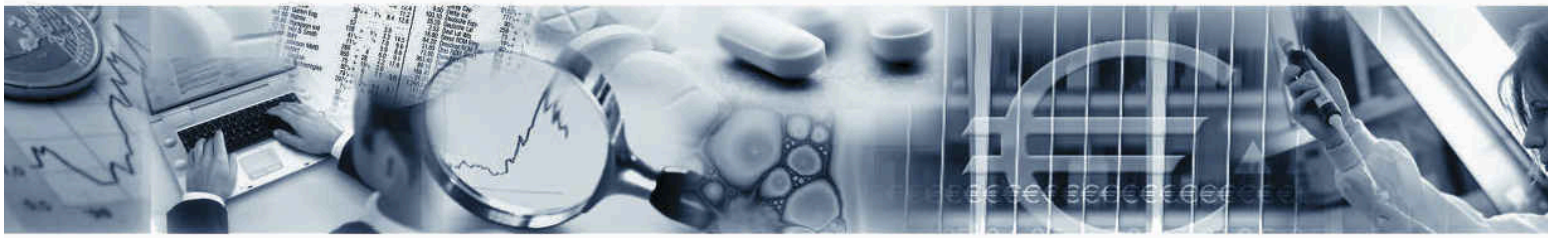

Research Note

Bone Therapeutics

At the Forefront in Regenerative Medicine

Chief Research Analyst

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Name:	**Bone Therapeutics**
Country:	**Belgium**
Price:	**EUR 8.31**
ISIN Code:	**BE0974280126**
Reuters Code:	**BOTHE.BR**
Market Cap (EUR m):	**56.9**
EV (EUR m):	**36.6**
Cash & cash eq. (EUR m):	**20.3**
Shares outstanding (m):	**6.85**
Volume:	**24,178**
Free float:	**75.3%**
52-week Range:	**6.34-16.99**

EUR million	2015A	2016A	2017E
Total Revenues	3.82	4.01	5.00
Net (Loss)/Profit	(14.09)	(13.02)	(12.00)
Net (loss)/profit ps	(2.06)	(1.91)	(1.75)
R&D costs	12.91	13.65	15.00
Cash increase/(decrease)	22.04	(13.31)	(14.00)
Cash and marketable sec.	33.61	20.30	6.30

Executive Summary

- Bone Therapeutics is a leading biotechnology company specializing in the development of cell therapy products intended for orthopaedics and bone diseases. The company is developing a range of innovative regenerative products containing osteoblastic/bone-forming cells, administrable via a minimally invasive percutaneous technique; a unique proposition in the market. The company's therapeutic areas include: Osteonecrosis, Non-union fractures, Delayed-union fractures and Degenerative spine disorders.

- The company has several programs in late stage development, which include: ALLOB® - an allogeneic osteoblastic cell therapy product and PREOB®, an autologous osteoblastic cell therapy product. ALLOB® is in Phase II for the treatment of delayed-union fractures and lumbar fusion for degenerative disease of the spine. PREOB® is currently in pivotal Phase IIB/III clinical studies for two indications: osteonecrosis and non-union fractures.

- The market space in which the Company operates covers hip surgery, fracture repair spinal implants, bone growth stimuli and orthobiologics (excluding the osteoporosis market) and represents a global market of around $ 25 billion for the treatment of around 12 million patients. The Company's products target about 2 million patients in Europe, the USA and Japan in this space1. The market addressed by the Company is characterized by high unmet medical needs.

- The Company's cash position at the end of 2016 is EUR 20.3 million which should be sufficient to carry out the further development of its pipeline into 2018Q2. Net cash used in operating activities during the full year ended December 31, 2016 was EUR 13.6 million, compared to EUR 12.2 million for the same period last year.

- **Based on NPV based valuation, we believe that Bone Therapeutics is substantially undervalued at the current share price of EUR 8.31. Using our valuation model and taking into account the future revenues from ALLOB® and PREOB®, the company's current total value should be EUR 103 million, or EUR 15.00 per share.**

[1] Orthoworld, The Orthopaedic Industry Annual Report for 2013 (relating to fracture repair procedures and spine procedures) – Transparancy Market Research, Osteoporosis Drugs Market – Global Industry Analysis, Pipeline Analysis, Size, Share, Growth, Trends & Forecast, 2014-2020 (relating to treatment of osteoporosis patients).

Company Profile & Technology Platform

Bone Therapeutics (BOTHE.BR) is a leading biotechnology company specializing in the development of cell therapy products intended for orthopaedics and bone diseases. The company is developing a range of innovative regenerative products containing differentiated osteoblastic/bone-forming cells, administrable via a minimally invasive percutaneous technique; a unique proposition in the market. The company's therapeutic areas include: delayed-union & non-union fractures, degenerative spine disorders and osteonecrosis Its primary clinical focus is ALLOB®, an allogeneic "off-the-shelf" cell therapy product derived from stem cells of healthy donors, which is in Phase II studies for the treatment of delayed-union fractures and spinal fusion. The Company also has an autologous bone cell therapy product, PREOB®, obtained from patient's own bone marrow and currently in Phase III development for osteonecrosis and non-union fractures.

In order to maximize value creation and ensure the best use of resources, the Company has decided to focus on:

1. The allogeneic platform ALLOB®, which the Company believes offers the strongest commercial and industrial perspectives and potential for partnerships based on clinical advantages and larger addressable markets. The Company will therefore focus resources on its allogeneic clinical programs in Europe. The Company has therefore decided not to initiate the clinical development of its autologous product PREOB® in the US.
2. Completion of the Phase III clinical trial in osteonecrosis to bring its first product to market. The Company believes this will clearly demonstrate and confirm the high added value of Bone Therapeutics' bone forming cell therapy products and propel the Company to the commercialization stage.
3. It recently announced that it has completed the recruitment of the 44 treated patients

required for the planned interim analysis of the Phase III trial for the treatment of osteonecrosis of the hip with its autologous bone cell therapy product, PREOB®. If results from this interim analysis, based on a 12-month follow up of patients document a strong efficacy signal for PREOB®, the study recruitment could be terminated prematurely. Results from the 12-month follow up are expected in 2018Q3.

4. The interim analysis will be based on an updated clinically relevant endpoint, endorsed by the European Medicines Agency, which reflects the value added to patients and uses a composite responder analysis combining the original co-primary variables, without impacting the design and data collection of the study. This more stringent primary endpoint criterion in the revised analysis has enabled a reduction of the number of patients to be enrolled, to 118 from 130. Also, as stated in the protocol approved by the Competent Authorities in the countries where the study is being conducted, a strong efficacy signal at the interim analysis could enable the early termination of the study. The study is underway at centres in Belgium, France, Germany, the Netherlands and the United Kingdom.

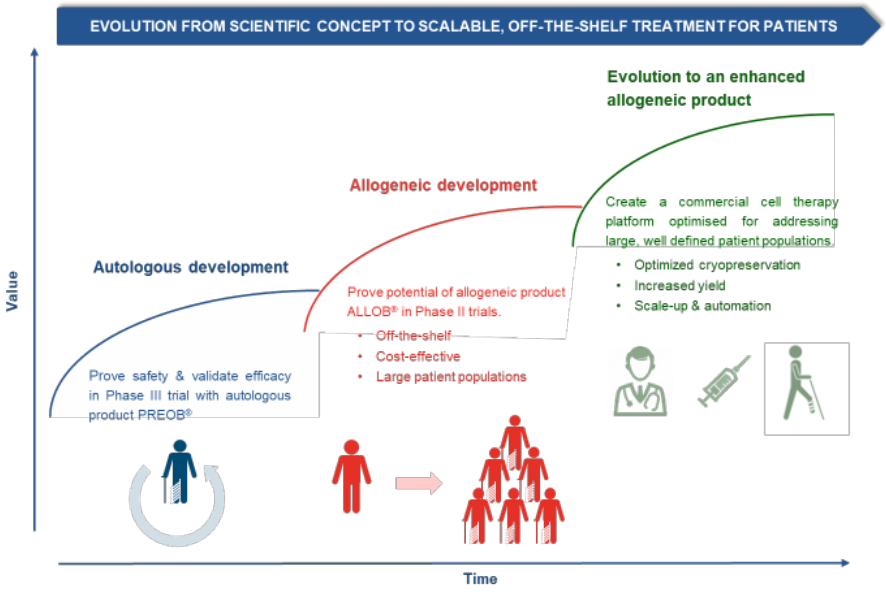
In line with recent priority resetting, the Company is putting more focus on its allogeneic programs. When the phase IIa interim results for the treatment of delayed-union fractures with ALLOB® will become available, the Company will evaluate the opportunity and the feasibility of addressing both – closely linked – indications (non-union and delayed-union fractures) in a single development program with ALLOB®. This could allow the Company to maximally capitalize on its investment in the allogeneic platform.

Business Strategy

The Company intends to leverage its R&D and manufacturing capabilities to efficiently expand its pipeline to indications for which it believes its products have therapeutic potential. The

accumulated data should reduce the time and costs associated with early-stage clinical trials for additional diseases and disorders. Its aim is to become a leading regenerative company in the field of orthopaedics and bone diseases by:

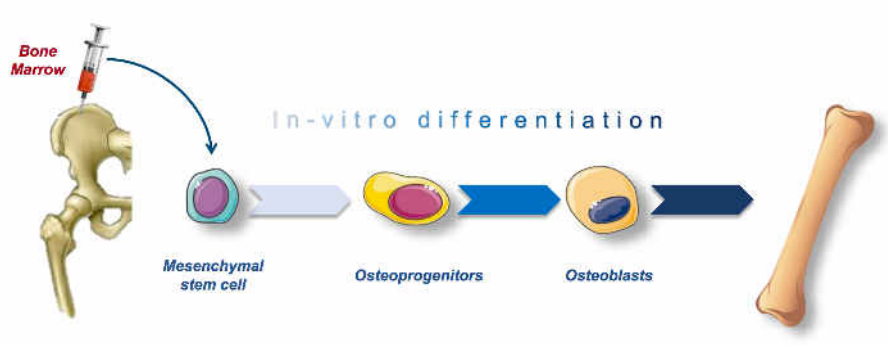
- Finalizing promising Phase I/II trials with its promising allogeneic product ALLOB® in larger indications better served with an allogeneic approach, and moving into late-stage studies
- Progressing and completing Phase III trials with its autologous product PREOB® to deliver proof of concept of a cell therapy in the field of orthopaedics and bone diseases to ultimately advance towards market authorization
- Scaling-up of manufacturing capabilities
- Building development and commercial partnerships
- Leveraging the cell differentiation platform and advancing the preclinical pipeline



The Company's strategy for selecting partners for osteonecrosis, non-union and delayed-union will be dependent on the region and indication. In Europe, the Company currently envisages pursuing a stand-alone approach for the development of its products although it may consider going into a partnership for distribution. In the US, the Company may consider looking for a partner to go into co-development. In Japan it will pursue licensing opportunities for its products and indications.

Technology Platform

The Company's technology platform is based on a unique approach in which mesenchymal stem cells (MSC), derived from bone marrow of patients or donors, are stimulated to differentiate into osteoblasts (i.e., bone-forming cells). There are two important types of cells in the body that are involved in bone homeostasis, namely osteoblasts and osteoclasts, which regulate the dynamic and constant remodeling of the skeleton.



Osteoblasts are responsible for bone matrix synthesis and subsequent mineralization, while osteoclasts resorb the bone. Local implantation of biologically active osteoblastic cells (pre-osteoblasts and osteoblasts) at the bone defect site is intended to mimic the natural process of bone formation and repair. More specifically, the mode-of-action is dual. On the one hand, the osteoblastic cells will replace the defective or missing osteoblasts by new osteoblasts that will form

new bone and repair the defective bone. On the other hand, the presence of osteoblastic cells will create a healthy bone environment by recruiting haematopoietic and osteoprogenitor cells and secreting matrix proteins. The implanted cells are expected to adhere onto the existing tissue and matrix, where they will produce new bone matrix that will be calcified. Finally, the cells will differentiate into osteocytes and become imbedded into the calcified new bone matrix.

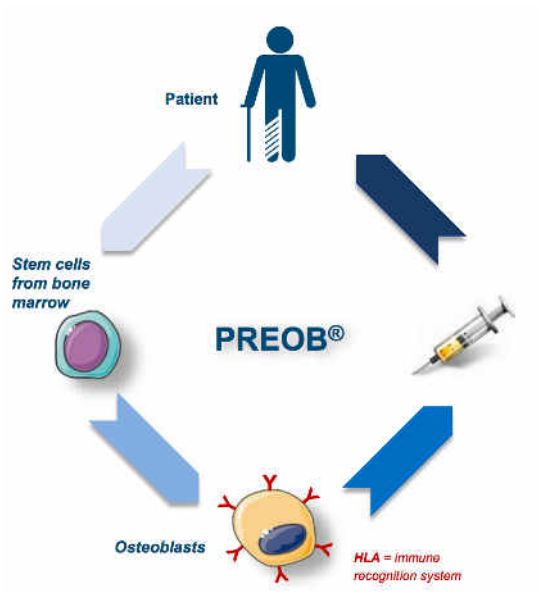
With its innovative technology to deliver differentiated cells, the company aims to deliver a product which provides:

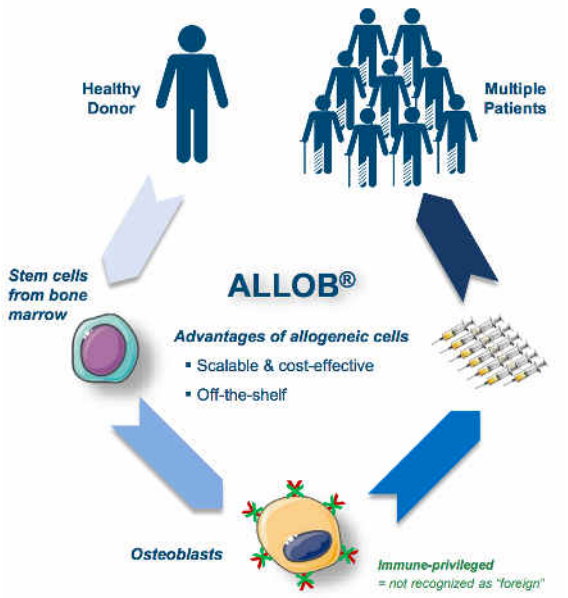
- Increased efficacy: bone forming cells perform better than MSCs – better bone forming capacity

- Safer in use: There are no unwanted cell types and there is no unwanted activity

Pipeline: Focus on ALLOB and PREOB

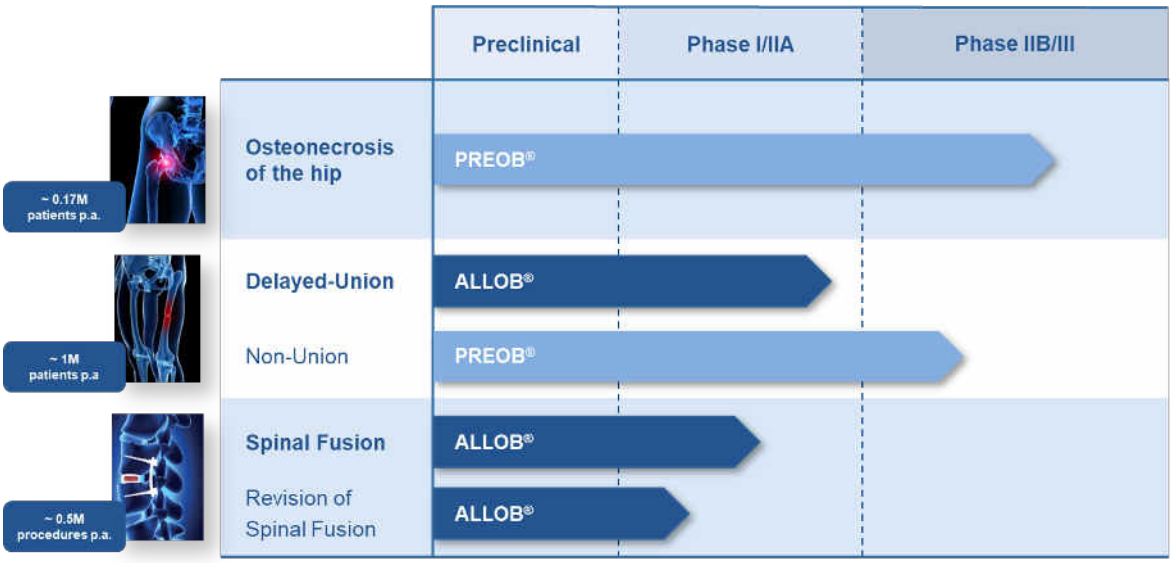
The Company has developed two first-in-class products, ALLOB® and PREOB®, which target five indications and offer the potential for additional product extensions. PREOB® is a cell-based medicinal product ("CBMP") derived from MSCs of patient's own bone marrow. A bone marrow aspirate is performed from the iliac crest of the patient under local anesthesia, after which MSC are isolated, expanded and differentiated. The active part of the product thus comprises human autologous osteoblastic cells – including pre-osteoblasts and osteoblasts. The manufacturing process is performed in strict GMP compliance and follows procedures that ensure aseptic manufacturing, full traceability, and quality control.





ALLOB® is the Company's allogeneic product that consists of human allogeneic bone-forming cells derived from cultured bone marrow MSC of healthy adult volunteer donors. ALLOB® has been

classified as Tissue Engineered Product (non-combined) by the EMA. ALLOB® cells express master osteoblast genes, mesenchymal and bone matrix adhesion markers and display bone-forming properties. The cells are able to adhere, synthesize and mineralize new bone matrix. Engraftment of the ALLOB® cells as well as bone-forming and bone repair capacity was demonstrated in mouse models by local administration at the defect site.

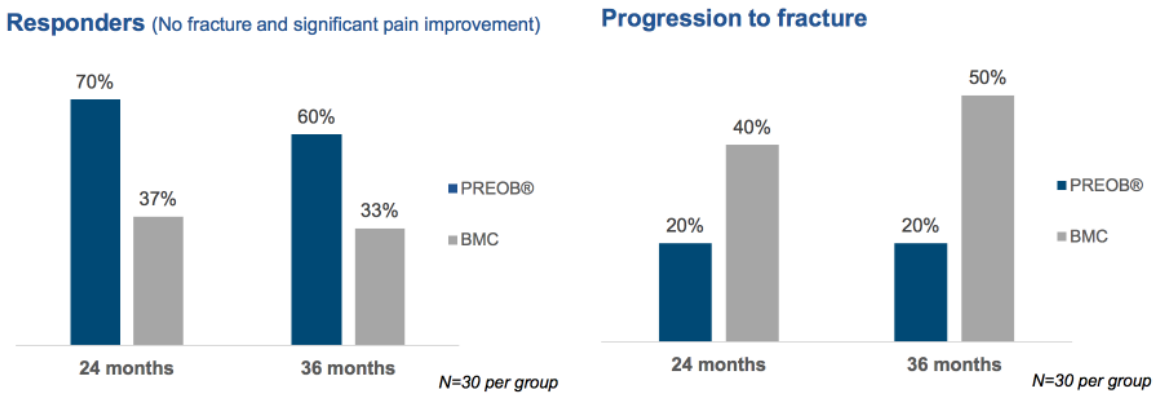


Source: Bone Therapeutics

PREOB in Osteonecrosis of the hip

At the EULAR of June 2016 data of the Phase IIB osteonecrosis study was published. The objective of this study was to evaluate the safety and efficacy of a single PREOB® administration in a randomized comparison with the current standard of care (bone marrow concentrate implantation BMC) in osteonecrosis of the hip. Out of 63 patients (hips) treated, 60 were assessable for efficacy analyses (n=30 PREOB®, n=30 BMC). The primary efficacy endpoint was the proportion of responders at 24 months, with responders defined as the absence of progression to fracture and a clinically significant pain improvement. The results show that at 24 months, only 37% of patients

(hips) in the standard of care group had responded to treatment versus 70% of the PREOB® group (p=0.011) and that the proportion of hips that progressed to fracture was reduced by 50% by PREOB® group versus standard of care. Similar results were observed at 36 months. In terms of clinical improvement, which was measured using the WOMAC pain scale, patients treated with PREOB® had a clinically relevant and statistically significant improvement in joint pain and function at all study time points (from 3 to 36 months), compared to no improvement in patients treated with the standard of care. PREOB® is currently being evaluated in a European Phase III trial for osteonecrosis.

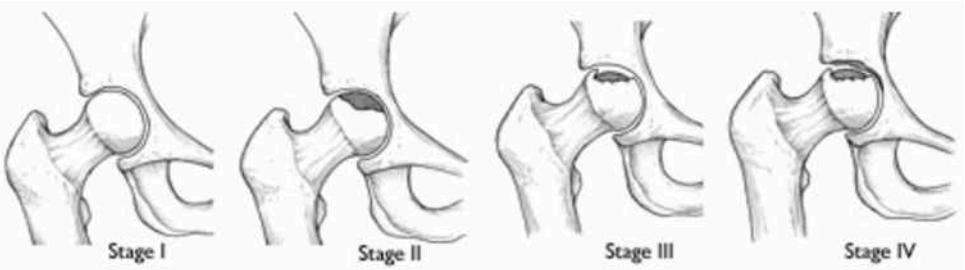


The study is currently recruiting 118 patients in a 1-to-1 versus placebo. Primary endpoints are absence of progression to fractural stage and clinically significant pain improvement. Early June, Bone Therapeutics announced that it completed the recruitment of 44 patients that are required for the planned interim analysis of the Phase III trial. If this analysis show a strong efficacy signal for PREOB®, the study recruitment could be terminated prematurely. Results are expected in 2018Q3.

The interim analysis will be based on an updated clinically relevant endpoint, endorsed by the European Medicines Agency, which reflects the value added to patients and uses a composite

responder analysis combining the original co-primary variables, without impacting the design and data collection of the study. This more stringent primary endpoint criterion in the revised analysis has enabled a reduction of the number of patients to be enrolled, to 118 from 130.

Osteonecrosis of the hip is characterized by the death of bone cells and loss of the associated marrow elements. It is a painful condition in which the joint degenerates progressively, ultimately leading to collapse of the femoral head, requiring a total hip replacement. Different stages of osteonecrosis can be distinguished of which stages I & II represent the stages before fracture and stages III & IV the stages after fracture. The condition typically affects people between the ages of 30 and 50, for whom hip replacement is not an appropriate long-term solution due to the limited lifespan of prostheses. Generally, the disease leads to a total hip replacement in less than two years and this before the age of 40 in half of the patients. Osteonecrosis is recognized as an orphan disease with more than 170,000 patients in the US, Europe and Japan. There is a highly unmet medical need with very limited therapeutic options.



Osteonecrosis can progress from a normal, healthy hip (Stage I) to the collapse of the femoral head (Stage IV).

Reproduced with permission from Beaule PE, Amstutz, HC: Management of ficat stage III and IV osteonecrosis of the hip. J Amer Acad Orthop Surg 2004; 12: 96-105.

ALLOB in Delayed-Union Fractures

The ongoing Phase I/IIA study is a six-month open-label trial to evaluate the safety and efficacy of ALLOB® in the treatment of delayed-union fractures of long bones. Patients receive a single percutaneous administration of ALLOB® directly into the fracture site. The study is targeting the recruitment of 32 patients, but is flexible and could be prematurely stopped on the basis of efficacy after an interim data analysis of the first 16 patients. To date, eight patients with a fracture that had failed to consolidate after a minimum of three and a maximum of seven months, have completed the six-month follow-up without any treatment-related safety concerns. In this cohort of eight patients, radiological scores showed a statistically significant improvement of 77% at six months. Overall, pain at the fracture site improved by 68% and health status by 50% at six months (all statistically significant).

A delayed-union fracture is defined as a fracture that has not united within a period of time that would be considered adequate for bone healing for severe fractures. Inadequate reduction of a fracture leading to instability or poor immobilization may be a reason for delay in fracture union. Other factors such as age, smoking, alcohol consumption or a medical condition can increase the risk of a delayed-union. Currently a "wait and see" approach is mostly adopted in the treatment of delayed-union fractures, sometimes for several months, which delays the patient's return to a normal life.

There are more than 1 million patients per year suffering from delayed-union fractures with very limited treatment options. ALLOB® would offer a viable therapeutic option for this high unmet medical need by offering a minimally invasive procedure in a situation where patients remain untreated today.

ALLOB in Lumbar Spinal Fusion

Spinal fusion is the current standard of care for degenerative disc disease in which an interbody cage with bioceramic granules is implanted to achieve fusion of the lumbar vertebrae resulting in pain relieve and functional improvements. However, progression to fusion with current treatments is slow, usually taking 18 to 24 months. Furthermore, the surgery may result in lack of fusion and continuing pain, leaving up to 35% of patients unsatisfied with their surgery.

The company has initiated a Phase IIA trial in lumbar spinal fusion designed to evaluate the safety and initial efficacy of the addition of ALLOB® to the standard of care procedure for degenerative disc disease. The aim is to decrease the failure rate of spinal fusion surgeries. Primary endpoints of the study are radiological evaluation of fusion, improvement in pain and functional disability and safety. In October 2016, the company reported positive safety and preliminary efficacy data for the Phase IIA spinal fusion trial with ALLOB®. The initial results of the first 8 patients in the study showed that more than 85% of the patients were responders according to the study protocol. The study targets a recruitment of 32 patients and the company has completed the recruitment of the first 16 patients required for the interim analysis. Results of the interim analysis is expected during late summer 2017 following a follow-up period of 12 months. Completion of recruitment of 32 patients is expected around year end. Development in the US is under evaluation and is subject to the positive Phase IIA results.

Lumbar spinal fusion leads to around half a million procedures per year of which up to 35% show failure. There is clearly a high unmet medical need with a high demand for fusion promoting measures. ALLOB® would be able to improve the success rate and could limit the number of complex rescue procedures. This would lead to lower costs while the patient show quicker and better recovery.

Near Term Milestones

In the coming 12 months we expect a number of important mile stones that can drive the stock price upwards. These are:

- 2017Q3: Interim analysis ALLOB® Delayed-Union – 16 patients
- 2017Q3: Interim analysis ALLOB® Spinal Fusion – 16 patients
- 2017Q4: Completion recruitment 32 patients ALLOB in Spinal Fusion
- 2018Q3: DSMB Report PREOB® in Osteonecrosis
- 2018Q3: Initiation Phase IIB ALLOB® in Delayed-Union (if interim analysis is conclusive)

Analyst: Marcel Wijma MSc
Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoeck Research (VLR) to SNS Securities in 2006, he established an award winning analyst team in biotech/life sciences at SNS Securities. In 2009, Marcel was awarded by Financial Times/Starmine as being one of the Top-3 biotech analysts in Europe. Later that year, Marcel purchased VLR from SNS Securities after which the company was reconstituted. At VLR, he leads the professional VLR research organisation, which is augmented by selected external financial researchers with a specialisation in Life Sciences. Mr. Wijma has a Masters degree in Financial Economics from Erasmus University in Rotterdam.