Gene Therapy in Sickle Cell Disease

10 November 2018

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Conflict of Interest Declaration

- Co-investigator: Cincinnati Children's Hospital Medical Center
- Co-investigator: CRISPR therapeutics
- Member of DSMB: Bioverativ/Sanofi
My Take on the Future of SCD Treatment

- Symptom Control
- Disease Control
- Side Effects
- Disease Modifier
- SCD Complications
- Personal Value and Preferences
- Prediction tool?
Tempering Hope with Reality

• 1 out of 8 participants
Typical Process of Gene Therapy for Sickle Cell Disease

- Erythrocytapheresis for > 2 months prior to mobilization
- Plerixafor mobilization
- Target 2 x 10^6 CD34+ cells/kg
- Busulfan or melphalan myeloablation
- Cyclophosphamide sparing since immunoablation is not necessary in an autologous setting
- ~10 weeks from mobilization to transplant
Advantages of Gene Therapy over HSCT

- Graft rejection
- GvHD
- Transplant-related complications
- Increased risk with age
- Increasing disease-related morbidity with age
- Infertility
- Therapy-related malignancies
- Donor availability
  - survival MRD > MUD > UD > Haplo
- Cost

Disease-related

Conditioning Regimen
## Current Gene Therapy Trials in Sickle Cell Disease

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Approach</th>
<th>Age</th>
<th>Genotype</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cincinnati Children's Hospital Medical Center</td>
<td>γ-globin Lentivirus vector</td>
<td>18 – 35</td>
<td>S/β⁰, S/β⁺</td>
<td>Active</td>
</tr>
<tr>
<td>Boston Children's Hospital</td>
<td>shRNA targeting BCL11A Lentivirus vector</td>
<td>1: 18-35</td>
<td>SCD with HbF&lt;10%</td>
<td>Active</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: ≥12-&lt;18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3: ≥3-&lt;12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bluebird Bio</td>
<td>β²⁰⁰-T₈⁷⁰ Q Lentivirus vector</td>
<td>12 – 50</td>
<td>S/S, S/β⁰, S/β⁺</td>
<td>Active</td>
</tr>
<tr>
<td>UCLA</td>
<td>βAS3-FB Lentivirus vector</td>
<td>≥18</td>
<td>S/S, S/β⁰</td>
<td>Active</td>
</tr>
<tr>
<td>CRISPR therapeutics</td>
<td>CRISPR</td>
<td></td>
<td></td>
<td>FDA IND</td>
</tr>
<tr>
<td>Bioverativ/Sagamo</td>
<td>ZFN BCL11A enhancer</td>
<td></td>
<td></td>
<td>FDA IND</td>
</tr>
</tbody>
</table>

Orkin SH and Bauer DE. Annu. Rev. Med. 2019. 70:23.1–23.15
clinicaltrials.gov, abstracted on 2018 Nov 10
# SCD-Specific Indications in Current Gene Therapy Trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cincinnati Children's Hospital Medical Center</td>
<td>Severe phenotype Failed HU</td>
<td>Abnormal PFT PHT Chronic transfusion</td>
</tr>
<tr>
<td>Boston Children's Hospital</td>
<td>Severe phenotype Failed HU Chronic transfusion for stroke prophylaxis</td>
<td>Has a MSD or MRD donor</td>
</tr>
<tr>
<td>Bluebird Bio</td>
<td>Severe phenotype Failed HU</td>
<td>Stroke, abnormal TCD, Moyamoya, Steno-occlusive disease</td>
</tr>
<tr>
<td>UCLA</td>
<td>Severe phenotype Failed HU (but off HU 90 days before enrollment) Stroke Chronic transfusion TRJV &gt; 2.5 m/s Osteonecrosis</td>
<td>Has a MSD or MRD donor</td>
</tr>
<tr>
<td>CRISPR therapeutics</td>
<td>Pending</td>
<td>Pending</td>
</tr>
</tbody>
</table>
“Severe” Sickle Cell Disease Phenotype

• Definition varies

• Usually mirrors or similar to SCD bone marrow transplant trials

• Example (Boston Children’s):
  • ≥2 ACS in the past 2 years
  • ≥3 hospitalized pain crises in the past 2 years
  • > 2 priapism in the past 2 years
  • >2 RBC antibodies from transfusion
  • On chronic transfusions for stroke prophylaxis
Various Approaches to Gene Therapy in Sickle Cell Disease

Hoban MD, Orkin SH, Bauer DE. Blood. 2016; 127(7):839-848
**Lentiviral Modified Globin Vector**

- The modified lentiviral vector is replication defective, self-inactivating (reduces insertional oncogenesis)
- $\beta^{A-T87Q}$-globin (mutation derives from $\gamma$-globin)
- LCR required for high level erythroid-specific expression
- Insulator protects trans-gene from being silenced
- Interrupts polymerization of $\beta^S$

Hoban MD, Orkin SH, Bauer DE. Blood. 2016; 127(7):839-848
O2 Dissociation Curve of $\beta^{A-T87Q}$

HGB-204/5/6 Study Schema

Mobilization

- Apheresis
  - GCSF + plerixafor

Pre-infusion Conditioning

- Busulfan myeloablation

Infuse Cells after BB305 transduction

Subject Treatment

- BM harvest in HGB-206 (severe SCD) study

Centralized Manufacturing

- Select CD34+ cells
- Transduce with BB305 lentiviral vector
- Cryopreserve, test and release

2 years follow-up

Extension study
Up to 15 years total follow-up

HGB-206 (Severe SCD)

- Patient characteristics:
  - 8 Recurrent VOC
  - 7 ACS
  - 1 overt stroke
  - 3 TRJV > 2.5 m/s
- 1 SAE pain from bone marrow harvest
- 3 SAEs post-infusion: 1 bacteremia, 2 VOC
- 9 other AEs: fever, mouth pain, mucositis, febrile neutropenia, anorexia, fatigue, dyspnea, bacteremia

Kanter J ASH 2015 Abstract 3233
Result of one participant from HGB-205/6 Study

- Neutrophil engraftment at Day 38
- Discharged on Day 50
- Grade 3 infection with *Staphylococcus epidermidis* (with positive results on blood culture)
- No dominant clone
HbF Induction by Genome Editing

Genome Editing Delivery Methods

**Electroporation**
- Electric pulse applied
- Pores created in membrane
- Cell transfected with DNA or protein

**Mechanical deformation**
- Cell passed through constriction with dimension smaller than cell diameter
- Cell deforms, creates transient pores in membrane
- Pores close, cell transfected with DNA or protein
# Comparison of Gene Editing Methods

<table>
<thead>
<tr>
<th></th>
<th>ZFN</th>
<th>CRISPR</th>
<th>TALEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>Can tolerate small number of positional mismatches</td>
<td>Positional and Multiple consecutive mismatches tolerated</td>
<td></td>
</tr>
<tr>
<td>Target constraints</td>
<td>Difficult to target non-G-rich sequences</td>
<td>5’ targeted base must be a T</td>
<td>Targeted sequence must precede a PAM</td>
</tr>
<tr>
<td>Ease of engineering</td>
<td>Difficult</td>
<td>Moderate</td>
<td>Easy</td>
</tr>
<tr>
<td>Ease of <em>ex vivo</em> delivery</td>
<td>Easy: viral transduction or electroporation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of <em>in vivo</em> delivery</td>
<td>Easy</td>
<td>Difficult</td>
<td>Moderate</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>? Low</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Potential and Theoretical Risks

• Engraftment failure
• Immunogenicity
  • CRISPR, TALEN and FokI in ZFN are derived from bacteria
• Semi-random integration
• Off-target effects
• Unrepaired double strand breaks
• Insertional mutagenesis
• Clonal dominance
• Cellular transformation

Ways to Mitigate the Risks

• FDA-mandated 15 year follow-up
• Secondary malignancy surveillance
• Off-target editing surveillance (peripheral blood and bone marrow)
• Vector copy number analysis
Systematic review of 47 cases of gene therapy in hemoglobinopathy

- Abstract 2194, Fazeel HF, et al.
- N = 47 patients, 35 patients (74.4%) TDT, 12 patients (25.5%) SCD
- Follow-up 2 to 36 months
- Lentivirus BB305 Hb\textsuperscript{AT87Q} in 81% patients (n=38)
- Conditioning regimen:
  - Myeloablative conditioning: busulfan 81% cases (n=38), Treosulfan + thiotepa in 7 cases
  - Non-myeloablative conditioning with busulfan was used in 2 cases (both TDT)
  - Bone marrow harvest was the source of HSCs in all SCD cases
- Range of vector copy number was 0.3-1.5 copies per diploid genome
- Hemoglobin reported for 62% cases (n=29) was > 88 g/l
- No transfusion free state was noted in SCD cases
- 75% SCD cases (n=9) had a 30-100% reduction in the frequency of VOCs
- Toxicity mainly from conditioning, no therapy-related leukemia or new malignancy
ASH 2018 Update
Abstract 1021

• Gene Therapy for Sickle Cell Anemia Using a Modified Gamma Globin Lentivirus Vector and Reduced Intensity Conditioning Transplant Shows Promising Correction of the Disease Phenotype
• Malik P et al., Cincinnati Children's Hospital Medical Center, Cincinnati, OH
• Reduced Intensity Conditioning (RIC)
• Phase I/II Pilot
• modified γ-Globin LV (NCT02186418),
• 2 SCA patients (35yo and 25yo) with S/β0
• Time to ANC ≥ 0.5 - day 9 and 7 post-transplant (PT)
• Time to platelet > 50 - day 14 PT in both
• HbF*/(HbF*+HbS) = 20% and 21% in P1 and P2 at day 180 PT
• VCN 0.2-0.4
• Integration site analysis demonstrated highly polyclonal pattern of integration
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LG-001</th>
<th>HGB 204</th>
<th>HGB 205</th>
<th>HGB 206</th>
<th>HGB 207</th>
<th>TIGET BTHAL</th>
<th>TNS 9.3.55</th>
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<tbody>
<tr>
<td>Study reporting</td>
<td>Cavazzana, M.</td>
<td>Kwałkowksi, J</td>
<td>Cavazzana, M.</td>
<td>Kante, J.</td>
<td>Waters, M.</td>
<td>Markel, S.</td>
<td>Bouhad, F.</td>
</tr>
<tr>
<td>Total Patients (n)</td>
<td>1</td>
<td>18</td>
<td>7</td>
<td>9</td>
<td>3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Thalassemia (n, genotype)</td>
<td>β0/β0</td>
<td>β0/β0</td>
<td>β0/β0</td>
<td>non-β0/β0</td>
<td>non-β0/β0</td>
<td>non-β0/β0</td>
<td>2, non-β0/β0</td>
</tr>
<tr>
<td>Sickle cell Anemia (n, genotype)</td>
<td>N/A</td>
<td>N/A</td>
<td>3, βS/βS</td>
<td>9, βS/βS</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>18</td>
<td>12- 35</td>
<td>13- 21</td>
<td>18- 42</td>
<td>20-22</td>
<td>6-13 (n= 4); 31-35 (n= 3)</td>
<td>N/A</td>
</tr>
<tr>
<td>Median Follow up (range, month)</td>
<td>19</td>
<td>25.5 (15- 38)</td>
<td>23.4 (14.4- 42.2)</td>
<td>18.3 (14.9- 23.8)</td>
<td>3 (2- 6)</td>
<td>13 (6- 22)</td>
<td>(18- 23)</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>MA; busulfan</td>
<td>MA; busulfan</td>
<td>MA; busulfan</td>
<td>MA; busulfan</td>
<td>MA; busulfan</td>
<td>MA; treosulfan+ thiopeta</td>
<td>NMA; Busulfan (total 8 mg/kg)</td>
</tr>
<tr>
<td>Stem cell harvest</td>
<td>BMH</td>
<td>PBSC; G-CSF+pleraixafer</td>
<td>SCDS= BM; TDT= PBSC</td>
<td>BMH</td>
<td>PBSC; G-CSF+plerixafer</td>
<td>PBSC; leugemastim+ plerixafer</td>
<td>PBSC; filgrastim</td>
</tr>
<tr>
<td>DP-VCN, median (range)</td>
<td>0.6</td>
<td>0.7 (0.3- 1.5)</td>
<td>TDT= (0.8- 1.5); SCDS= (0.5- 1.2)</td>
<td>(0.3- 3)</td>
<td>3 (2.4- 4)</td>
<td>(0.7- 1.5)</td>
<td>(0.21-0.39)</td>
</tr>
<tr>
<td>Dose infused (10^6 cells/kg)</td>
<td>3.9</td>
<td>8.1 (5.2-18.1)</td>
<td>TDT= 8.8- 12; SCDS= 3- 5.6</td>
<td>1.6- 5.1</td>
<td>N/A</td>
<td>16- 19.5</td>
<td>8.4- 11.8</td>
</tr>
<tr>
<td>Immediate safety concerns i.e. infusion reactions</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

### Disease specific outcomes

| Total Hb (g/dl) | 9-10 | 9.3- 13 | TDT= 8.3- 13; SCDS= 8.8- 12.4 | N/A | 3.4-13.3 | N/A |
| Tx free period: no. of pts (n, months) | 24 mo | β0/β0: n=2, l2 mo; non-β0/β0: n=8, 27 mo | TDT= 23-42 mo; SCDS= none | N/A | n= 1.5 mo | n= 3 |
| Tx Independence | yes | yes; non-β0/β0: (n=6) | N/A | N/A | No | No |
| Tx reduction (percentage range of reduction) | 100% | 30-90% | N/A | N/A | N/A | N/A |
| Vaso-occlusive crises | N/A | N/A | N/A | 14-100% reduction | N/A | N/A |
| HbAT87Q level (g/dl) | 3.7 | N/A | TDT= 6.6-10; SCDS= 1.5- 6.1 | 0.4-2.4 | 0.3- 8.4 | N/A |
| VCN in recipient blood (copies/diploid genome) | 2.9% positive erythroblasts | β0/β0= 0.6- 0.9, non-β0/β0= 0.1- 1 | TDT= 0.9- 2.1; SCDS= 0.3- 2.3 | 0.1- 2.6 | 2.2- 11.2 | 0.37-1.35 | 5-7% blood cells |
| Toxicity profile | N/A | MA related, no ≥ grade 3 Drug related AEs | MA related, no ≥ grade 3 Drug related AEs | MA related, no ≥ grade 3 Drug related AEs | MA related, no ≥ grade 3 Drug related AEs | MA related, no ≥ grade 3 Drug related AEs | N/A |
| Clonal dominance | Yes (JMGA2 genotype) | No | No | No | N/A | No | N/A |
| Post-Rx leukemia | No | No | No | No | No | No | No |
| RCL | No | No | No | No | No | No | No |

**Table-1: Summary of outcomes of the gene therapy trials**

**Abbreviations:** AEs= adverse effects, BMH= Bone marrow harvest, DP-VCN= Drug product vector copy number, G-CSF= Granulocyte-colony stimulating factor, g/dl= grams per deciliter, MA= myeloablation, mo= months, N= number of patients, N/A= not applicable, NMA= non myeloablation, PBSC= peripheral blood stem cells, Rx= treatment, RCL= Replication competent lentivirus, SCDS= Sickle cell disorder, TDT= transfusion dependent thalassemia, Tx= Transfusion, VCN= Vector copy number,
Abstract 1026

- Current Results of Lentiglobin Gene Therapy in Patients with Severe Sickle Cell Disease Treated Under a Refined Protocol in the Phase 1 Hgb-206 Study
- John F. Tisdale, et al. (BlueBirdBio)
- BB305 lentiviral vector Hb\textsuperscript{AT87Q}
- Cell dose 7.1 (3 – 8) x 10\textsuperscript{6} CD34+ cells/kg, VCN 4.0 (2.8 – 5.6) copies/diploid genome, 81 (78 – 88) % transduced cells.
- Neutrophil engraftment at a median of 19 (18 – 20) days
- Platelet engraftment was achieved at a median of 28 (12 – 64) days in 4 patients; pending in 2 patients.
- Grade ≥3 AEs
  - 2/11 patients - 4 events associated plerixafor mobilization/HSC collection: vaso-occlusive pain, hypomagnesaemia, vaso-occlusive pain, non-cardiac chest pain
  - Febrile neutropenia (n=5), stomatitis (n=4)
- Serious AEs in 3 patients: splenic hematoma, non-cardiac chest pain and mucosal inflammation.
- No graft failure, vector-mediated replication competent lentivirus, or clonal dominance
- 3 patients @ 3 months: Hb 11.7, 9.8, 9.2 g/dL, HbA\textsuperscript{AT87Q} 4.7 g/dL, 3.2 g/dL and 3.5 g/dL
- 1 patient @ 6 months: off transfusions, Hb 14.2 g/dL, 62% (8.8 g/dL) HbA\textsuperscript{AT87Q}, 36% (5.1 g/dL) HbS.
Abstract 1023

• Flipping the Switch: Initial Results of Genetic Targeting of the Fetal to Adult Globin Switch in Sickle Cell Patients
• Erica B. Esrick, et al.
• shRNAs (shRNAmiR) lentiviral vector (LVV) targeting BCL11A
• N = 3
• No Grade 3 or 4 AEs were attributed to mobilization and collection
• Cell doses 3.3 - 6.7 x 10^6 CD34+ cells/kg
• VCN 3.3 – 5.1 copies per cell
• >95% vector-positive CD34+-derived colonies.
• Neutrophil engraftment 22 days.
• 23.3% HbF, 51.8% HbS and 22.3% HbA
• HbF/(HbF+HbS) ratio of 29.7%.
• Adverse events observed from the start of conditioning until latest follow-up were consistent with myeloablative conditioning
• No product-related adverse events and no SCD-related complications.
<table>
<thead>
<tr>
<th></th>
<th>Hb A1</th>
<th>Hb F</th>
<th>HbS</th>
<th>%F / (%F+HbS)</th>
<th>Hb (g/dL)</th>
<th>HbF+ cells</th>
<th>Retic</th>
<th>LDH (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline(^1)</td>
<td>60.2%</td>
<td>0.3%</td>
<td>36.5%</td>
<td>0.8%</td>
<td>10.4</td>
<td>0.3%</td>
<td>11.5%, 4.5%</td>
<td>538*, 167</td>
</tr>
<tr>
<td>Day +31</td>
<td>74.3%</td>
<td>7.5%</td>
<td>15.6%</td>
<td>32%</td>
<td>10.9</td>
<td>15.4%</td>
<td>6.3%</td>
<td>229</td>
</tr>
<tr>
<td>Day +41</td>
<td>60.2%</td>
<td>14.0%</td>
<td>23.3%</td>
<td>38%</td>
<td>11.3</td>
<td>ND</td>
<td>4.7%</td>
<td>251</td>
</tr>
<tr>
<td>Day +62</td>
<td>39.5%</td>
<td>20.1%</td>
<td>38.0%</td>
<td>35%</td>
<td>10.8</td>
<td>47.6%</td>
<td>3.5%</td>
<td>237</td>
</tr>
<tr>
<td>Day +76(^2)</td>
<td>22.3%</td>
<td>23.3%</td>
<td>51.8%</td>
<td>30%</td>
<td>10.9</td>
<td>59.7%</td>
<td>3.8%</td>
<td>187</td>
</tr>
</tbody>
</table>

\(^1\)Prior to a routine monthly exchange transfusion  
\(^2\)64 days after last pRBC transfusion  
*Values from 2010, prior to patient’s first exchange transfusion
Abstract 2190

• Ex Vivo Gene-Edited Cell Therapy for Sickle Cell Disease: Disruption of the BCL11A Erythroid Enhancer with Zinc Finger Nucleases Increases Fetal Hemoglobin in Plerixafor Mobilized Human CD34+ Cells

• Moran K, et al. (Bioverativ/Sanofi and Sangamo)

• BIVV003 (ZFN targeting the GATA motif within an intronic erythroid-specific enhancer (ESE) of BCL11A)

• Healthy donors, plerixafor mobilization

• On target effect: >75% of alleles modified, measured by MiSeq deep sequencing

• 77% post-editing viability

• in vitro HbF protein levels and HbF+ cell frequencies within erythroid progeny of edited cells were increased by >4 and 3-fold

• Both alleles of BCL11A were targeted at 91-94% of edited cells within erythroid progeny

• High levels of replicable GATA-disrupting indel patterns

• Each edited allele contributed on average an additional 17.6% increase in HbF production in vitro

• Increase in HbF level for biallelic edited vs. unedited controls (3.4 fold)

• Injection of BIVV003 into immune-deficient NBSGW mice resulted in 21 weeks long-term engraftment
Abstract 1080

- Outcomes for Initial Patient Cohorts with up to 33 Months of Follow-up in the Hgb-206 Phase 1 Trial
- Kanter J, et al. (BlueBirdBio)

The first 7 patients (Group A) received DP from bone marrow harvested (BMH) HSCs and demonstrated stable but sub-optimal gene therapy-derived hemoglobin (HbA^{T87Q}).

Protocol was amended to include pre-harvest transfusions, increased target busulfan levels and a refined DP manufacturing process (Group B).

Group C treated under modified protocol and including DP manufactured from plerixafor-mobilized HSCs.

Group B had higher VCNs, cell doses and % transduced cells compared to Group A.

Toxicity profile was consistent with myeloablative conditioning.

Serious AEs were reported in 8 patients; vaso-occlusive pain (n=5) was most common.

No grade ≥3 DP-related Aes, no evidence of graft failure, veno-occlusive liver disease, replication competent lentivirus or clonal dominance.

Table 1. DP Characteristics, Total and Gene Therapy-Derived Hb, and Hemolysis Markers

<table>
<thead>
<tr>
<th></th>
<th>Cell Dose 10^6 CD34+ cells/kg</th>
<th>DP VCN (copies/diplided genome)</th>
<th>Transduced Cells (%)</th>
<th>PB VCN (copies/diplided genome)</th>
<th>Total Hb (g/dL)</th>
<th>HbA^{T87Q} (g/dL)</th>
<th>% Change from Baseline*</th>
<th>LDH</th>
<th>Total Bilirubin</th>
<th>Absolute Neutrophil Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A Median (min - max)</td>
<td>2.1 (1.6 - 3.1)</td>
<td>0.6 (0.3 - 1.1)</td>
<td>25 (8 - 42)</td>
<td>0.1 (0.1 - 0.8)</td>
<td>8.9 (7.1 - 11.4)</td>
<td>0.8 (0.5 - 1.3)</td>
<td>-24 (-49 - -61)</td>
<td>-46 (-67 - -67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B Patient 1313</td>
<td>2.2</td>
<td>1.4/3.3*</td>
<td>46/83*</td>
<td>0.6</td>
<td>11.0</td>
<td>3.2</td>
<td>-55</td>
<td>-64</td>
<td>-58</td>
<td></td>
</tr>
<tr>
<td>Group B Patient 1317</td>
<td>3.2</td>
<td>2.9/5.0*</td>
<td>90/95*</td>
<td>2.5</td>
<td>12.8</td>
<td>7.2</td>
<td>-29</td>
<td>-25</td>
<td>-69</td>
<td></td>
</tr>
</tbody>
</table>

*2 DP los per patient

*1 patient, still receiving chronic transfusions, is excluded
*negative (-) indicates decrease and positive (+) indicates increase

Figure 1. Change in Annualized VOEs at Last Visit Post-Treatment vs 2 Years Pre-Treatment

VOEs (vaso-occlusive events) include VOEs (vaso-occlusive crisis) or ACS (acute chest syndrome), with VOE described as pain episode lasting ≥2 hours and requiring care at medical facility; and ACS defined as an acute event with pneumonia-like symptoms and the presence of a new pulmonary infiltrate; Patient 1309 was excluded from this analysis since he was on pre-treatment RBC transfusions and has not experienced any VOEs post-Len/Nil/leno DP treatment.
Future Directions in Sickle Cell Gene Therapy

• Safe and efficient gene transfer
• Correction of long-term repopulating HSCs
• High-level and stable gene expression
• Gene modification is appropriately regulated
• Current insertion/editing is still semi-random (hitting innocent bystanders)
• Reduction of the risk of insertional mutagenesis, clonal dominance and cellular transformation
• Reduction of side-effects of myeloablation
Supplemental Slides
Plasmid for Transfer Vector pBB305

LentiGlobin BB305 provirus