>	3.5 (1.5, 16.5) <sup>d</sup>
<b>Annualized number of adjudicated sVOEs<sup>a,b,c</sup> median (min, max)</b>	3.3 (0.5, 13.0) <sup>d</sup>
<b>Annualized number of pRBC transfusions,<sup>a</sup> median (min, max)</b>	3.8 (0, 17.0) <sup>e</sup>
<b>Total Hb, median (min, max),<sup>f</sup> g/dL</b>	8.7 (6.1, 12.5)
<b>Prior hydroxyurea use, n (%)</b>	51 (87.9)

Characteristic Median (min, max)	Total N=58
<b>Mobilization and engraftment</b>	
<b>No. of mobilization cycles</b>	2.0 (1, 4)
<b>Time to neutrophil engraftment,<sup>g,h</sup> days</b>	20.0 (12, 35)
<b>Time to platelet engraftment,<sup>h,i</sup> days</b>	36.0 (19, 157)
<b>Duration of hospitalization,<sup>j</sup> days</b>	36.0 (26, 65)
<b>Drug product characteristics</b>	
<b>Total CD34+ cell dose, ×10<sup>6</sup> cells/kg</b>	6.6 (3.0, 13.3)
<b>VCN, copies/diploid genome</b>	4.1 (2.3, 6.8)
<b>%LVV+ cells</b>	83.0 (63, 93)

- Demographics and treatment/drug product characteristics are consistent with previous reports
- 83% of participants required only 1 or 2 mobilization cycles

<sup>a</sup>In the 24 months prior to consent. <sup>b</sup>Transplant-VOE population. <sup>c</sup>As confirmed by the Independent Event Adjudication Committee after participant enrollment. <sup>d</sup>n=38. <sup>e</sup>n=42. <sup>f</sup>Baseline total Hb is defined as the 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 pRBC transfusion within 3 months prior to each Hb assessment. <sup>g</sup>Neutrophil engraftment was defined as achieving 3 consecutive laboratory values of ≥0.5×10<sup>9</sup> cells/L (after initial postinfusion nadir) obtained on different days by day 43 post infusion; time to neutrophil engraftment was measured from infusion (day 1) to the first day of the 3 consecutive measurements. <sup>h</sup>Following data cutoff, all participants achieved neutrophil and platelet engraftment. <sup>i</sup>Platelet engraftment was defined as achieving 3 consecutive laboratory values of ≥50×10<sup>9</sup> cells/L (after initial postinfusion nadir) obtained on different days without receiving any platelet transfusions for 7 days immediately preceding and during the evaluation period; time to platelet engraftment was measured from infusion (day 1) to the first day of the 3 consecutive measurements. <sup>j</sup>Duration of hospitalization from conditioning to discharge.

# Summary of Safety From Day 1 Through Last Follow-Up: Transplant Population (HGB-206 Group C and HGB-210)

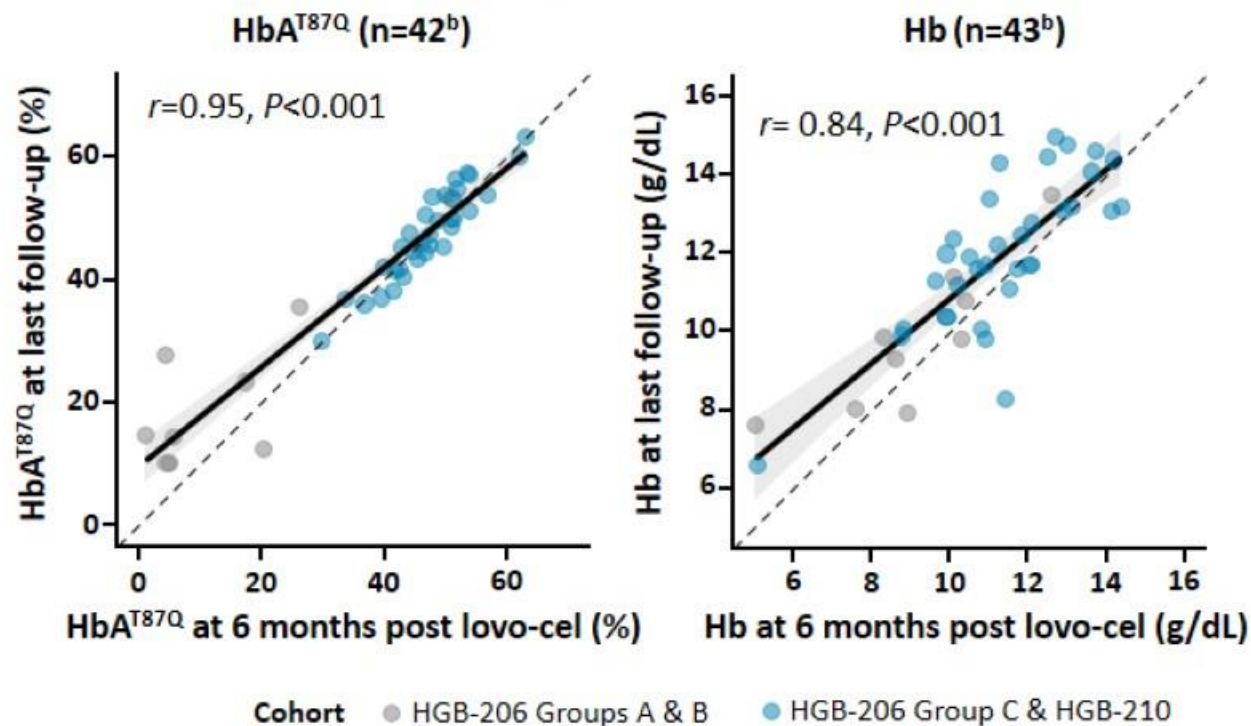
	Total N=58
<b>TEAEs, n (%)</b>	
Any grade	58 (100)
Grade ≥3	56 (96.6)
<b>Lovo-cel–related AEs,<sup>a</sup> n (%)</b>	<b>4 (6.9)</b>
Anemia <sup>b,c</sup>	2 (3.4)
Abdominal discomfort	1 ( 1.7)
Blood pressure diastolic decreased	1 (1.7)
Myelodysplastic syndrome <sup>b,c</sup>	1 (1.7)
Nasal congestion	1 (1.7)
<b>Participants with any serious TEAE, n (%)</b>	<b>48 (82.8)</b>
<b>Participants with lovo-cel–related serious AEs<sup>a</sup></b>	<b>2 (3.4)</b>

- Consistent with previous reports, the lovo-cel treatment regimen safety profile reflects the known effects of underlying SCD and myeloablative conditioning
- A majority of TEAEs occurred within 1 year post lovo-cel infusion and were known consequences of conditioning with busulfan
- The previously reported diagnosis of MDS at month 30 is still under investigation as of month 48. CBC is stable, and the participant is clinically well and has not required any treatment for MDS
- There was 1 case of grade 3 veno-occlusive disease of the liver in the HGB-210 study that resolved
- There were no cases of graft failure or GVHD
- There were no vector-related complications and no insertional oncogenesis or clinically significant oligoclonality

<sup>a</sup>Sponsor assessed. <sup>b</sup>Serious AE. <sup>c</sup>Two participants had  $\beta^2/\beta^1$  and  $\alpha$ -thalassemia trait ( $-\alpha^{3.7}/-\alpha^{3.7}$ ). One was diagnosed with MDS by the principal investigator based on findings of cytopenia, dysplasia, and karyotype.

# Durability of Pharmacodynamic (PD) Parameters and Total Hemoglobin From 6 Months to Last Follow-Up

## Correlation analyses at 6 months and last follow-up<sup>a</sup>

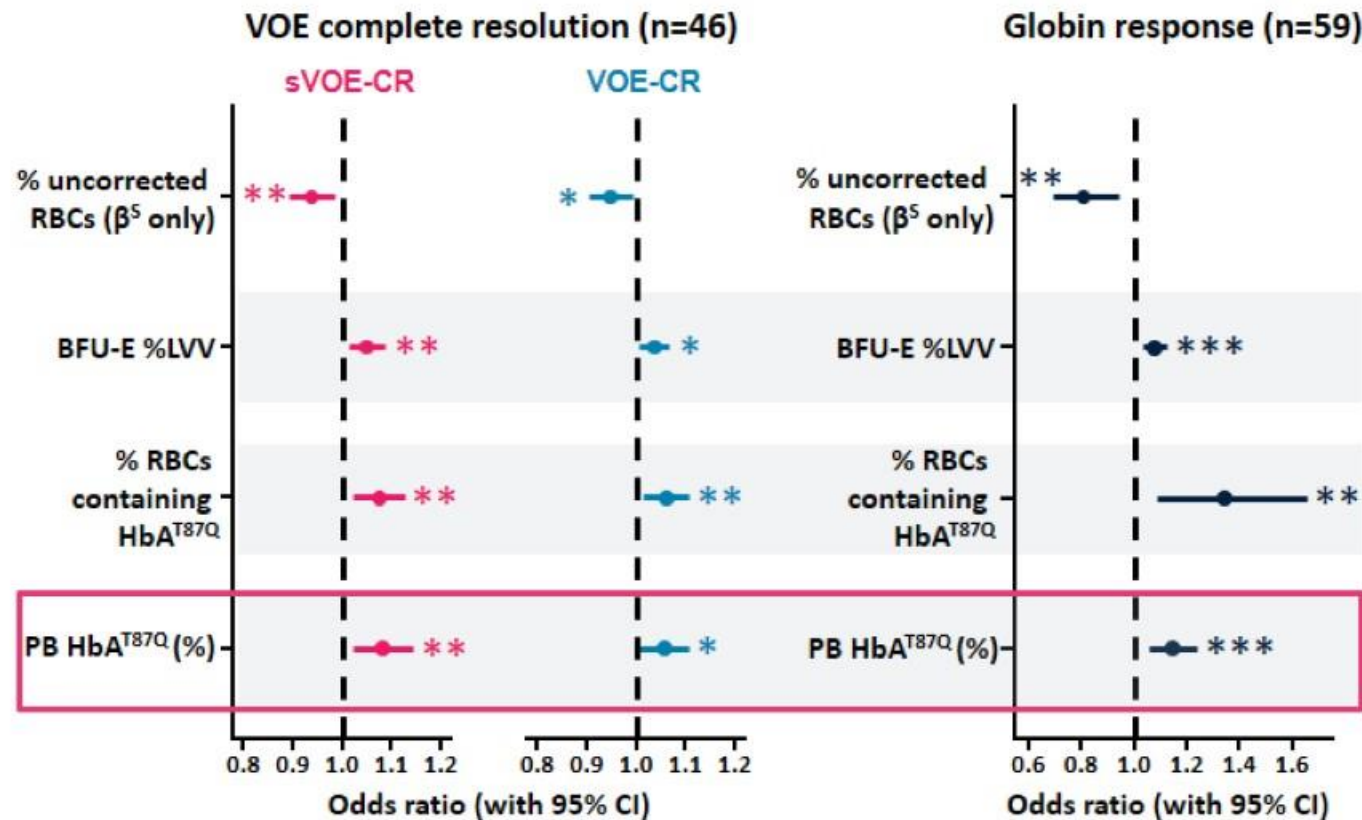
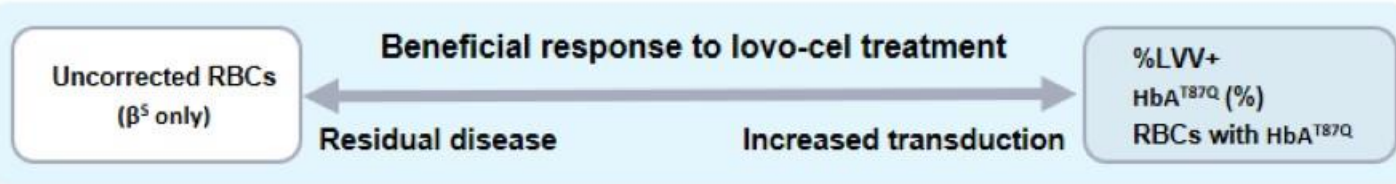


Includes participants with  $\geq 24$  months of follow-up; HGB-206 (Groups A, B, and C) and HGB-210. Pearson correlation coefficients and associated  $P$  values shown in inset.

<sup>a</sup>Nontransfused. <sup>b</sup>Includes 2 participants with dual  $\alpha$ -globin deletions. <sup>c</sup>All participants with  $\geq 6$  months of follow-up. <sup>d</sup>Globin response requires meeting the following criteria for a continuous period of  $\geq 6$  months: weighted average HbA<sup>T87Q</sup>  $\geq 30\%$  of nontransfused total Hb and weighted average increase in nontransfused total Hb of  $\geq 3$  g/dL vs baseline total Hb or weighted average nontransfused total Hb of  $\geq 10$  g/dL.

- In the subset of participants treated with the current manufacturing process (N=58):
  - Measurements at 6 months significantly correlated to those at last follow-up for both HbA<sup>T87Q</sup> and Hb
    - Median (min, max) % HbA<sup>T87Q</sup> at 6 months was 50.1% (29.8%, 63.0%)
    - At last follow-up, median (min, max) % HbA<sup>T87Q</sup> was 49.7% (27.3%, 63.2%) (n=52<sup>c</sup>), and total Hb at last visit was 12.4 (6.6, 15.1) g/dL (n=53<sup>c</sup>) and was stable without transfusion support post engraftment
  - Among 50 evaluable participants, 45 (90.0%) achieved globin response,<sup>d</sup> a composite endpoint of Hb and HbA<sup>T87Q</sup>; all maintained through last visit
    - After the evaluation period, 2 additional participants met globin response
  - Reticulocytes, indirect bilirubin, and lactate dehydrogenase levels approached normal ranges and were maintained through last follow-up

# HbA<sup>T87Q</sup> is Associated With VOE Resolution and Globin Response



➤ Increased transduction efficiency results in a high proportion of RBCs containing HbA<sup>T87Q</sup>, which is associated with biologic and clinical outcomes<sup>1</sup>

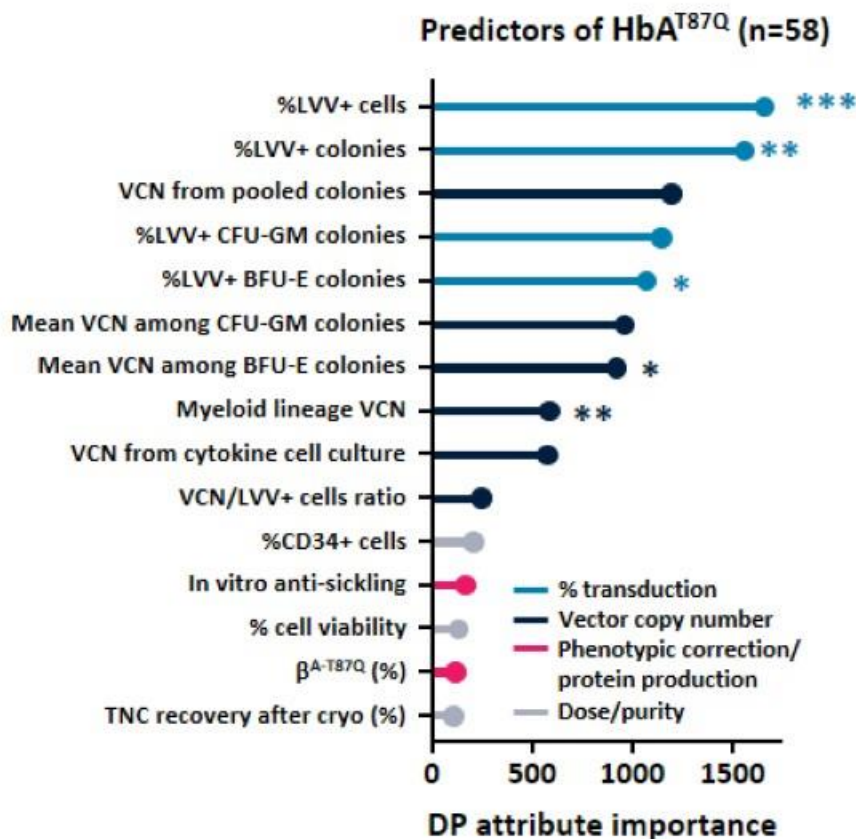
➤ PD parameters are significantly correlated ( $P < 0.05$ ) with clinical outcomes, including resolution of VOEs 6-18 months post infusion and achieving globin response

➤ Increased HbA<sup>T87Q</sup> is associated with VOE-CR and sVOE-CR

➤ Participants with HbA<sup>T87Q</sup> levels  $\geq 30\%$  were more likely to achieve VOE-CR

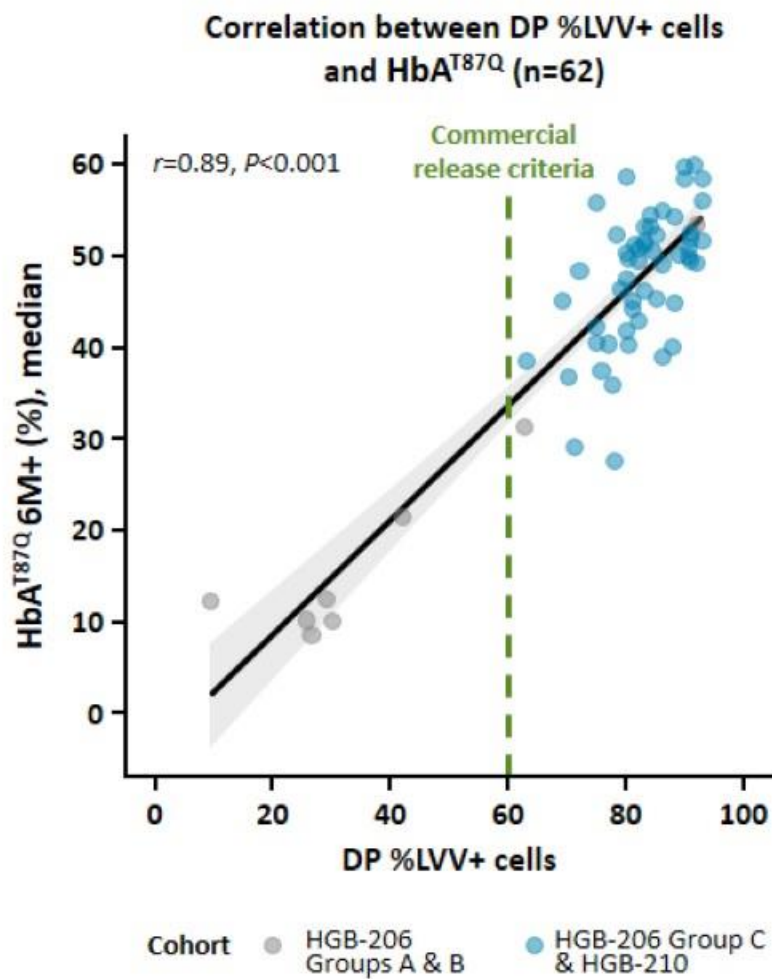
\* $P < 0.05$ . \*\* $P < 0.01$ . \*\*\* $P < 0.001$ . All PD measurements are median of values from 6 months post infusion to the last follow-up; includes HGB-206 groups A, B, and C and HGB-210, VOE evaluable population for VOE complete resolution and transplant population for globin response. n=46 evaluable for (s)VOE-CR ( $\geq 18$  months of follow-up); n=59 evaluable for globin response (achieve globin response, have or would have  $\geq 18$  months of follow-up).

# Drug Product Assays Predict HbA<sup>T87Q</sup> Expression



Random forest:  
MSE=38.5,  $r^2=0.80$

Multiple linear regression:  
 $P<0.001$ , adjusted  $r^2=0.88$

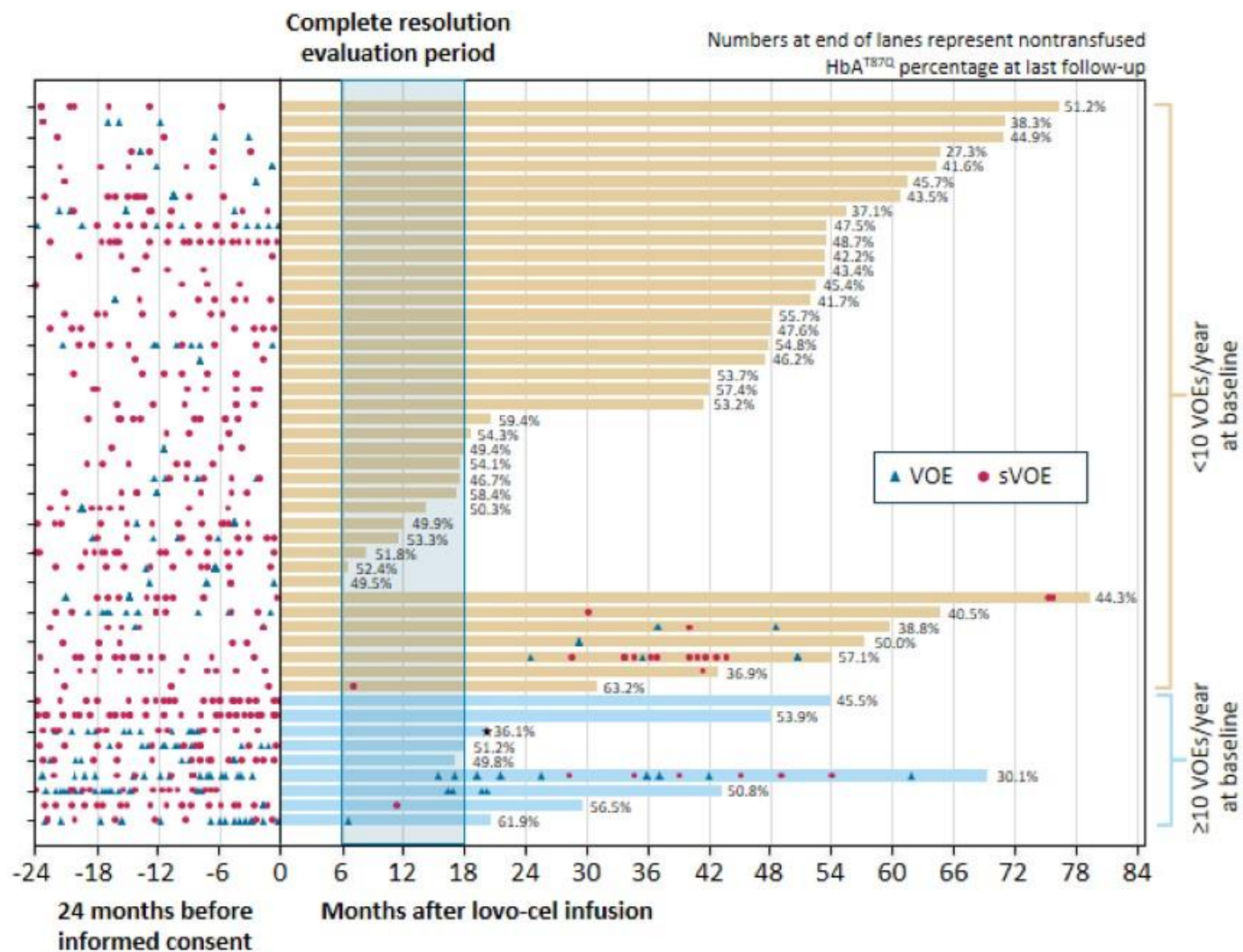


- Multiple release assays are used to characterize the DP
- An analysis of all HGB-206 groups and HGB-210 showed the HbA<sup>T87Q</sup> level is established at the DP level, as PD response is significantly correlated with the DP %LVV+ cells ( $r=0.89, P<0.001$ ), similar to what has been shown with beti-cel<sup>1</sup>
- The median (range) %LVV+ cells in HGB-206 Group C and HGB-210 is 83% (63%-93%), corresponding to a median 48% HbA<sup>T87Q</sup>
  - Commercial lovo-cel must meet a minimum 60% DP LVV+ threshold for release

\* $P<0.05$ . \*\* $P<0.01$ . \*\*\* $P<0.001$ . Based on multiple regression.

Importance metric derived from random forest regression (mean decrease in accuracy). Missing DP data were imputed using kNN, with  $k=5$ .

# 86.8% (33/38) of Participants Achieved Complete Resolution of All VOsEs (Primary Endpoint, 6-18 Months)



**VOE-CR<sup>a</sup>**  
86.8% (33/38)

**sVOE-CR<sup>a</sup>**  
94.7% (36/38)

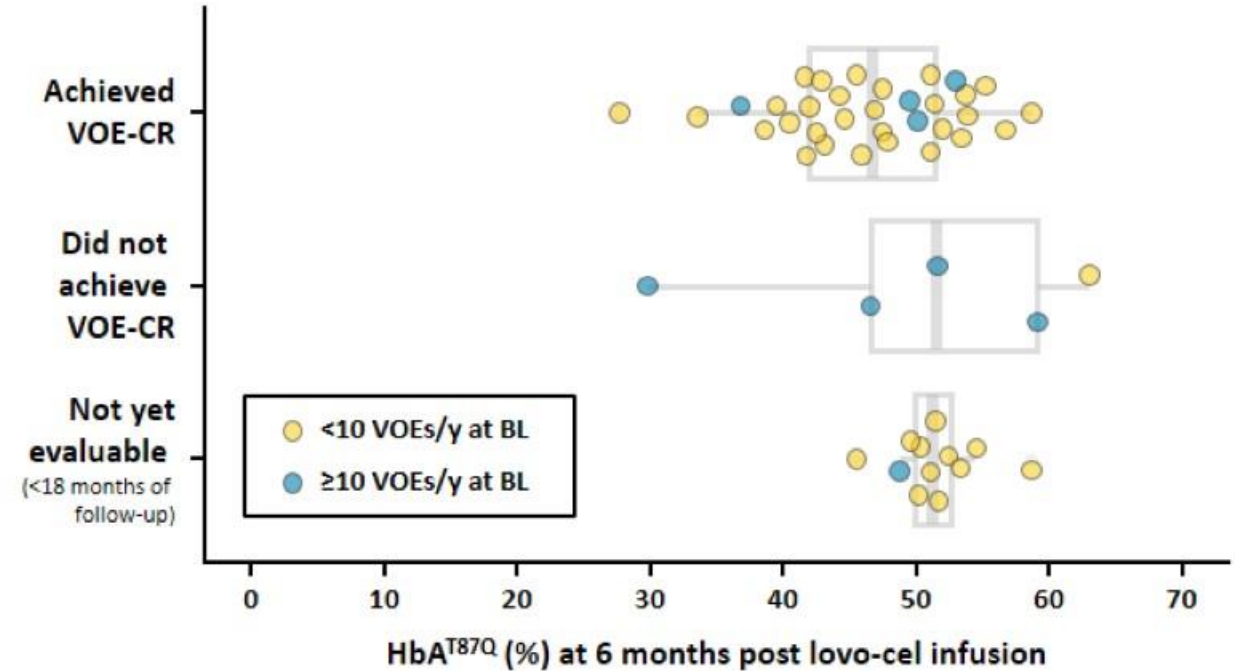
- Duration VOE-free among participants who achieved VOE-CR: 42.4 (12.2, 70.5) months<sup>b</sup>
- **100%** (10/10) of pediatric participants (<18 years) achieved VOE-CR
- 11 participants had VOsEs post infusion, 6 participants experienced VOsEs after the 6- to 18-month assessment period
  - In the 11 participants who had VOsEs post infusion, there was an average of 84% reduction in annualized VOsEs (range, 46%-97%), with 7/11 participants having >90% reduction
- Four of the 5 participants who did not achieve VOE-CR had ≥10 annualized VOsEs at baseline

★ Death, due to significant baseline SCD-related cardiopulmonary disease; not considered related to lovo-cel. An Independent Event Adjudication Committee confirmed VOsEs met protocol criteria. Single VOsEs for 2 participants shown here were retracted by the investigator post adjudication. <sup>a</sup>In the 6-18 months post infusion; participants with ≥18 months of follow-up and ≥4 VOsEs ≤2 years pre-enrollment. <sup>b</sup>Median (min, max).

# VOE-CR is Associated with Baseline Level of VOEs

Parameter	VOEs/year at baseline	
	<10 VOEs (n=30)	≥10 VOEs (n=8)
VOE-CR, n (%)	29 (96.7)	4 (50)
sVOE-CR, n (%)	29 (96.7)	7 (87.5)
Globin response, n (%)	26 (86.7)	7 (87.5)
HbA <sup>T87Q</sup> % at 6 months, median (min, max) <sup>a</sup>	47.4 (33.5, 63.0) <sup>a</sup>	49.8 (29.8, 59.1)
<b>Annualized VOEs</b>		
Baseline, median (min, max)	3.5 (1.5, 9.5)	10.8 (10, 16.5)
6 mo to last follow-up, median (min, max)	0 (0, 3.5)	0 (0, 2.8)
% change from baseline, median (min, max)	-100 (-100, -46.4)	-100 (-100, -73.0)
<b>Annualized VOE-related hospital days</b>		
Baseline, median (min, max)	15.5 (1.5, 90.0)	40 (8, 136.0)
6 mo to LFU, median (min, max)	0 (0, 12.0)	0 (0, 1.9)
% change from baseline, median (min, max)	-100 (-100, -31.7)	-100 (-100, -76.4)

- (s)VOE-CR rates were higher among participants with fewer VOEs at baseline despite similar expression of HbA<sup>T87Q</sup>
- Participants with more severe disease still saw marked reductions in annualized VOEs and hospitalization days



- There may be confounding variables, including baseline disease severity, that impact the presence of reported VOEs
- Among participants who are not yet evaluable for VOE-CR (<18 months of follow-up; n=12), the median (range) % HbA<sup>T87Q</sup> is 51% (45%-59%) at 6 months

<sup>a</sup>n=27.

# Conclusions

- One-time lovo-cel treatment results in durable biologic effect and clinical benefit
  - Sustained HbA<sup>T87Q</sup> production
  - Elimination of VOEs and sVOEs in a majority of participants through last follow-up (median, 47.7 months)
    - 100% of pediatric participants achieved VOE-CR and sVOE-CR
    - 96.7% of participants with <10 annualized VOEs/year at baseline achieved VOE-CR and sVOE-CR
- The safety profile of the lovo-cel treatment regimen was consistent with underlying SCD and known effects of myeloablative conditioning
- Models developed in a post hoc analysis enable prediction of the likelihood of VOE-CR and sVOE-CR using measurements as early as 6 months post treatment
- In the 11 participants who had VOEs >6 months post drug product infusion, there was an average 84% reduction in annualized VOEs (range, 46%-97%), with 7/11 participants having >90% reduction
- Participants with ≥10 VOEs/year had durable clinical benefit, with 50% achieving VOE-CR. In addition, there was a marked reduction in annualized VOE events and VOE-related hospitalization days post lovo-cel
- Patients who experienced VOEs during long-term follow-up had other clinical factors that may have contributed to the pain event. Occurrence was independent of HbA<sup>T87Q</sup> levels. Further investigation of the complex causes of pain during long-term follow-up is needed and ongoing
- Ongoing follow-up in HGB-210 and LTF-307 will continue to assess the safety and long-term impact of lovo-cel

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