Interim Safety and Efficacy Results From a Phase 1/2 Study of Zinc Finger Nuclease-Modified Autologous Hematopoietic Stem Cells for Sickle Cell Disease (PRECIZN-1)

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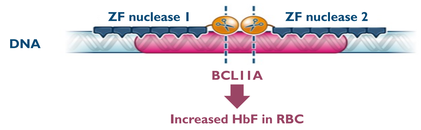
Introduction

- Sickle cell disease (SCD) is caused by pathologic variants in both alleles of the β-globin gene
- Elevated fetal hemoglobin (HbF) levels inhibit sickle cell formation, ameliorate symptoms, and improve survival in patients with SCD
- BIVV003: novel product candidate comprising autologous CD34 hematopoietic stem and progenitor cells (HSPCs) modified *ex vivo* by zinc finger nucleases (ZFNs) specifically targeting the *BCL11A* gene erythroid-specific enhancer (ESE) to increase endogenous HbF production in red blood cells (RBC)

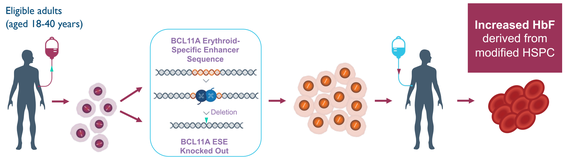


Release the brake: Inactivation of *BCL11A* ESE turns off a gene that stops HbF production in RBC

- Cell therapy is a combination of gene-editing technology and process development. We have introduced a new process that we believe will result in more long-term progenitor cells essential to maximizing engraftment and HbF levels.
- Here we describe long-term data from Group 1, comprising the first 4 subjects treated with the initial manufacturing process and the first data from Group 2, showing the first subject treated with the improved manufacturing process
- A second subject in Group 2 was dosed with BIVV003 after the cutoff date

Methods

Figure 1. BIVV003 Autologous Cell Therapy: ZFN-driven Disruption of the BCL11A Enhancer in CD34⁺ HSPC



Apheresis	Manufacturing process begins	ZFN-driven genome editing	Edited cell culture and harvest	Myeloablative conditioning and infusion	Engraftment of edited cells
Mobilization and collection of autologous CD34⁺ HSPCs via apheresis with plerixafor 240 μg/kg/day for up to 3 days	Process the collected cells to enrich for long-term progenitors	HSPCs transfected ex vivo with ZFN mRNA targeting the BCL11A ESE to manufacture BIVV003	• Patients receive BIVV003 as a single IV infusion • Minimum dose of 3 × 10⁶ CD34⁺ HSPC/kg	• Busulfan 3.2 mg/kg/day IV × 4 days, with PK-based dose adjustment • Single IV infusion of BIVV003, minimum dose of 3 × 10⁶ CD34⁺ HSPC/kg	

[a]Dose adjustment based on pharmacokinetics. HSPC, hematopoietic stem cells and progenitor cells; IV, infusion; PK, pharmacokinetics; ZFN, zinc finger nucleases.

PRECIZN-1 Study Design and Endpoints

- First-in-human, open-label, single-arm, multicenter study (NCT03653247)
- Primary objective: To evaluate the safety and tolerability of BIVV003 in subjects with severe SCD
- Sample size: approximately 8
  - Group 1: First 4 subjects dosed with a product candidate (PC) manufactured using the initial process
  - Group 2: Remaining 4 subjects were/will be dosed with PC manufactured using the improved process
- Study methods are depicted in Figure 1
- Endpoints: Time to stem cell engraftment and hematopoietic recovery
  Adverse events (AEs) and SCD-related events
  Clinical and laboratory hemolysis markers, total hemoglobin (Hb)
  HbF/normal adult hemoglobin (HbA)/normal variant (HbA2)/sickle hemoglobin (HbS) fractionation, RBC-containing HbF (F cells)

Results

Table 1. Baseline Characteristics of First 5 Subjects Dosed

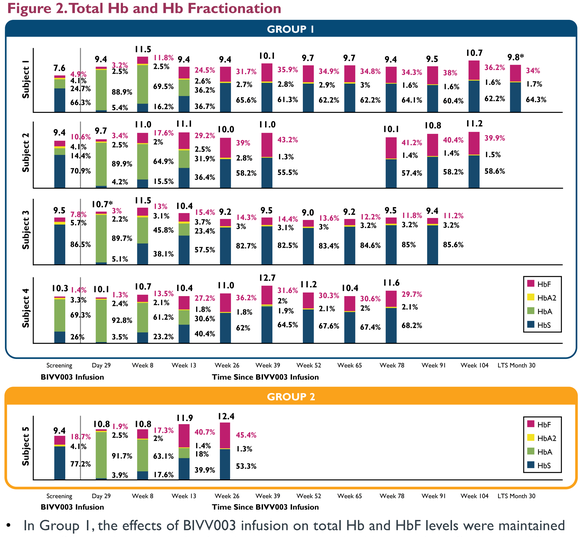
	Group 1				Group 2
Subject	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Genotype	HbSS	HbSS	HbSS	HbSS	HbS-β⁰
Gender	Female	Female	Male	Male	Male
Race	African American	African American	African American	African American	African American
Age at consent, years	35	20	18	25	27
sVOC/2 years pre-ICF	12	22	3	6	9
Hydroxyurea, Y/N	N	Y	Y	N	Y
Chronic RBC transfusion therapy, Y/N	N	Y	Y	Y	N

- As of the September 30, 2022 cutoff date:
  - Group 1 Subjects 1–4 received infusions of BIVV003 manufactured with the initial process and have had up to 30 months of follow-up
  - In Group 2, Subject 5 received BIVV003 manufactured using an improved process shown in internal experiments to increase the number of ZFN-modified long-term progenitors in the PC and has had 5 months of follow-up, excluding any data collected post cutoff

Hematopoietic Reconstitution and Engraftment

- All subjects had hematopoietic reconstitution; none have required rescue HSPC
- A median number of 5 packed RBC transfusions (range, 3-9) were given in the first 45 days post-BIVV003 infusion
- The average time to neutrophil and platelet engraftment was 22 days and 32 days, respectively

Figure 2. Total Hb and Hb Fractionation



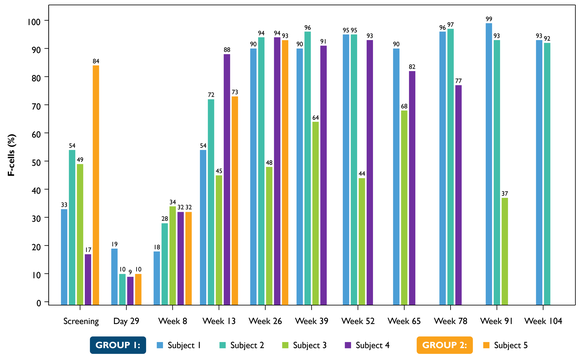
- In Group 1, the effects of BIVV003 infusion on total Hb and HbF levels were maintained up to 30 months post dosing for the longest treated subject as of the September 30, 2022, cutoff date
  - In 3 of the 4 Group 1 subjects (initial process), percentage of HbF levels stabilized at ≥30% by 26 weeks post-BIVV003 infusion and persisted for up to 30 months (2.5 years)
  - Subject 3 had an HbF level <15% from Week 26 onwards, suggesting poor engraftment of edited HSPCs. There may have been insufficient suppression of endogenous erythropoiesis in this subject in the weeks prior to the BIVV003 infusion and/or the mobilized cell population from this subject contained a relatively lower proportion of long-term progenitor stem cells.
- In Group 2, Subject 5, who received PC manufactured using the improved process, had a HbF level of 40.7% and total Hb of 11.9 g/dL by 13 weeks post-infusion; the latest sample collected post data cutoff showed an HbF level of 45.4% and total Hb of 12.4 g/dL at week 26
- In all Group 1 subjects, the PC had on-target *BCL11A* gene modification (61–78% indels)
  - In bone marrow aspirates 26 weeks post-infusion from Group 1 subjects (initial manufacturing process), the frequency of cells containing indels at the *BCL11A* ESE target locus was in the range of 17–34% and was stably maintained through the latest assessment, as of the September 30, 2022 cutoff

Table 2. Group 1: BCL11A ESE Indel Frequency in Bone Marrow Cells

Subject	Week 26	Week 52	Week 104
1	28%	26%	24%
2	34%	32%	
3	17%	17%	
4	20%	18%	

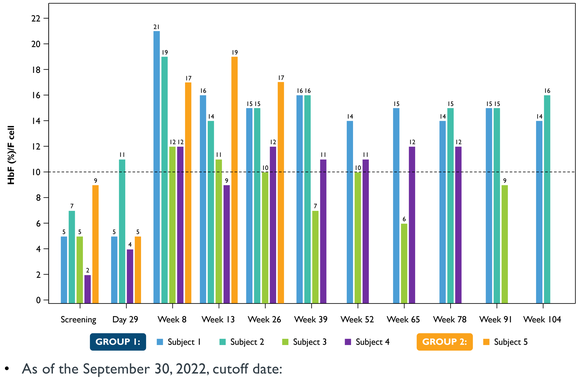
- Data from Group 2 subjects (improved process) will be collected in due course

Figure 3. Percentage F Cells



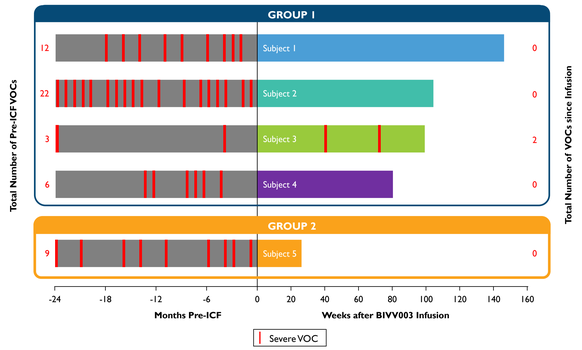
- As of the September 30, 2022, cutoff date:
  - Group 1: The percentage of F cells persisted at high levels (77–99%) for up to 104 weeks in 3 of the 4 treated subjects
  - Group 2: Subject 5 showed 93% F cells at week 26 in the latest sample collected post data cutoff

Figure 4. HbF/F Cell Levels Above Protective Threshold



- As of the September 30, 2022, cutoff date:
  - Group 1: By 26 weeks post-infusion, 3 out of 4 subjects had reached a protective level of ≥10 pg HbF/F cells, which inhibits HbS polymerization[2], and this level (dashed line) was sustained in 3 out of the 4 subjects for up to 104 weeks
  - Group 2: By week 13 post-infusion, Subject 5 achieved a level of 19 pg HbF/F cell; the latest sample collected post data cutoff showed 17 pg HbF/F cell at Week 26

Figure 5. Absence of VOC After BIVV003 Infusion



- Three of the first 4 subjects in Group 1 have not had recurrence of severe vaso-occlusive crises (VOCs) post-infusion compared to each subject experiencing between 6 to 22 severe VOCs in the 2 years pre-study
  - Subject 3 with significantly lower levels of HbF (11–14%) and who did not sustain a level ≥10 pg HbF/F cells, experienced 2 severe VOCs at 9 and 16 months post-infusion
- In Group 2, Subject 5, treated with the PC manufactured using the improved process, has not had any recurrence of VOCs to date

Safety and Tolerability

- The AEs reported were consistent with plerixafor mobilization and busulfan myeloablative conditioning
- No AEs related to BIVV003 were reported in any of the 5 subjects
- Two post-infusion serious AEs of sickle cell anemia with crisis were reported in one subject; no other SCD-related serious AE was reported in the 5 subjects

Conclusions

- BIVV003 has been well tolerated by all 5 subjects infused as of September 30, 2022, with no AEs related to BIVV003
- In Group 1:
  - Three of the 4 subjects who received BIVV003 manufactured using the initial process had stable engraftment of ZFN-modified HSPCs, resulting in sustained elevated HbF levels >30% and absence of severe VOCs post-BIVV003 administration
  - In Subject 3 (initial process), low HbF levels (11–14%) were associated with 2 severe VOCs
- In Group 2:
  - Subject 5 received BIVV003 manufactured using an improved process that has been shown in internal experiments to increase the number of ZFN-edited long-term progenitors in the final product candidate. The HbF level of 45% and total Hb of 12.4 g/dL at week 26 post-infusion in the latest sample collected post data cut-off were greater than the levels observed in Group 1 at week 26
  - A sixth subject was dosed with BIVV003 after the cutoff date, the second subject to be dosed with a product candidate manufactured using the improved process
- These interim phase 1/2 safety and efficacy results confirm the potential therapeutic value of ZFN-mediated modification of the *BCL11A* ESE region and are promising for the improved process

References

1. Hebert N, et al. *Am J Hematol*. 2020;95:1235-1245.
2. Steinberg MH, et al. *Blood*. 2014;123:481-485.

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