

Participants With a History of Stroke in Lovotibeglogene Autotemcel (Lovo-cel) Clinical Trials

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- Lovotibeglogene autotemcel (lovo-cel) is a one-time gene addition therapy for people ≥ 12 years old with sickle cell disease (SCD) and a history of vaso-occlusive events (VOEs)¹
- Here, we report interim outcomes in participants with histories of overt or silent stroke enrolled in the phase 1/2 HGB-206 and phase 3 HGB-210 clinical trials of lovo-cel in SCD

1. Lyfgenia (lovotibeglogene autotemcel). Prescribing information. bluebird bio, Inc.; 2023.

Baseline Characteristics for Participants with a History of Overt Stroke

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As of July 2024, 67 participants had received lovo-cel in HGB-206 or HGB-210

Participant	Study	Gender	Genotype	Age at time of stroke, y	Age at ICF, y	Time from stroke to ICF, y	Age starting regular transfusions	Time from regular transfusions to ICF, y	Follow-up, mo
1	HGB-206 Group A	M	β^S/β^S ; $\alpha\alpha/\alpha\alpha$	NA	34	>5	NA	NA	103.5
2	HGB-206 Group A	M	β^S/β^S ; $\alpha\alpha/-\alpha3.7$	10	26	15	11	15	100.8
3	HGB-206 Group C	M	β^S/β^S ; $\alpha\alpha/\alpha\alpha$	4	19	15	4	15	77.2
4	HGB-206 Group C	M	β^S/β^S ; $\alpha\alpha/\alpha\alpha$	9	21	12	9	12	70.4
5	HGB-206 Group C	F	β^S/β^S ; $\alpha\alpha/-\alpha3.7$	9	19	10	9	10	62.1
6	HGB-206 Group C	F	β^S/β^S ; $\alpha\alpha/\alpha\alpha$	15	19	4	2	17	77.6

- Six participants (HGB-206 Group A, n=2; HGB-206 Group C, n=4) had a history of overt stroke
- These participants had been receiving regular pRBC transfusions for 10-18 years prior to lovo-cel treatment
- Median (range) follow-up for participants with stroke history was 77.4 (62.1-103.5) months

F, female; ICF, informed consent form; M, male; NA, not available; pRBC, packed red blood cell.

Outcomes in Group A Participants with Overt Stroke

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- Both Group A participants with overt stroke history remain stable without recurrent stroke up to 9 years post treatment. Both had improvements in total Hb and some expression of HbA^{T87Q} that remained stable, but neither achieved globin response at last follow-up
- Biologic efficacy outcomes in participants with overt stroke history are consistent with the overall Group A study population¹
- Across Group A (n=7 participants) there was an 82.6% reduction in VOs at 2 years; no participant achieved globin response

1. Kanter J, et al. *Am J Hematol.* 2023;98(1):11-22.

Outcomes in Group C Participants with Overt Stroke

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Biologic efficacy

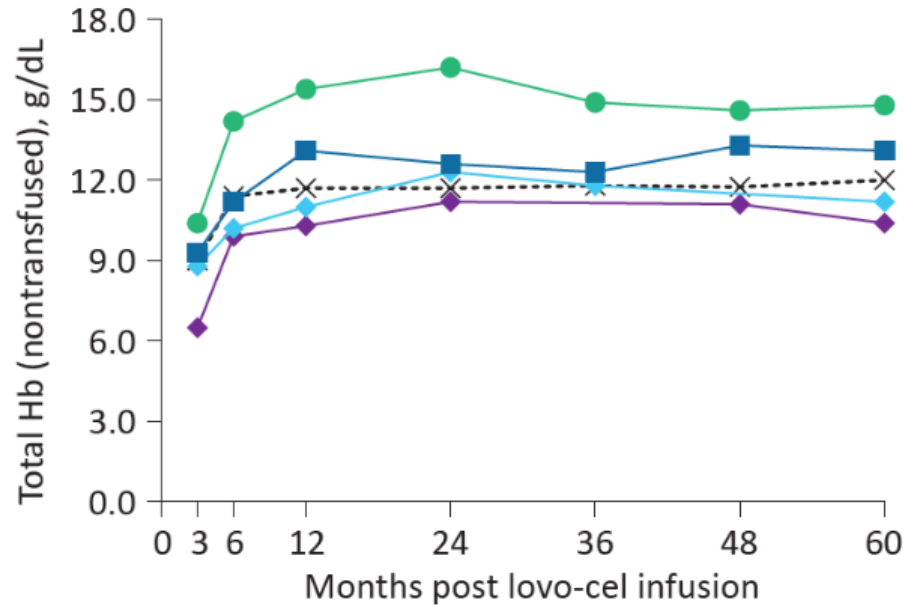
- The 4 participants with overt stroke history from Group C were all adults at time of enrollment and receiving chronic pRBC transfusions (defined as ≥ 8 transfusions/year)
- All 4 achieved globin response post lovo-cel infusion
- Single-cell western analysis from Group C participants showed 78.6%-91.6% of red blood cells contained HbA^{T87Q} between 6 months and last follow-up

1. Kanter J, et al. *Am J Hematol.* 2023;98(1):11-22.

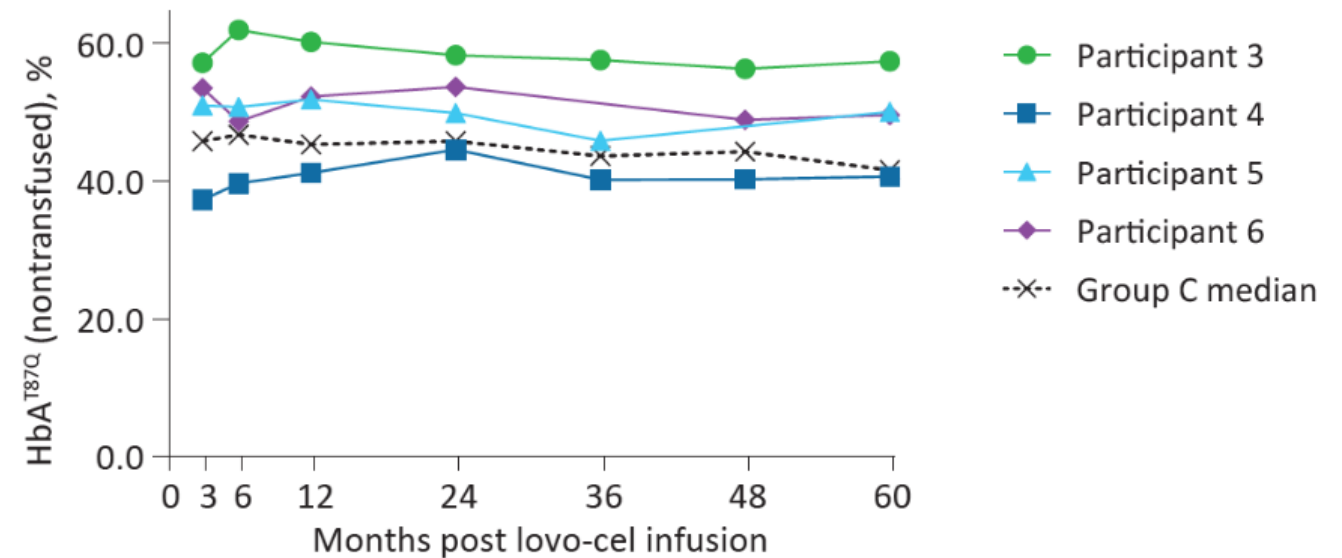
HbA^{T87Q} levels and globin response^a were maintained over time in Group C participants with a history of stroke^{b,c}

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A. Nontransfused total Hb



B. Nontransfused HbA^{T87Q}



^aGlobin response defined as meeting the following criteria for a continuous period of ≥6 months: weighted average HbA^{T87Q} ≥30% of nontransfused total Hb AND weighted average increase in nontransfused total Hb of ≥3 g/dL vs baseline total Hb OR weighted average nontransfused total Hb of ≥10 g/dL.

^bBaseline levels were not available as all participants were on transfusions at baseline. ^cFor the Group C population overall at 3 months post treatment and at last follow-up, median (range) total Hb (nontransfused) g/dL was 9.0 (1.6-12.5) and 12.0 (6.6, 15.0) and nontransfused HbA^{T87Q} % was 45.8 (25.0-57.2) and 45.6 (0.0-63.2), respectively. BL, baseline; Hb, hemoglobin; HbA^{T87Q}, anti-sickling Hb.

Outcomes in Group C Participants with Overt Stroke

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VOEs and stroke

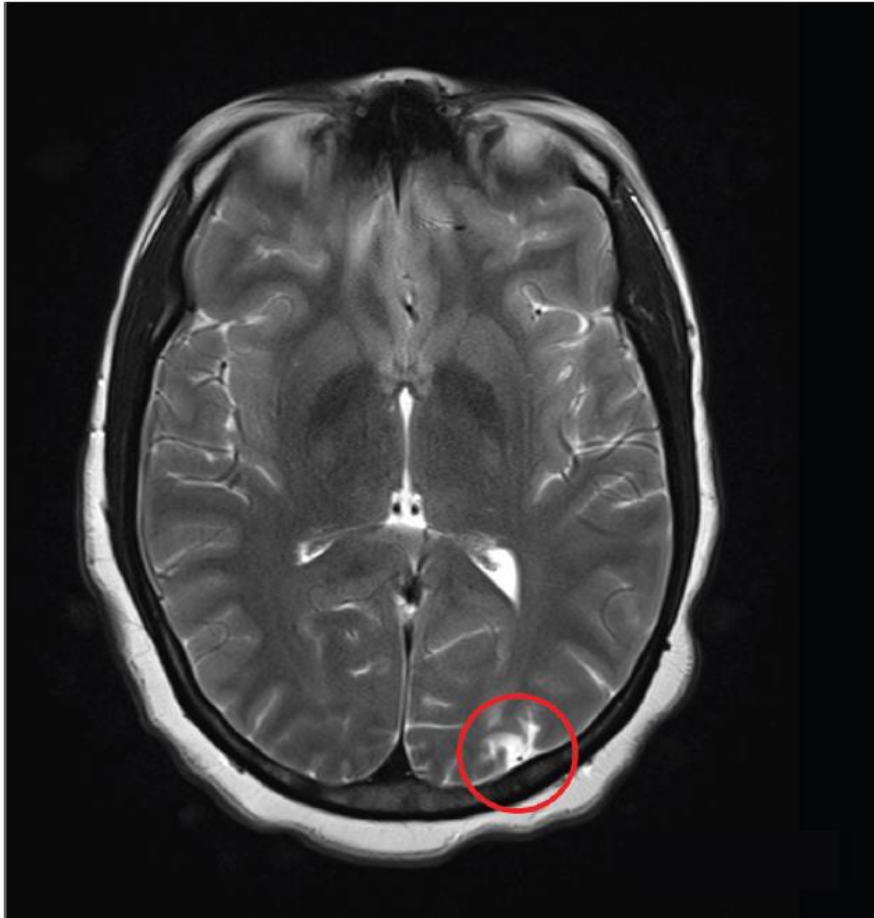
- None of the 4 stroke participants were evaluable for complete resolution of VOEs (VOE-CR) due to a lack of VOEs at baseline
 - None of these participants experienced a VOE during the VOE-CR evaluation period
 - Participant 4 experienced a single VOE of acute pain with no attributable cause 3.9 years after treatment. They received oral oxycodone and IV ketorolac, did not receive IV opioids, and have had no further VOEs 5 years post treatment
- There were no reports of stroke post lovo-cel infusion in Group C participants with overt stroke history
- All Group C participants with overt stroke history were on transfusions for >10 years at baseline and are transfusion independent post lovo-cel infusion without recurrent stroke up to 77.6 months
- Efficacy outcomes in the 4 Group C participants with overt stroke history are consistent with the overall Group C study population

IV, intravenous; VOE, vaso-occlusive event.

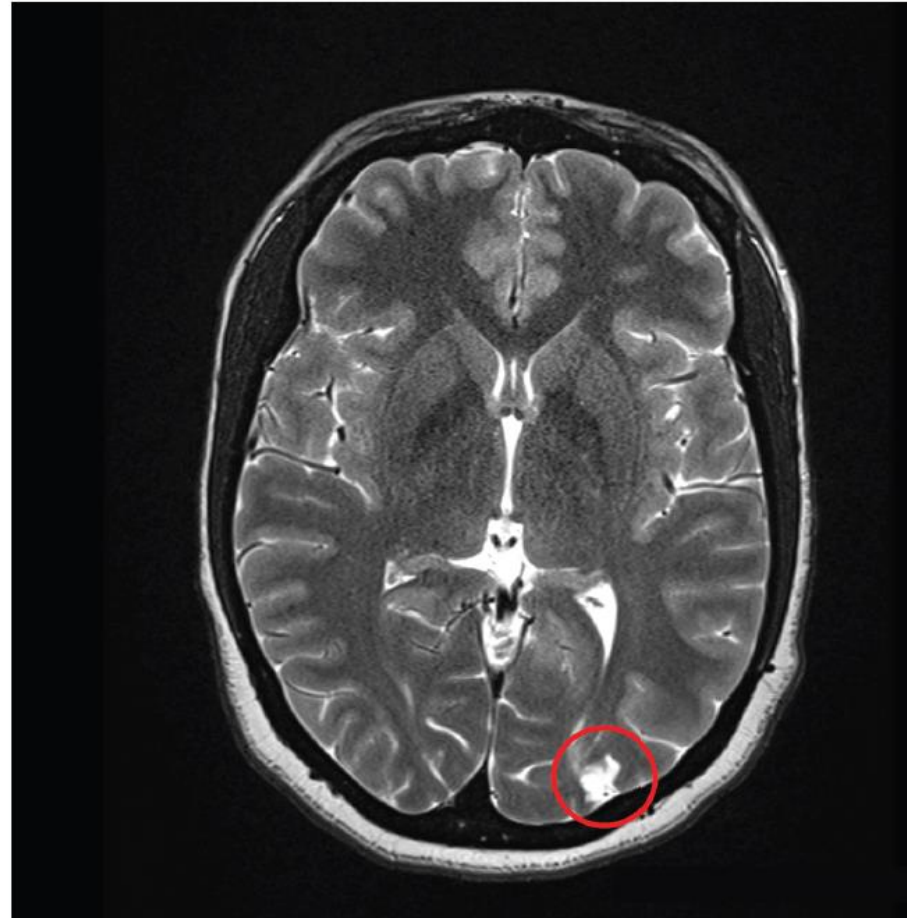
MRIs for Participant 5 Pre- and Post Lovo-cel Infusion

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Pre



Post



Red circles represent no change in overt stroke from pre- to post lovo-cel infusion.
MRI, magnetic resonance imaging.

Outcomes in Group C Participants with Overt Stroke

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Safety

- Safety findings for participants with history of overt stroke did not differ from safety findings in the overall treatment group. No increase in hypertension, bleeding issues, prolonged thrombocytopenia, or catheter-related thromboses were observed in these participants
 - One participant was on antihypertensives prior to lovo-cel infusion and discontinued 4 months after treatment
 - None received anticoagulants following infusion, with the possible exception of one participant noted as having remote aspirin with no stop date provided
- All participants achieved successful engraftment
- As expected with autologous therapy, there were no reports of graft-versus-host disease or posterior reversible encephalopathy syndrome

Outcomes in Participants with Silent Stroke

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- Twenty-one out of 40 participants (52.5%) that had MRI data available at screening had evidence of silent stroke, which is similar to the SCD population overall¹
- There were no reports of recurrent overt or silent stroke in any participant with a history of silent stroke (follow-up range, 0.9-77.0 months)
- In the 41 participants with MRIs available at 12 or 14 months, there were no new silent strokes observed
- These analyses were limited by MRI availabilities at screening and post infusion. Long-term follow-up is ongoing in LTF-307

MRI, magnetic resonance imaging; SCD, sickle cell disease.

1. Houwing ME, et al. *BMC Med.* 2020;18(1):393.

- These data show hematologic response to lovo-cel in participants from Group C with a history of stroke was consistent with the overall respective population (Group A or Group C)^{1,2}
- No recurrent stroke; all Group C participants are transfusion-independent post lovo-cel therapy
- Safety findings for participants with a history of overt stroke were similar to other participants
- Longer follow-up will be required to understand the impact on neurovasculature and risk of stroke recurrence

1. Kanter J, et al. *Am J Hematol.* 2023;98(1):11-22. 2. Kanter J, et al. Presented at: ASH; Dec 9-12, 2023; San Diego, CA. Oral presentation; abstract #1051.