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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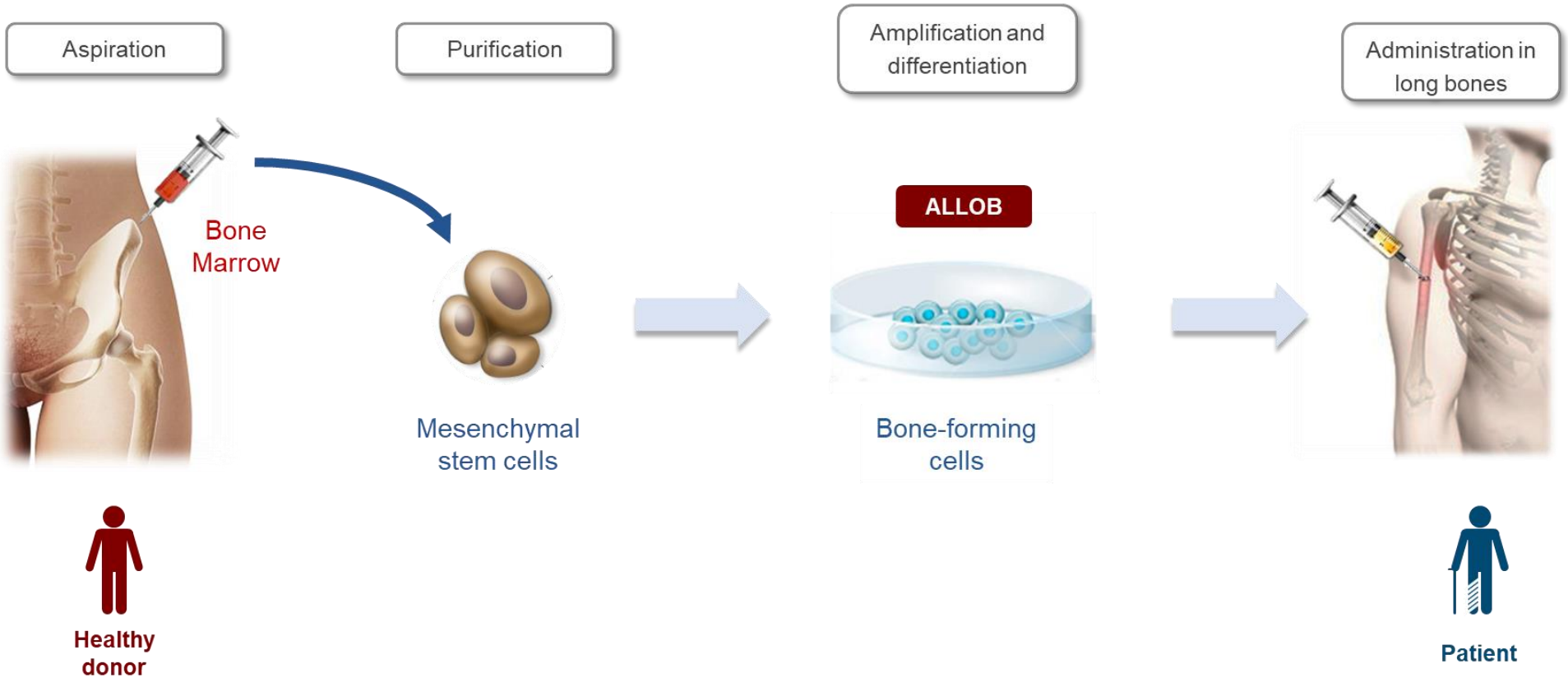
DELAYED-UNION FRACTURES:
A LARGE MARKET WITH VERY LIMITED THERAPEUTIC OPTIONS

> 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



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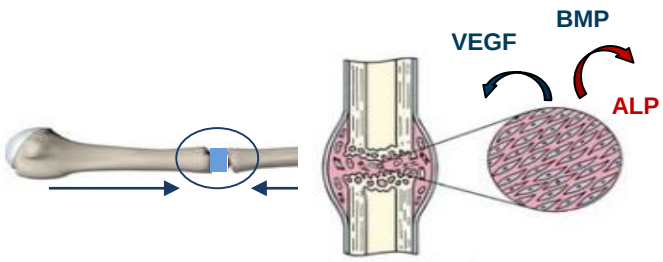
ALLOB PRESENT OSTEO-INDUCTIVE AND OSTEOGENIC PROPERTIES

AMPLIFICATION OF NATURAL PROCESS OF REGENERATION

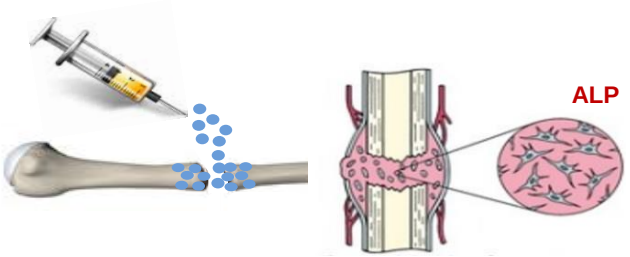
(OSTEO-INDUCTIVE)



- 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

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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

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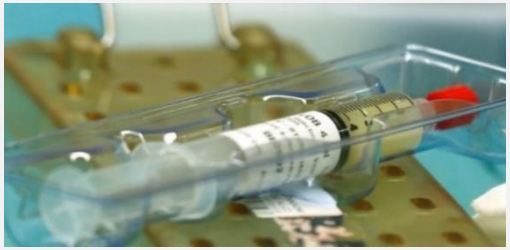
MINIMALLY-INVASIVE IMPLANTATION PROCEDURE

ALLOB

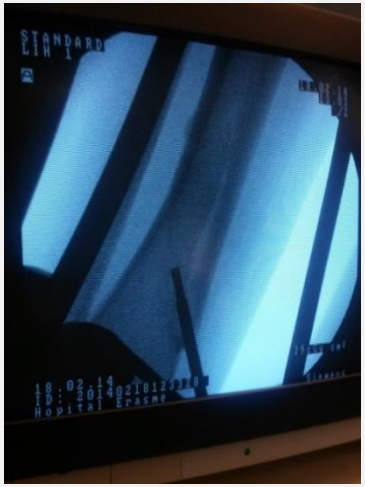
(2/3/4 ml*)

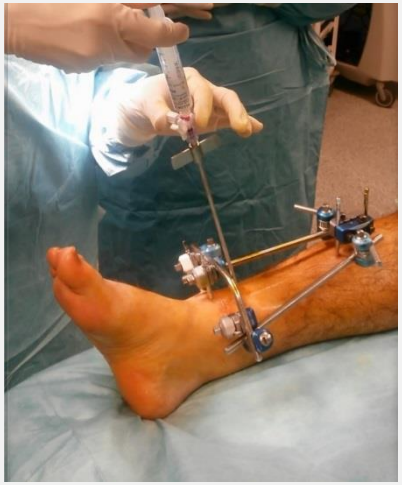


Percutaneous administration via a trephine

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

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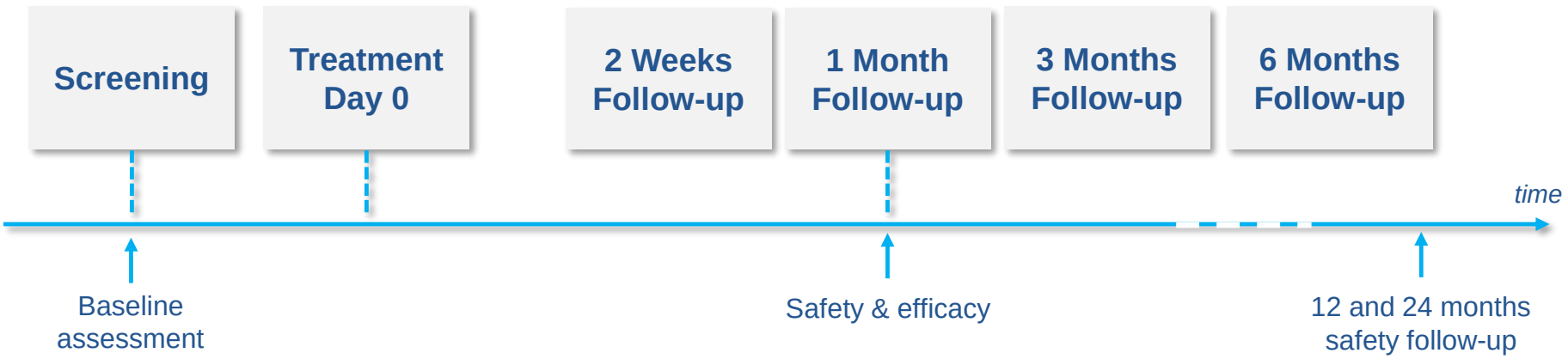
STUDY ENDPOINTS



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)

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PATIENT DEMOGRAPHY

	Statistics	Overall
Age (Years)	Mean (SD)	47.3 (13.96)
Gender (Male/Female)	n (%)	13 (59.1%) / 9 (40.9%)
Time (months) from fracture to implant	Mean (SD)	6,59 (1.159)
Fractured Bone		
Tibia	n (%)	8 (36.4%)
Humerus	n (%)	5 (22.7%)
Femur	n (%)	3 (13.6%)
Ulna	n (%)	3 (13.6%)
Fibula	n (%)	2 (9.1%)
Radius	n (%)	1 (4.5%)
Type of Osteosynthesis		
External	n (%)	3 (13.6%)
Internal	n (%)	19 (86.4%)
- Plate	n (%)	13 (68.4%)
- Nail	n (%)	4 (21.1%)
- Nail/Metal Crew	n (%)	1 (5.3%)
- Nail/Screw	n (%)	1 (5.3%)

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.

n=22

PRIMARY ENDPOINT BASED ON RADIOLOGICAL AND CLINICAL CRITERIA

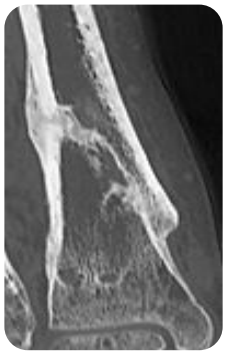
Primary Endpoint

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 score has increased by **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:

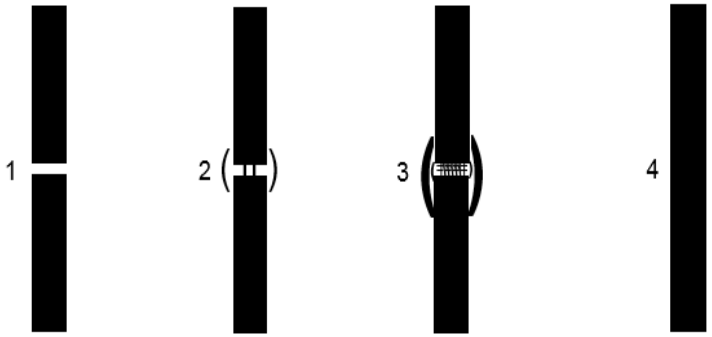
Score 1 = Callus is Absent and Fracture line is Visible

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

	TUS			
Lateral cortex	1	2	3	4
Medial cortex	1	2	3	4
Anterior cortex	1	2	3	4
Posterior cortex	1	2	3	4



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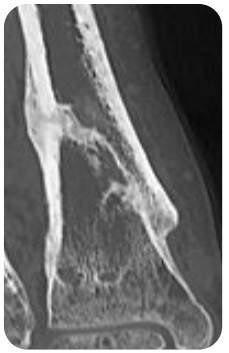
100 % OF PATIENTS MET THE PRIMARY ENDPOINT

PATIENT RESPONDER at Month 6

- No rescue surgery

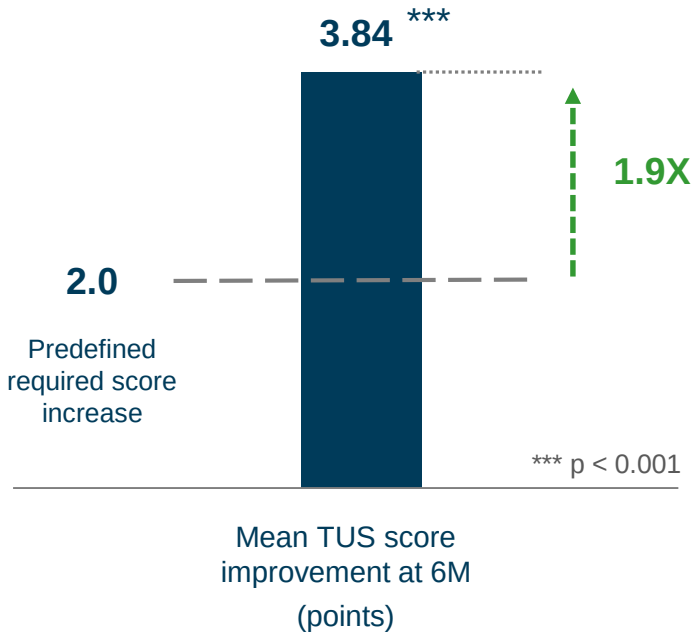
AND

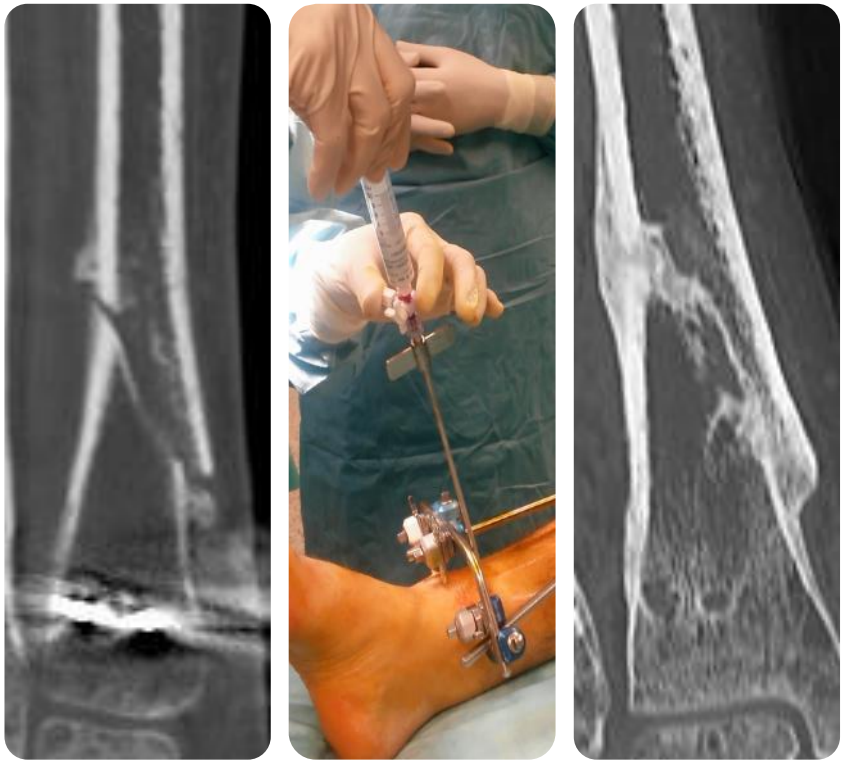
- The GDE score as perceived by the patient has improved by **at least 25%** *OR* the TUS has increased by **at least 2 points**



	Statistics	Overall (N=21)
No rescue surgery	n (%)	21 (100%)
Improvement of GDE score by at least 25%		
Yes	n (%)	16 (76.2%)
No	n (%)	5 (23.8%)
Increase of TUS (CT scan) by at least 2 points		
Yes	n (%)	16 (76.2%)
No	n (%)	5 (23.8%)
Responder patients		
Yes	Rate (%)	100%

SIGNIFICANT RADIOLOGICAL EVOLUTION OF FRACTURE HEALING





Baseline | Administration | Month 6

- 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

TUS: Tomographic Union Score * p < 0.05 / ** p < 0.01

n=21

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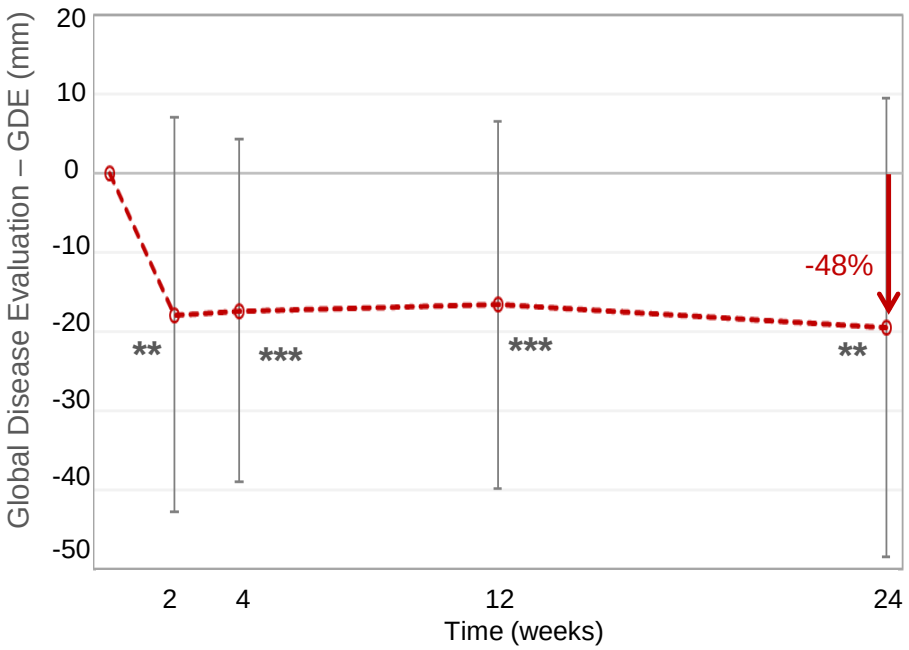
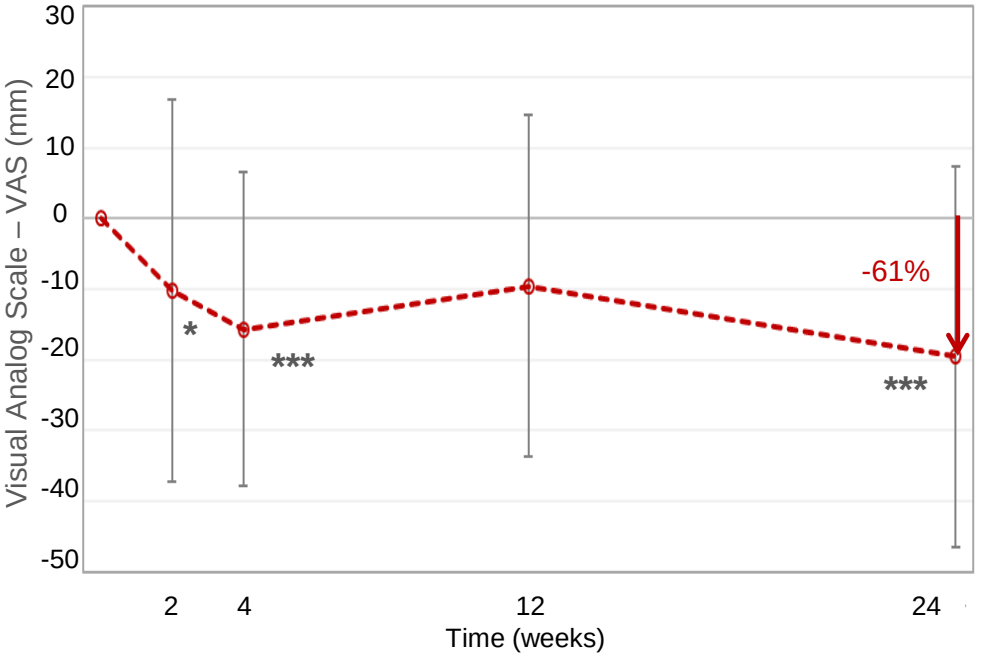
SIGNIFICANT CLINICAL IMPROVEMENT IN GENERAL HEALTH AND PAIN

General health status



Pain at palpation



- 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

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CASE REPORT – PATIENT CASE 1

Age: 35 years old

Gender: Male

Smoking Status: Never used

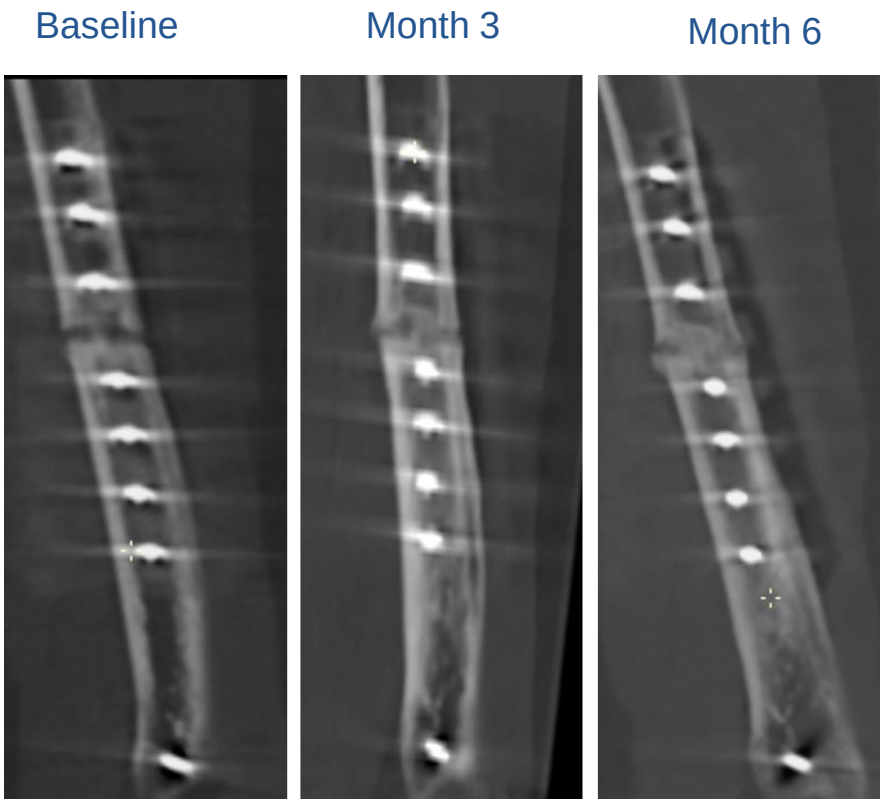
Fracture age: 8 months

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)



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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

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