Treatment of delayed-union fractures of long bones with minimally invasive administration of allogeneic bone-forming cells differentiated from mesenchymal stem cells: a pilot clinical trial

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Wendy Sonnet¹, Carolina Aznar-López², Anna Tury¹, Ching Man Choi², Florian Crokaert², Sandra Pietri², Delphine De Troy², Olivier Delahaut³, Arndt P. Schulz⁴,⁵, Martijn van Griensven⁶, Richard Witvrouw⁷, Lothar Seefried⁸, Marc Jayankura⁹ and Guy Heynen²
DELAYED-UNION FRACTURES: A LARGE MARKET WITH VERY LIMITED THERAPEUTIC OPTIONS

- > 700,000 delayed-union cases p.a. worldwide
- 5+% increase p.a. of fracture market
- “Wait & See” is current standard of care
- High disease burden
INNOVATIVE TECHNOLOGY FOR BONE REPAIR BASED ON DIFFERENTIATED BONE-FORMING CELLS

Aspiration

Purification

Amplification and differentiation

Bone-forming cells

Administration in long bones

Healthy donor

Patient

Bone Marrow

Mesenchymal stem cells

ALLOB

Bone Therapeutics
ALLOB PRESENT OSTEO-INDUCTIVE AND OSTEOGENIC PROPERTIES

AMPLIFICATION OF NATURAL PROCESS OF REGENERATION (OSTEO-INDUCTIVE)

- Secretion of bone factors
- Recruitment of patient's cells
- Re-creation of a healthy bone environment

INITIATION OF BONE FORMATION (OSTEOGENIC)

- Local action at bone site
- Replacement of missing/defective bone cells
- Formation of new bone
DESIGN OF A FIRST-IN-MAN STUDY

ALLOB-DU1 Phase I/IIa Pilot Open Multicentre Non-Controlled Trial

**Study objectives:** Safety & efficacy of a single administration of ALLOB cells in the treatment of delayed-union (DU) fractures

**Key inclusion criterion:** Patients with non infected DU fracture (3-7 months post fracture) of a long bone (femur, tibia, fibula, humerus, ulna and radius)

**Countries:** Belgium, Germany

**Target number of patients:** maximum 32 treated patients
- Safety population n=22
- Efficacy population n=21
MINIMALLY-INVASIVE IMPLANTATION PROCEDURE

Screening | Treatment
---|---
Baseline assessment | Safety & efficacy

2 Weeks Follow-up | 1 Month Follow-up | 3 Months Follow-up | 6 Months Follow-up

Baseline assessment | Safety & efficacy | 12 and 24 months safety follow-up

**ALLOB** (2/3/4 ml*)

*Volume of IMP depending upon the size of the fracture interline and surgical approach chosen by the Investigator*

Percutaneous administration via a trephine

Local, loco-regional or general anaesthesia

24- or 48-hour hospitalization

* Volume of IMP depending upon the size of the fracture interline and surgical approach chosen by the Investigator
STUDY ENDPOINTS

SAFETY
- Occurrence of (Serious) Adverse Event ((S)AE)
- (S)AE suggesting immune-mediated reactions
- Immunogenicity

EFFICACY
Primary endpoint: Number (percentage) of responders at Month 6
Secondary endpoints:
- Clinical endpoints: Global disease evaluation (GDE) score, Pain at palpation (VAS)
- Radiological endpoint: Tomographic Union Score (TUS)
### PATIENT DEMOGRAPHY

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong> Mean (SD)</td>
<td>47.3 (13.96)</td>
</tr>
<tr>
<td><strong>Gender (Male/Female)</strong> n (%)</td>
<td>13 (59.1%) / 9 (40.9%)</td>
</tr>
<tr>
<td>Time (months) from fracture to implant Mean (SD)</td>
<td>6.59 (1.159)</td>
</tr>
</tbody>
</table>

### Fractured Bone

<table>
<thead>
<tr>
<th>Bone</th>
<th>n (%)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibia</td>
<td>8</td>
<td>36.4%</td>
</tr>
<tr>
<td>Humerus</td>
<td>5</td>
<td>22.7%</td>
</tr>
<tr>
<td>Femur</td>
<td>3</td>
<td>13.6%</td>
</tr>
<tr>
<td>Ulna</td>
<td>3</td>
<td>13.6%</td>
</tr>
<tr>
<td>Fibula</td>
<td>2</td>
<td>9.1%</td>
</tr>
<tr>
<td>Radius</td>
<td>1</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

### Type of Osteosynthesis

<table>
<thead>
<tr>
<th>Osteosynthesis</th>
<th>n (%)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External</strong> n (%)</td>
<td>3</td>
<td>13.6%</td>
</tr>
<tr>
<td><strong>Internal</strong> n (%)</td>
<td>19</td>
<td>86.4%</td>
</tr>
<tr>
<td>- Plate</td>
<td>13</td>
<td>68.4%</td>
</tr>
<tr>
<td>- Nail</td>
<td>4</td>
<td>21.1%</td>
</tr>
<tr>
<td>- Nail/Metal Crew</td>
<td>1</td>
<td>5.3%</td>
</tr>
<tr>
<td>- Nail/Screw</td>
<td>1</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

n=22
ALLOB WAS WELL TOLERATED IN ALL TREATED PATIENTS

A total of 56 Treatment Emergent Adverse Event (TEAE) were reported in 18 patients, of which:

- 53 were non-serious TEAE
- 3 non-serious TEAE were related to the IMP: oedema peripheral, arthralgia, pruritus
- 9 TEAE (among serious and non-serious) were classified as related to the procedure: oedema peripheral, arthralgia, pruritus, procedural pain, dysesthesia
- 3 serious TEAE were reported in two patients:
  - 2 of them were classified as “not related” by the PI, but “Likely related” by the Sponsor. These events were reported as Suspected Unexpected Serious Adverse Reaction (SUSAR): angioedema and urticaria

Concerning immunogenicity, it was observed that blood samples of about half of the patients contained donor-specific antibodies, either pre-existing or developed after administration.
PRIMARY ENDPOINT BASED ON RADIOLOGICAL AND CLINICAL CRITERIA

PATIENT RESPONDER at Month 6

- No rescue surgery
- The GDE score as perceived by the patient has improved by \textbf{at least 25\%} OR the TUS score has increased by \textbf{at least 2 points}

GDE score aims to assess patient general health. It uses a 100-mm VAS where 0 means the best possible health status (“very well”) and 100 means the worst possible health status (“extremely bad”).

TUS score aims to assess bone healing. The 4 cortical areas (anterior, posterior, laterals) at fractures site are evaluated on CT-scan by an independent reader and scored as followed:

- Grade 1 = Presence of cortical discontinuity and absence of callus
- Grade 2 = Presence of cortical discontinuity and callus
- Grade 3 = Absence of cortical discontinuity and presence of callus
- Grade 4 = Absence of cortical discontinuity and callus

The 4 sub-scores added up to obtain the TUS ranging from 4 to 16
RADIOLOGICAL PRIMARY ENDPOINT

• Tomographic Union Score (TUS) assessed on CT scan by an Independent Reader

The scores used in the imaging interpretation are:
Score 1 = Callus is Absent and Fracture line is Visible
Score 2 = Callus is Present and Fracture line is Visible
Score 3 = Callus is Present and Fracture line is Invisible
Score 4 = Callus is Absent and Fracture line is Absent

<table>
<thead>
<tr>
<th>TUS</th>
<th>Lateral cortex</th>
<th>Medial cortex</th>
<th>Anterior cortex</th>
<th>Posterior cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
100 % OF PATIENTS MET THE PRIMARY ENDPOINT

PATIENT RESPONDER at Month 6

- No rescue surgery

**AND**

- The GDE score as perceived by the patient has improved by **at least 25%** **OR** the TUS has increased by **at least 2 points**

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Overall (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rescue surgery</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>Improvement of GDE score by at least 25%</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (76.2%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (23.8%)</td>
</tr>
<tr>
<td>Increase of TUS (CT scan) by at least 2 points</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (76.2%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (23.8%)</td>
</tr>
<tr>
<td>Responder patients</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100%</td>
</tr>
</tbody>
</table>
76% of patients (16/21) achieved the minimum 2-point increase -> significant evolution of fracture healing (TUS Score)

1.9X improvement compared to set endpoint
SIGNIFICANT CLINICAL IMPROVEMENT IN GENERAL HEALTH AND PAIN

➢ 76% of patients (16/21) achieved the minimum 25% decrease for general health score -> significant evolution of clinical signs

➢ 1.8X improvement compared to set endpoint

* p < 0.05 / ** p < 0.01 / *** p < 0.001

n=21
CASE REPORT – PATIENT CASE 1

**Age:** 35 years old

**Gender:** Male

**Smoking Status:** Never used

**Fracture age:** 8 months

**Fracture:** Closed transverse fracture of left humerus

**Fracture Interline:** Below 0.5cm

**GDE change:** -16 (-61.54%)

**TUS change:** 6 (Baseline= 6; Visit#6= 12)
CONCLUSION AND NEXT STEP

- ALLOB was shown to be well tolerated
- At six months post-administration, 100% of the patients met the primary endpoint
- The results from ALLOB-DU1 study indicate that ALLOB was well tolerated and provide preliminary evidence for potential effectiveness in the treatment of delayed-union fractures

Next step: Submission clinical trial application (CTA) expected in H2 2019
Contact

Florian CROKAERT
Clinical Study Officer

Phone: +32 71 12 11 99  Fax: +32 71 12 10 01
E-mail: florian.crokaert@bonetherapeutics.com
Website: www.bonetherapeutics.com