Maximize Myeloablation Without Immunosuppression

(2x10^8 unsorted BM cells/Kg kept for rescue)

Bone Marrow Harvest

CD34+ cells

Vector + Cytokines

Maximize % Transduced HSCs

Testing and Release While Frozen

Bone Marrow Conditioning

Busulfex

Maximize Myeloablation Without Immunosuppression

(>2x10^6 CD34+/Kg) (Spontaneous Homing)

IV Infusion Transduced Cells
HPV569 (protocol LG001) vs BB305 (protocol HGB205)
Differences in vector’s structure

HPV569: protocol LentiGlobin LG001

BB305: protocol LentiGlobin HGB205

O.Negre et al., Current Gene Therapy 2015
# Hematological characteristics after gene therapy in lentiglobin protocols: β-Thalassemia Major Subjects

<table>
<thead>
<tr>
<th></th>
<th>Subject 1201</th>
<th>Subject 1202</th>
<th>Subject 1203</th>
<th>Subject 1206</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype</strong></td>
<td>β0/βE</td>
<td>β0/βE</td>
<td>β0/β0</td>
<td>β0/βE</td>
</tr>
<tr>
<td><strong>Neutrophil engraftment</strong></td>
<td>Day + 13</td>
<td>Day + 15</td>
<td>Day + 28</td>
<td>Day + 16</td>
</tr>
<tr>
<td><strong>Platelet engraftment</strong></td>
<td>Day + 17</td>
<td>Day + 24</td>
<td>Day + 24</td>
<td>Day + 18</td>
</tr>
<tr>
<td><strong>Non-laboratory ≥ Grade 3 Serious Adverse Events</strong></td>
<td>• Mucositis</td>
<td>• Mucositis</td>
<td>• Mucositis</td>
<td>• Mucositis</td>
</tr>
<tr>
<td></td>
<td>• Premature menopause</td>
<td>• Herpetic gingivostomatitis</td>
<td>• Wisdom tooth infection</td>
<td>• Diarrhea (grade 2) • Vomiting (grade 1)</td>
</tr>
<tr>
<td><strong>Number of infused CD34+ (10⁶/Kg)</strong></td>
<td>8.9</td>
<td>13.6</td>
<td>8.79</td>
<td>15.1</td>
</tr>
<tr>
<td><strong>Months needed for Hbβ^{AT87Q} stabilisation after gene therapy</strong></td>
<td>4.5</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>g/dL of Hbβ^{AT87Q} at the stabilisation after gene therapy</strong></td>
<td>7.1 - 7.3</td>
<td>9 - 9.5</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Characteristics of subject with severe sickle cell disease (1204)

<table>
<thead>
<tr>
<th>Indication for transplant</th>
<th>Age at Consent</th>
<th>Sex</th>
<th>Genotype</th>
<th>pRBC Transfusion Requirement (mL/kg/year)$^a$</th>
<th>Cell source</th>
<th>CD34$^+$ VCN in Drug Substance $^b$</th>
<th>CD34$^+$ Cell Dose (x10$^6$/kg)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple VOCs</td>
<td>13</td>
<td>Male</td>
<td>$\beta^S/\beta^S$</td>
<td>170</td>
<td>Bone marrow</td>
<td>1.2 / 1.0</td>
<td>5.6</td>
<td>6M</td>
</tr>
<tr>
<td>ACS$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent cerebral infarct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ mean pRBC requirement per year, over the past 2 years prior to consent

$^b$ VCN= number of vector copies per diploid genome

$^c$ ACS=acute chest syndrome

### Clinical safety for infused subject

<table>
<thead>
<tr>
<th></th>
<th>Subject 1204</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>$\beta^S/\beta^S$</td>
</tr>
<tr>
<td>Neutrophil engraftment</td>
<td>Day + 37</td>
</tr>
<tr>
<td>Platelet engraftment</td>
<td>Day + 91</td>
</tr>
<tr>
<td>Non-laboratory $\geq$Grade 3 AEs</td>
<td>None</td>
</tr>
<tr>
<td>SAEs post-infusion</td>
<td>None</td>
</tr>
</tbody>
</table>
Globin-chains detection after gene therapy by HPLC

Hemoglobin g/dL

Hb tot = 10.5 g/dL
Hb T87Q = 7.3 g/dL
HbE = 2.7 g/dL
HbF

Hb tot = 8.2 g/dL
Hb T87Q = 6.4 g/dL
HbE = 2.7 g/dL
HbF

Hb tot = 13.5 g/dL
Hb T87Q = 10.1 g/dL
HbE = 2.7 g/dL
HbF

Hb tot = 10.6 g/dL
Hb T87Q = 7.9 g/dL
HbE = 2.2 g/dL
HbF

* Last follow-up
Months after GT
Globin-chains detection after gene therapy by HPLC: SCD patient

18 months: 12.5 g/dL of Hb tot and 6.4 g/dL of Hb T87Q!

Necker’s results by RP-HPLC
% of HbT87Q at the same time point after gene therapy
Vector copy number in the subpopulations: 1201 and 1202

Graph showing the change in vector copy number (VCN) over months after gene therapy (GT) for subpopulations 1201 and 1202.

Legend:
- PBMC
- T cells
- B cells
- Monocytes
- Neutrophils
Correction of dyserythropoiesis

Red blood cells (x10^6/µL)

Reticulocytes (x10^5/µL)

Months after GT

HGB205-1201

HGB205-1202

HGB205-1203

HGB205-1206
Correction of dyserythropoiesis in the SCD patient
SCD patient’s oxygen dissociation curve at 12 months of follow-up is similar to asymptomatic heterozygote.
Severe SCD Subject 1204: Improvement in clinical status and hemolytic markers at 12 months

**Pre-Treatment**

- **Transfusions**: Chronic transfusions
- **Clinical Status**: Multiple hospitalizations before starting transfusion regimen
- **Hemolysis**: Baseline reticulocyte count $238.3 \times 10^9$/L and LDH 626 U/L while on transfusions

**1 Year After Treatment**

- **Weaned off transfusions**: Last transfusion on Day + 88 (> 9 months ago)
- **No hospitalizations or acute SCD-related events**
- **Reticulocytes**: $143.1 \times 10^9$/L
- **LDH**: 274 U/L

Data as of November 10, 2015
Preliminary Conclusions

- Both the HGB-205 (France) and HGB-204 (US) studies demonstrate continued promise of gene therapy with LentiGlobin BB305 Drug Product in β-thalassemia major.

- Early results with gene therapy with LentiGlobin BB305 Drug Product show sufficient vector-derived hemoglobin production to reduce or eliminate transfusion requirements.

- The safety profile is consistent with autologous transplantation, without gene-therapy related adverse events, and with tri-lineage engraftment and polyclonal reconstitution.

- HGB-205 (France) shows promising data in the first subject with severe sickle cell disease treated with gene therapy with positive clinical signs and production of anti-sickling hemoglobin (45%, and still increasing) at 6 months well above the threshold (30%) that may show meaningful therapeutic effects.
Coût de la thérapie génique aujourd’hui et demain

Greffe autologue CSH : 30 000 €
Greffe allogénique CSH = 100 000 €, Greffe incompatible : 350 000 € et 1 000 000 €
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