European Medicines Agency
Evaluation of Medicines for Human Use

London, 19 November 2009
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REFUSAL ASSESSMENT REPORT
FOR
GEMESIS

International Nonproprietary Name:
becaplermin

Procedure No. EMEA/H/C/000997

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The Applicant BioMimetic Therapeutics, Ltd. submitted on 17 March 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Gemesis, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Licensing status:
Gemesis is marketed as a medical device outside the European Union (in USA and Canada).

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Cristina Sampaio** Co-Rapporteur: **Ian Hudson**

CHMP Peer reviewer(s): Pirjo Laitinen-Parkkonen

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 17 March 2008.
- The procedure started on 26 March 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2008.
- On 16 July 2008, the Biologics Working Party (BWP) adopted a recommendation to the CHMP for the list of questions related to quality aspects.
- During the meeting on 21-24 July 2008, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant. The final consolidated List of Questions was sent to the Applicant on 24 July 2008.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 16 January 2009.
- The summary report of the inspection carried out at the following site(s) AAI Pharma Inc. between 28-29 August 2008 was issued on 1 December 2008
- The Rapporteurs circulated the Joint Assessment Report on the Applicant’s responses to the List of Questions to all CHMP members on 27 February 2009.
- On 9-11 March 2009, the Biologics Working Party (BWP) adopted a recommendation to the CHMP for the list of outstanding issues related to quality aspects.
- During the CHMP meeting on 16-19 March 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the Applicant.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant’s responses to the List of Outstanding Issues to all CHMP members on 9 June 2009.
- During the BWP meeting on 15-17 June 2009, outstanding quality issues were addressed by the Applicant during an oral clarification before the BWP and the BWP adopted a recommendation to the CHMP with respect to quality aspects.
- The Rapporteurs circulated the Updated Joint Assessment Report on the Applicant’s responses to the List of Outstanding Issues to all CHMP members on 23 June 2009.

- During the CHMP meeting on 23 June 2009, outstanding issues were addressed by the Applicant during an oral explanation before the CHMP.
- During the meeting on 20-23 July 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Gemesis on 23 July 2009.

1.3 Steps taken for the re-examination of the CHMP Opinion

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: Dr. Tomas Salmonson Co-Rapporteur: Dr. Sol Ruiz

- On 22 September 2009, the applicant submitted the detailed grounds for the re-examination of the grounds for refusal.
- During the plenary meeting on 21-24 September 2009, the CHMP nominated the experts of the ad-hoc expert group on Gemesis to be held on 10 November 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 26 October 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 26 October 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's grounds for reexamination to all CHMP members on 6 November 2009.
- On 10 November 2009 the ad-hoc expert group on Gemesis considered the questions from the CHMP and considered the oral clarifications provided by the applicant on the grounds for re-examination.
- During the meeting on 9-11 November 2009, the BWP adopted a recommendation to the CHMP with respect to quality grounds for re-examination.
- On 13 November 2009, the ad hoc expert group circulated their report.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's grounds for reexamination to all CHMP members on 13 November 2009.
- During the meeting on 16-19 November 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Gemesis on 19 November 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Periodontal disease is a chronic inflammatory condition, resulting from long-term bacterial (plaque) accumulation on the surfaces of teeth, affecting the supporting tissues of the dentition. It is generally a progressive, destructive condition that leads to loss of bone and periodontal ligament, resulting in poor oral and systemic health and compromised dental function. Treatment of mild forms of the disease is usually accomplished through non-surgical procedures. Moderate to severe disease requires surgical intervention to allow thorough removal of diseased tissue (defect debridement) and incorporation of techniques designed to regenerate the periodontium. The most common periodontal regenerative procedure is osseous grafting, which utilises autogenous, allogenic or alloplastic (synthetic) bone grafting materials to physically fill the intrabony defect and provide the scaffold upon which cells of the periodontium are able to attach and deposit matrix, eventually leading to regeneration of the affected site.

Although the gold standard for regenerative grafting procedures is autogenous bone transplant (autograft), the use of synthetic grafting materials is less inconvenient for the patient. One such synthetic material which has been shown to yield successful clinical results in the treatment of periodontal defects is beta-tricalcium phosphate (β-TCP). β-TCP is a porous, biocompatible, biodegradable (resorbable) sintered ceramic material, which has been used in a variety of bone grafting procedures in dental, maxillofacial and orthopaedic surgery for over 25 years.
Gemesis was developed for use only in adult patients as a synthetic grafting system for bone and periodontal regeneration in the treatment of periodontally related defects, including intrabony/infrabony periodontal defects and gingival recession associated with periodontal defects.

The product is a kit for implant that contains becaplermin (recombinant human platelet derived growth factor, rhPDGF also called rhPDGF-BB), as the active substance, presented as a sterile formulation in a syringe at a concentration of 0.3mg/ml and a CE-Marked bone void filler, β-tricalcium phosphate (β-TCP). After combining the becaplermin medicinal component with the β-TCP medical device matrix, the mixture is implanted into the bone defect. Becaplermin is the same active substance as in the centrally authorised product Regranex.

The rationale for combining becaplermin and β-TCP is that in this combination:

- β-TCP provides a mineralised bone-like scaffold which aids in preventing the collapse of soft tissues and promotes stabilisation of blood clots; this scaffold provides a framework for revascularisation and penetration by connective tissue cells that deposit bone matrix, leading to regeneration of the original defect;

- becaplermin substitutes for PDGF (platelet derived growth factor) which is one of the body's main initiators of healing, whether the injury is in soft tissue (e.g. the gingiva) or hard tissue (e.g. bone). PDGF has chemotactic (i.e. it stimulates directed migration of cells) and mitogenic (proliferative) properties. In addition, it stimulates osteoblast type I collagen synthesis, the predominant component of bone matrix as well as many types of connective-tissue cells including those of the periodontium, i.e. periodontal ligament (PDL) fibroblasts, cementoblasts, and osteoblasts.

Gemesis has been approved as a Class III combination product regulated as a medical device in the USA (PMA P040013, November 2005) and as a Class IV combination product regulated as a medical device in Canada (Device Licence No. 71464, May 2006). Gemesis is marketed as a medical device in the USA and Canada under the invented name GEM 21S. In view of its claimed properties, Gemesis is considered to fall within the definition of a medicinal product in the European Union and has to comply with the EU medicinal product legislation. Scientific Advice was not sought for the development of Gemesis.

The marketing authorisation application dossier for Gemesis was submitted as a full application through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

2.2 Quality aspects

Introduction

Gemesis is presented in the form of a kit for implantation. It consists of a sterile formulation of the i) active substance, becaplermin (recombinant human platelet-derived growth factor BB homodimer) presented in a pre-filled syringe, at a concentration of 0.3mg/ml and ii) a CE-marked medical device: a pre-filled cup containing a bone-void filler, β-tricalcium phosphate (β-TCP).

More specifically, the Gemesis kit contains the following components:

- 0.5 ml of becaplermin (0.3 mg/mL) aseptically filled into a Hypak 1 ml borosilicate glass syringe with a butyl rubber stopper in a sealed aluminum tube with an inner lacquer. An application device is included to provide reproducible doses.

- 0.5 ml of synthetic β-TCP in granule form (nominal particle size 250 to 1000 μm) provided in a clear plastic polyethylene terephthalate-glycol (PETG) laminate cup heat-sealed with a pre-printed foil lid; the cup is terminally sterilised by gamma irradiation.

Drug Substance

- Manufacture

Manufacturing process

The active substance becaplermin is manufactured by two manufacturers in the U.S.A. in compliance with Good Manufacturing Practice (GMP). An inspection of these manufacturers was not deemed necessary for the purpose of the evaluation of the drug substance.

The manufacturing process has been appropriately described and documented. The in-process controls used to monitor the production process are considered acceptable. The manufacturing process was appropriately validated (on the basis of 3 batches for fermentation/recovery and 3 batches for purification). Major concerns are however raised by the CHMP with respect to the occurrence of forms with reduced potency.

Source materials used for the production of becaplermin

The company provided appropriate documentation on the generation of the host yeast strain, the construction of the expression plasmids which followed standard genetic manipulation of yeast strains, the sources of the DNA components and the cloning strategy.

A two-tier cell banking system is in place for the production of becaplermin in accordance with EU guidelines. An initial Master Cell Bank (MCB) was prepared following transformation of S. cerevisiae with the expression plasmid. The Working Cell Bank (WCB) was prepared from a thawed vial of the MCB. The characterisation tests carried out on the MCB and WCB are in accordance with current regulatory standards and results were satisfactory.

The genetic stability (structure and copy number) during storage of cell banks and throughout and beyond normal production was confirmed with studies from three fermentations. Cells were harvested at the end of three fermentations processes and tested as End of Production Cells for purity, phenotype marker retention, plasmid copy number, plasmid structural integrity by restriction mapping and plasmid structural integrity by sequence analysis. The results showed that plasmid retention and copy number decreased over fermentation. However, the decrease was not substantial and does not affect the overall yield of becaplermin. Post-production cells were generated from the End of Production Cells and also tested. Overall, results confirm the genetic stability of cell banks and during production and support the production fermentation limit proposed by the company.

Characterisation and impurities

Characterisation studies establish that each molecule of the becaplermin dimer is a homodimeric glycosylated protein consisting of antiparallel polypeptide chains joined by two interchain disulphide bonds. Each monomer also contains three intra-chain disulphide bonds. Reduction of the inter-chain disulphide bonds results in loss of biological activity.

During synthesis and purification of becaplermin, a number of post-translational modifications occur, which result in a complex mixture of molecules present in the drug substance.
Appropriate control of these drug substance related impurities is considered critical.

- Specification

The specifications for the routine testing of bulk drug substance are in compliance with ICH Q6B ("Specifications: Test procedures and acceptance criteria for biotechnological/biological products - CPMP/ICH/365/96"). Tests include identity by peptide mapping, protein content, bioburden, purity, bacterial endotoxins, host cell protein, and total DNA.

Biological activity is measured using a mitogenic bioassay. The potency of becaplermin is determined by comparison to a qualified in-house reference standard and the results are expressed as percentage potency relative to the standard. The qualified reference standard is calibrated against the international WHO international standard for PDGF-BB (94/728).

Except for the test and specification for forms with reduced potency, analytical procedures were adequately justified, documented and validated and specifications are considered to be appropriate for the routine control of the bulk drug substance.

- Stability

The stability of the drug substance has been monitored in well controlled and justified stability studies under normal and accelerated storage conditions. Results from a sufficient number of commercial batches (12 commercial batches) support the claimed shelf life under the proposed storage conditions. The stability was also confirmed over several rounds (five) of freezing and thawing.

Drug Product

Most of the information presented in the application pertain to production of the pre-filled becaplermin syringes with additional data on biocompatibility with the β-TCP matrix. Much of the data relating to the device component itself has already been assessed as part of the CE certification and therefore did not require evaluation by the CHMP.

- Pharmaceutical Development

The active substance is formulated with appropriate compendial excipients (see table below) in a 1 ml borosilicate glass syringe.

- with a butyl rubber stopper. An application device is included to provide reproducible doses.

- 0.5 cc of synthetic β-TCP provided in a clear plastic polyethylene terephthalate-glycol (PETG) laminate cup heat-sealed with a pre-printed foil lid; the cup is terminally sterilised by gamma irradiation.

Composition of becaplermin solution

Component		Function	Quality
rhPDGF-BB		Growth/chemotactic factor	Manufacturers specifications
Sodium acetate trihydrate		Buffer to pH 6.0	Ph. Eur. 0411
Hydrochloric acid		pH adjustment	Ph. Eur. 0003
Sodium hydroxide		pH adjustment	Ph. Eur. 0677
Water for injection		Diluent	Ph. Eur. 0169

The pre-filled syringe with formulated becaplermin is presented together with a medical device: β-tricalcium phosphate (β-TCP) granules contained in a heat sealed laminate cup which is terminally sterilised by gamma irradiation. Both the becaplermin and β-TCP are mixed to form the product administered to the patient.

The medical device (β-TCP cup) called "GEMatrix" is certified by a CE-certificate (CE number CE06.20400.01) issued by a European Notified Body (TNO Certification B.V.) on 16 May 2007.

According to the certificate:

- the device falls in the category of calcium phosphate bone void fillers for non-load bearing applications;

- the device consists of β-TCP ceramic granules (0.5cc +/- 5%) packed in a laminate cup, heat sealed using a PET/PE/Foil lid, and provided gamma sterile (min 25kGy). The expiry date of 36 months when stored below 30°C has been approved.

The same device was used throughout product development including clinical and release studies and is the same as the device proposed for commercial use.

The company has performed studies to evaluate the compatibility of becaplermin with the β-TCP matrix once both components are mixed. The set of tests included purity, related substances, and a bioassay . Following assessment of test results, it is considered that the studies performed are not sufficient and that the compatibility of becaplermin with the β-TCP matrix has not been unequivocally demonstrated.

Changes to the manufacturing process (manufacturing site transfer and scale-up) were introduced during development of the product and comparability data to demonstrate that changes did not affect the quality of the product were evaluated and considered insufficient. Although the comparability exercise confirmed compliance with specifications of lots before and after the manufacturing changes, further investigation of the occurrence of forms with reduced potency for which specifications are lacking and the impact on disulfide bridges is considered necessary to confirm that changes did not adversely impact on the quality of the commercial product.

- Manufacture of the Product

The becaplermin pre-filled syringe is manufactured and controlled by a manufacturer in compliance with GMP and also tested by a second manufacturer. The medical device (β-TCP cup) is manufactured by another manufacturer. The becaplermin pre-filled syringe and the medical device are assembled and packaged by a manufacturer in compliance with GMP. Compliance with GMP for each site proposed for the sterilisation of the components of the final becaplermin syringe container closure system has not been demonstrated and evidence of satisfactory EU GMP inspections is required.

The method of manufacture of the becaplermin pre-filled syringe is a simple process consisting of thawing drug substance bulk, dilution in buffer, sterile filtration and aseptic fill into pre-sterilised syringes. This process is adequately described and documented and is controlled by adequate in-process controls.

Formulation and filling into syringes has been validated for three commercial scale batches. Maximum filled syringe holding time has been validated. Batch analysis for a number of commercial size lots was provided and satisfactorily demonstrates that the manufacturing process is capable of producing lots conforming to the defined specifications. Shipping of bulk drug substance from the USA to the manufacturer in the UK has been validated and is acceptable.

Batches for the EU are released based on the final packaged Gemesis kit and not just on becaplermin pre-filled syringes. The proposed batch release site is not acceptable for the batch release of biological products.

- Product Specification

Overall, the tests included in the drug product specifications are consistent with the tests included in the drug substance specifications and have been adequately validated. In addition to tests already performed on the drug substance and following evaluation, the company agreed to revise the specifications to include mass variance of filled units. Stability specifications have also been set, identifying appropriate stability indicating parameters. Specifications have only been partly justified. Of major concern is the inappropriate justification in terms of cross-reference to the quality of the material used in clinical trials and the inappropriate justification for not having a specification for forms with reduced potency at the level of the drug product.

- Stability of the Product

Overall, the container closure system has been detailed and is of a suitable quality for the proposed use. Microbial integrity of the filled container closure system has been demonstrated against a suitable challenge. The proposed shelf life of 36-month for becaplermin syringes when stored protected from light at 5+/- 3°C is supported by data from long-term stability studies conducted using 3 commercial-scale batches. Under accelerated conditions, the drug product does not appear to be very stable regarding impurities and related substances. Data regarding purity are not provided for the early time-points before 12 months and so it is difficult to assess whether the product will be stable to short-term temperature excursions (e.g. during transfer from the formulation and filling site and from this site to patients via distributors). The company provided more comprehensive data, from accelerated stability studies to

support temperature excursions. Results from the potency assay demonstrate a high assay variability, which the company committed to investigate and optimise. Calibration of becaplermin used in clinical trials material to the WHO reference standard (e.g. to support the conversion factor applied) has been confirmed and the Applicant committed to report and label in I.U./mg. Instructions regarding stability of becaplermin once mixed with β-TCP (i.e. maximum time before use) are included in the proposed product information. A concern with respect to a partition effect on product related impurities upon interaction with β-TCP is raised in relation to the occurrence of forms of reduced potency.

- Adventitious Agents

The materials of biological origin used in the manufacturing process of Gemesis are from animal and vegetable sources and have been sufficiently documented. These materials comply with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 2).

The TSE risk from these materials is negligible. Viral clearance/inactivation studies have not been presented for the drug substance and drug product. This is considered acceptable based on the risk of viral transmission from the materials of animal origin used in the manufacture of Gemesis which is considered low.

Discussion on chemical, pharmaceutical and biological aspects

Although to some extent, the data submitted provide evidence with respect to the quality of Gemesis, there are major issues related to the quality aspects of the product and their potential impact on efficacy and safety.

Comparability of the drug product

The company did not present convincing characterisation data to support the comparability of the drug product before and after the changes to the manufacturing process (i.e. change of site and scale) in relation to those forms that have a decreased biological activity. The method used for retrospective analysis of released batches does not distinguish between forms. Nevertheless the company presented an extensive characterisation for the qualification of reference standards. This was the only study presented where the content of other forms were performed using another method and demonstrated to be equivalent. The follow-up measure proposed by the company to analyse the previous clinical lots in terms of quantification of other forms by this other method was noted but at present and in the absence of data, it can not be concluded that no significant changes on the quality attributes occurred between the clinical batches and the commercial product.

Forms of reduced potency

The occurrence of high levels of forms with reduced bioactivity raises several concerns with respect to consistency of the quality of the product and its uniform clinical performance.

First, the company was not able to demonstrate that there is no partition effect on product related variants upon interaction with the β-TCP component. Results using the bioassay to quantify other forms and to demonstrate that there is no partition effect are not convincing given the wide variability of this bioassay and given that results are inconsistent with other results provided in the application. Therefore, a more direct quantification of the forms is required to unequivocally demonstrate that no partition occurs favouring the presence of less potent forms.

Second, there are high levels of forms of reduced potency in the drug substance and drug product which are not appropriately controlled. The company proposed to tighten the limit of the specification for other

forms in drug substance lots based on the claimed positive outcome of non-clinical and clinical data. The proposed reduction does not constitute a significant reduction of the other forms and it is not validated in light of the clinical results. Also, the possibility that the forms of reduced potency may also be a degradation impurity has not been adequately investigated and addressed. Since the possible partition effect cannot be ruled out, a significant reduction and adequate control of the other forms at the level of the drug product is important to ensure consistent product production and since these forms may have a detrimental impact on the uniform clinical performance of the product. It is possible that this will only be possible by making significant changes such as including additional purification steps for the drug substance.

2.3 Non-clinical aspects

Introduction

All toxicity studies presented were conducted in compliance with GLP. Exceptions to strict GLP compliance are the non-clinical pharmacology studies. These studies were performed under procedures similar to GLP requirements. The testing facilities were accredited (AALAS) facilities.

Pharmacology

The ability of rhPDGF-BB to activate all PDGF receptor combinations is considered key to its therapeutic utility by stimulating activities on cells that express either the α receptor, the β receptor, or both receptors. PDGF receptor binding and activation induces a number of cellular responses, including the stimulation of chemotaxis, mitosis and actin reorganisation, which are all critical events for appropriate tissue repair. The β-TCP component serves as an osteoconductive, resorbable bone void filler that prevents collapse of soft tissue and stabilises the blood clot. As the β-TCP is resorbed, bone and other connective tissues grow into the space previously occupied by the matrix. β-TCP is a porous, biocompatible, resorbable sintered ceramic material with a calcium:phosphate ratio similar to that of the hydroxyapatite phase of natural bone.

Primary Pharmacology studies include one dog study addressing the effects of Gemesis in periodontal defects and three additional non-clinical studies utilising Gemesis in other animal models (rabbit tibial defect, dog carpus arthrodesis, and rat calvarial defect).

Secondary Pharmacology studies were not conducted, based on the presumption that Gemesis components will be confined to the site of application, and on the low amount of the growth factor applied as combined to β-TCP (0.15 mg).

- Primary pharmacodynamics

The following in vivo pharmacodynamic studies were performed:

1. In this study the rat calvarial defect model was used to evaluate the effect on bone regeneration of test articles rhPDGF-BB (0.3 mg/mL and 1.0 mg/mL) and a control article (sodium acetate (NaAc) buffer) when used in conjunction with a β-TCP matrix and compared to an untreated surgical control group. A secondary purpose of the study was to assess the safety of these materials when implanted in the skull.

The outcome of this study was poor and failed to provide the intended evidence that β-TCP would improve bone growth and would lead to defect healing. The potential role of rhPDGF-BB was therefore not shown. No safety concerns were detected.

2. The study intended to evaluate the impact of rhPDGF-BB on remodelling in bone defects generated in a rabbit model. 30 New Zealand White rabbits were used. Unicortical, 5 mm osteotomies were created in

the proximal-medial tibial metaphyses of the animals. The animals were divided in three groups, treated with 1) β-TCP alone (control); 2) β-TCP containing 25 µg rhPDGF-BB (low concentration); 3) β-TCP containing 75 µg rhPDGF-BB (high concentration).

5 animals/group were euthanised at four and eight weeks after surgery and evaluated histologically.

The clinical and histological evaluations revealed that the three treatment groups responded equally well to the experimental treatments. The potential role of rhPDGF-BB was therefore not shown. There were no signs of toxicity observed in any of the treated animals and none of the treatments appeared to interfere with the formation of new bone across the drill hole.

3. This study evaluated the effectiveness of rhPDGF-BB in a dog model of bone fusion which consisted on the production of a partial arthrodesis of the radial carpal/3rd carpal and 3rd metacarpal done bilaterally in 30 dogs. 10 animals/group received 1) matrix only (autograft, β-TCP, or β-TCP/collagen) in Side A, and 2) the same matrix + rhPDGF-BB (0.3 mg/mL) in Side B.

The study showed that the addition of rhPDGF-BB to any of the matrices appeared to improve bone fusion when compared to matrix alone, and that the combination of the synthetic matrices with rhPDGF-BB was at least equivalent to autograft alone. The bone that formed in the treated joints was normal and no signs of acute or chronic toxicity were observed.

4. A dog periodontal defect model was used to assess the periodontal regenerative properties of rhPDGF-BB (0.3 mg/mL and 1 mg/mL) in combination with β-TCP or DFDBA (demineralised freeze-dried bone allograft, which is the current "gold standard" of care for a bone grafting material) in a randomised controlled way (study BMPI 2003-004). The non-clinical evidence for the effectiveness of Gemesis in a periodontal indication is derived from data generated in this beagle dog model of horizontal Class III furcation defects, which are critical-sized defects that would not otherwise heal.

60 defects were analysed in 15 animals. Clinical, radiographic and histomorphometric observations were performed in the animals at planned schedules. Treatment groups were analysed and biopsied at 8 weeks and at 16 weeks.

The selection of the rhPDGF-BB concentrations for this study was based on early experience in humans using rhPDGF-BB mixed with DFDBA for the treatment of periodontal defects, and biocompatibility data from tests conducted according to ISO 10993, where these concentrations were shown to be safe.

The results of 8 weeks post-treatment are summarised in the table below:

Histomorphometric Analyses Results at the 8-Week Time Point (mean ± standard deviation)					
Group	**Treatment**	**Bone fill [%]**	**Connective Tissue [%]**	**Void [%]**	**CNAA [%]**
1	β-TCP alone	28.0 ± 29.5	36.0 ± 40.99	12.0 ± 17.9	37.0 ± 22.8 [(d)]
2	β-TCP + 0.3 mg/mL rhPDGF-BB	84.0 ± 35.8 [(a, e)]	0.0 ± 0.0 [(c)]	8.0 ± 17.9	59.0 ± 19.1 [(b, e)]
3	β-TCP + 1.0 mg/mL rhPDGF-BB	74.2 ± 31.7 [(a)]	0.0 ± 0.0 [(c)]	0.0 ± 0.0	46.0 ± 12.3 [(b)]
4	DFDBA alone	6.0 ± 8.9	26.0 ± 19.5	30.0 ± 27.4	13.4 ± 12.0
5	DFDBA + 0.3 mg/mL rhPDGF-BB	20.0 ± 18.7	36.0 ± 13.4	18.0 ± 21.7	21.5 ± 13.3
6	DFDBA + 1.0 mg/mL rhPDGF-BB	46.0 ± 23.0 [(f)]	26.0 ± 5.48	8.0 ± 13.04	29.9 ± 12.4
7	Sham surgery (no graft)	34.0 ± 27.0	48.0 ± 35.64	10.0 ± 22.4	27.4 ± 15.0

(a) Groups 2 and 3 significantly greater than Groups 1, 4, and 7.
(b) Groups 2 and 3 significantly greater (<0.05) than Groups 4 and 7.
(c) Groups 2 and 3 significantly less ($p<0.05$) than Groups 4, 5, 6, and 7.
(d) Group 1 significantly greater ($p<0.05$) than Group 4.
(e) Group 2 significantly greater ($p<0.05$) than Group 5.
(f) Group 6 significantly greater than Group 4.

Overall the outcome was better when rhPDGF was combined with β-TCP than with DFDBA (Demineralised freeze-dried bone allograft).

Incorporation of 0.3 mg/ml rhPDGF-BB in β-TCP showed a better outcome than a higher dose of 1 mg/ml, evaluated by % bone fill, connective tissues, void and CNAA (complete new attachment apparatus). However the differences were not statistically significant. When compared to DFDBA alone, the 0.3 mg/ml and the 1 mg/ml rhPDGF-BB groups demonstrated trends for a positive dose-response even though the differences were only statistically significant for the increase in percent bone fill. The CHMP agreed with the Applicant that there may be no dose-response for rhPDGF-BB combined with β-TCP or with DFBA. However the CHMP pointed out that it could be that both doses (0.3 or 1mg/ml rhPDGF-BB) were too high and therefore at the ceiling of the dose-response curve or that the high variability in response may mask any statistical significance. In conclusion, the information available does not give a nonclinical support for the clinical dose selection, considering that the minimum effective dose should be used for safety reasons but might not have been determined.

In addition, to make human extrapolation of the animal results, the comparative pharmacological interactions of recombinant human PDGF (rhPDGF) in animals, particularly in dogs but also in rabbits and rats, and in human receptors has not been sufficiently clarified by the Applicant. An overview, prepared by the Applicant, of published studies showing comparative binding affinity of human PDGF

(hPDGF) to the target receptors of different species commonly used in toxicology studies suggest that no major binding differences of hPDGF across species exist. Nevertheless the more relevant values on comparative binding affinity of rhPDGF were not provided which reduces the value of the safety study results and again questions the basis for clinical dose selection.

- Secondary pharmacodynamics

Gemesis is implanted in patients as a single dose containing 0.15 mg rhPDGF-BB. Gemesis is not administered systemically and does not require systemic transport for availability. The applicant states that if the rhPDGF-BB component of Gemesis entered the circulatory system, in view of the short half-life of rhPDGF-BB and the small quantity of rhPDGF-BB delivered with the β-TCP (0.15 mg), the drug substance poses limited potential for systemic exposure or distribution to other organs or tissues. Consequently, no secondary pharmacology studies were conducted. This was deemed acceptable by the CHMP.

- Safety pharmacology programme

There were no adverse pharmacodynamic or pathophysiological effects observed in toxicology testing or in the clinical studies for Gemesis. Therefore, safety pharmacology studies were not warranted. This was deemed acceptable by the CHMP.

- Pharmacodynamic drug interactions

PDGF is a naturally occurring protein that is released from platelets at the site of an injury. As Gemesis is not administered systemically but is delivered locally, and is implanted in a single dose containing 0.15 mg rhPDGF-BB, the nonclinical programme did not include testing of rhPDGF-BB for drug interactions. This was deemed acceptable by the CHMP.

Pharmacokinetics

Classical ADME studies with Gemesis were not performed due to the fact that the product is mostly to be given for local single administration at a very low quantity (although repeated administration cannot be completely excluded). Even if rhPDGF-BB is reabsorbed from a local site of administration and reaches the systemic circulation, the amount to be distributed through tissues, then metabolised and eliminated might be low. Instead, Gemesis product was investigated with respect to the binding and subsequent release of biologically active rhPDGF BB from candidate bone substitute materials. The in vitro and in vivo studies determined characteristics of the rhPDGF BB/β-TCP interaction, and compared the release of rhPDGF-BB from different β-TCP matrix materials that might be used in dental surgery. Under procedures mimicking the proposed use of Gemesis in surgery, release of rhPDGF BB from various matrix materials was demonstrated to be equivalent. In addition, the availability of biologically active rhPDGF BB released from the various β-TCP matrices, and Gemesis in particular, was established and shown to be high during the first 30-60 min up to 72h after which around 90% of the protein was released. The remaining was seen to be slowly released up to 7 days. The release of rhPDGF from the site of application, and its subsequent disposition was discussed by the Applicant, and seems to be rapid, with distribution through several organs including thyroid, intestinal tract, and elimination in the faeces and urine (information from radioactivity evaluation). Therefore, there is a potential for organ exposure to rhPDGF which, though low or negligible after a single administration may be higher in case of multiple sites of application or repeated application.

Toxicology

- Single dose toxicity

Five single dose toxicity studies have been conducted in mice. Three of these studies investigated the acute systemic toxicity of rhPDGF-BB when combined with β-TCP from three different sources and the other two studies investigated the effect of aged rhPDGF-BB (without β-TCP). Extracts of the saturated matrix were used. The studies are more like quality "biocontrol" rather than a true acute toxicity test. No relevant toxicities were identified.

- Repeated dose toxicity

Only one rat repeated dose toxicity study is included in the file, which addressed the bone response to intramuscular injections of rhPDGF-BB for 2 and 8 Weeks. This in vivo study reassessed a previous study performed on rhPDGF-BB (Knight et al., 1998) except that this study examined longer term (8 week) effects. The purpose of this study was to evaluate the test substance, rhPDGF-BB, for its short and long term effects on muscle and bone tissues when injected multiple times in rats.

The Applicant's conclusion on this rat study was that rhPDGF-BB can be considered mildly reactive at a dose of 100 µg/mL in both soft tissue and skeletal tissue when injected in close proximity to skeletal tissues at volumes of 0.1 mL every other day for 2 weeks. This reaction was transient and was not present in either the soft tissue nor the skeletal tissue 6 weeks post final dose. These effects may be expected from the mechanism of action of rhPDGF-BB. Nevertheless, they were seen with 10 µg dose (0.1 mL of 100 µg/mL solution), which is more than 10 times less than the human dose proposed (150 µg single site dose). Although there might be a potential for increased (neighbouring) tissue reactivity in case of leakage of rhPDGF-BB from the site of application, it is acknowledged that the local reactivity by subcutaneous application could be higher as compared to a slower access of the molecule into neighbouring tissues, in particular the gingiva, the effect being difficult to differentiate from any reaction to the surgical process per se. rhPDGF-BB has not shown an effect in rat calvaria defect model, however, the model has been explained as appropriate to address the potential leakage of rhPDGF from the application site, but not appropriate to address efficacy. Given the uncertainty regarding the comparative pharmacological activity of rhPDGF in human and rodent species, it could not be clarified whether the rat reactivity pattern can be considered as a predictor for human tissue reactivity.

- Genotoxicity

Despite the fact that the rh-PDGF component of Gemesis might not need to be tested for mutagenic potential, since it is a recombinant human (biotechnology) protein, in vitro bacterial gene mutation assays were performed with extracts from β-TCP saturated with the rhPDGF-BB. The genotoxic concern (if any) could therefore be more derived from any (contaminating) component of the β-TCP matrix. All studies were negative. The concentration of rhPDGF used in these studies was lower than that to be used clinically, which questions the value of the study performed, since this may reflect also that the levels of matrix components reached in the extracts tested were insufficient for any potential to be detected. The Applicant has calculated that the concentration of rhPDGF at the site of application after one hour could be around 3.3 times lower than that in the test compound. Even if this would reflect the concentration of the matrix components also, such ratio is still insufficient. Immediately after application the local concentration could have been at the level of that in the test compound. A repetition of the genotoxicity study would have been necessary to clarify this point.

- Carcinogenicity

Carcinogenicity studies were not conducted with Gemesis. This is justified on the basis of the intended single application, with anticipated limited exposure duration and extension, since rhPDGF-BB will be

expected to be metabolised as any other protein and, even if distributed systemically, it would be of very low concentration and of short duration. Based on its activity as growth factor, only a persistent activation of receptors might be considered as a concern. Therefore, it was agreed with the Applicant that carcinogenicity studies were not warranted for the currently applied indication and short exposure duration. Gemesis is proposed to be contraindicated in patients with tumours. However, Gemesis could be used several times when several dental interventions are performed and therefore exposure may be extended into several multiples. In this perspective the labelling needs to reflect a concern for potential tumorigenesis.

- Reproductive toxicity

Reproductive toxicity studies were not conducted. The Applicant proposes that an effect of rhPDGF-BB on the bone foetal growth cannot be excluded. However, no studies to address the systemic distribution of the protein from the application site have been performed nor planned. The only study which has been conducted and might be meaningful with regard to this question is the proof of concept study performed in dogs. In at least one animal study blood sampling has been performed and preserved. Whether analysing the samples (if available) would be possible and meaningful has not been considered. The Applicant was requested to revisit this study and/or any others available in the literature where the systemic distribution of rhPDGF after periodontal application might have been evaluated. It has been concluded that the persistence at the site of application is short lasting and there is distribution through several organs followed by urinary and faecal elimination. Therefore transplacental passage and foetal exposure to rhPDGF cannot be excluded and this should be reflected in the labelling, excluding pregnant women from treatment. This is also important for labelling with respect to fertile women.

- Cytotoxicity

Assessments of potential cytotoxicity rhPDGF-BB + β-TCP (of different origins) was performed in mouse fibroblast cultures exposed to extracts of the rhPDGF-BB + β-TCP mixtures, β-TCP of the different origins also being tested in other studies. Neither test result showed cell lysis, indicating no evidence of cytotoxicity.

- Toxicokinetic data

No studies were performed but the CHMP requested calculations of the safety margins for the various safety data submitted in support of the approval of Gemesis. In a study to evaluate systemic toxicity, mice received a dose that exceeded the maximum human clinical dose (2.1 μg/kg body weight) by approximately 2,381-fold. No acute toxic outcomes were observed in the mice over a 7 day period following dosing in any of the studies conducted.
In a rabbit intramuscular implantation study of rhPDGF-BB combined with β-TCP the dose administered to rabbits exceeded the maximum human dose by approximately 24-fold. The Gemesis test article in these studies was evaluated histopathologically and found to be a slight irritant in comparison to controls 4 weeks after implantation.

A second rabbit study where aged rhPDGF-BB was injected intracutaneously and paravertebrally in five locations at a dose exceeding the maximum human clinical dose for Gemesis of approximately 36-fold the test substance was found non-irritant.

The CHMP acknowledged the further discussions of the Applicant on the calculation of "safety margins" for the rhPDGF used in the toxicity studies. The calculations however did not take into consideration the binding of rhPDGF to animal and human receptors, which might be acceptable in case no major difference exists.

- Other toxicity studies

Other studies conducted with Gemesis were irritancy, dermal sensitisation. As an added measure, rhPDGF-BB preparations stored for a minimum of 12 months at 5°C or 30°C were subjected to an abbreviated test panel to demonstrate there would be no new toxicity associated with use of rhPDGF-BB that might have been exposed to non-standard storage conditions. Also, intracutaneous irritation studies in rabbits have shown that VitOS, the matrix in Gemesis is of grade 2 potential, which was referred as not relevant. Since clinical information is available, this aspect will be better clarified from this information rather than from non-clinical data. Cytotoxicity studies using mouse fibroblasts also showed no evidence of toxic effects associated with aged rhPDGF-BB.

A number of standard non-clinical studies have not been performed with the Gemesis product, including pharmacokinetics/toxicokinetics, single-dose toxicity in a non-rodent species, and reproductive toxicology. Such assessments are not warranted for this product, based on the rationale that PDGF-BB is a naturally occurring protein, with a short half life, that is applied locally.

Ecotoxicity/environmental risk assessment

According to the CHMP Guideline on Environmental Risk Assessment (ERA) (EMEA/CHMP/SWP/4447/00) "Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment". Therefore Gemesis is not expected to pose a risk to the environment.

Discussion on the non-clinical aspects

Due to the fact that Gemesis is administered locally and implanted in a single dose containing 0.15 mg rhPDGF, a naturally occurring protein, the non-clinical program was abridged. The most relevant study for the human indication to treat periodontally related defects came from a dog periodontal defect model and gave only moderate evidence of efficacy. The lower dose of 0.3mg/ml rhPDGF appeared to be more effective than the higher dose of 1mg/ml, even though these differences were not statistically significant. Concerns were raised that both doses were too high and therefore at the ceiling of the dose-response curve or that the high variability in response may mask any statistical significance. Consequently the information presented did not give a non-clinical support for the clinical dose selection, considering that the minimum effective dose should be used for safety reasons but might not have been determined.
Furthermore, no studies were performed by the Applicant to study the affinity and interaction pattern of rhPDGF to the human receptors as compared to non-recombinant human PDGF, and to the target receptors in the species commonly used for pharmacology and toxicology studies. This reduces the value of the results of the safety studies performed and again questions the basis for clinical dose selection. The application of rhPDGF will be local, but a leakage from the site of application into periodontal tissue, namely the gingiva might be possible and the consequence is not clearly defined. Given the clinical experience with the matrix scaffold, no additional studies were requested. However, several concerns related to the safety of the rhPDGF were not sufficiently clarified by the Applicant. Overall the non-clinical dossier for Gemesis is only of moderate quality and the rationale for the inclusion of becaplermin (recombinant human platelet derived growth factor, rhPDGF) into the β-TCP scaffold was not strongly supported by the non-clinical program.

2.4 Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

No clinical data have been provided and this is partly justified. The Applicant failed to provide data on the amount of becaplermin bound to the matrix after both components are mixed, information on the resorption of the matrix over time, and data supporting that becaplermin is largely unavailable systemically.

No interaction studies have been performed. However, postoperative care includes analgesic and antibiotic treatment, and later, an antibacterial mouthwash such as chlorhexidine is usually prescribed. Relevant data from the clinical trial should have been used.

Pharmacodynamics

- Mechanism of action

The Applicant claims that becaplermin promotes the chemotactic recruitment and proliferation of cells involved in wound repair, thus promoting the growth of normal tissue for healing. The development program included in vitro and in vivo animal studies in order to demonstrate its potent (proliferative) and chemotactic (directed cell migration) effects on bone and periodontal ligament derived cells. β-TCP is frequently used as an osteoconductive synthetic bone substitute for numerous bone void applications. β-TCP provides a mineralized bone like scaffold for efficient penetration by connective tissue cells and subsequent stimulation of new bone.

- Primary and Secondary pharmacology

No clinical data have been submitted. The Applicant has provided a number of published references for in vitro experiments using animal and human cells including mainly PDL and gingival fibroblasts as well as osteoblasts. Other references relate to in vivo experiments in animal models using the rat, dog, miniature pig, and monkey. A significant number of these publications describe the results of the combination of growth factors, namely PDGF with IGF-I or TGF-1 β.

Clinical efficacy

Gemesis is intended for bone and periodontal regeneration in adult patients. The clinical development plan for the efficacy of Gemesis in the treatment of periodontally related defects (including intrabony/infrabony periodontal defects and gingival recession associated with periodontal defects) includes only one randomised, double blind, controlled, multicenter pivotal study (BMPI-2001-01). This study is summarised in the table below. Furthermore, the Applicant provided three publications as "proof of concept" studies, none of which are on the combination of rhPDGF-BB and β-TCP.

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
Study BMPI-2001-01	11 U.S. Centers	Randomised, Double-Blind, Controlled, Parallel-Arm	Group I: β -TCP + 0.3 mg/mL rhPDGF-BB Group II: β	Evaluate the Safety and Effectiveness of *Gemesis* for the Treatment of Periodontal Bone Defects	N=60 per group	10/05/02-07/05/03	At least 1 tooth requiring surgical intervention	Change in clinical attachment level (CAL) between baseline and 24 weeks comparing

	-TCP + 1.0 mg/mL rhPDGF-BB Group III: β-TCP + Buffer	Group I to Group III

- Dose response study(ies)

There are no specific dose-finding studies. The rhPDGF-BB concentrations for the provided clinical study were selected based upon previous clinical and non-clinical experience from different investigation groups. The clinical studies referred by the Applicant can be summarised as follows:

– Howell *et al*. (1997)
The primary objective of this study was to assess the safety of growth factors when applied to periodontal osseous defects in humans; a second objective was to investigate the therapeutic doses required to stimulate periodontal regeneration. Thirty eight patients with bilateral osseous periodontal lesions were assigned to one of two treatment groups in a split-mouth design: either a low dose (**0.05 mg/mL each** of rhPDGF-BB and rhIGF-I) or a high dose (**0.15 mg/mL each** of rhPDGF-BB and rh-IGF-I) in a gel vehicle. The control side was treated with periodontal flap surgery or surgery plus vehicle. Safety analyses included physical examination, haematology, serum chemistry, urinalysis, antibody titres, and radiographic evaluation of bony changes. The primary efficacy assessment was bone fill measured by surgical re-entry at 6 to 9 months.
No local or systemic issues were found, and no patients developed antibodies. Statistically significant increases in alveolar bone formation were noted for the high dose ($p<0.05$) at 9 months when compared to controls; this corresponded to an increase of 2.08 mm of new vertical bone height vs. 0.75 mm in the controls. No difference was seen at the low dose.

– Camelo et al. (2003)
The clinical and histological response to rhPDGF-BB delivered with demineralised freeze-dried bone allograft was evaluated in four advanced Class II furcation defects. rhPDGF-BB was applied on the root surfaces and saturated the bone allograft; two concentrations were used (0.5 mg/mL and 1.0 mg/mL, two cases each). Clinical probing depth and attachment levels were obtained pre-surgically and 9 months post-surgical, after which the teeth and surrounding tissues were removed en bloc.
Both concentrations of rhPDGF-BB resulted in substantially improved horizontal (mean 3.5 mm) and vertical (mean 4.25 mm) probing depths and clinical attachment levels (CAL; mean 3.75 mm). Histological evaluation revealed periodontal regeneration, including new bone, cementum, and periodontal ligament coronal to the reference notch.

– Nevins et al. (2003)
The regenerative effects of rhPDGF-BB incorporated in bone allograft for the treatment of interproximal intrabony and/or Class II furcation defects were evaluated in 9 adult patients (11 sites) with advanced periodontitis. The same methodology as in the previous trial was used; three concentrations of rhPDGF-BB were tested (0.5, 1.0 or 5.0 mg/mL). Four other sites were treated with an organic bovine bone (ABB). Clinical and radiographic data were analysed for change from baseline by defect type and rhPDGF-BB concentration. The histologic specimens were analysed for the presence of regeneration of a complete new attachment apparatus coronal to the reference notch.
Interproximal defects treated with rhPDGF-BB/DFDBA (n=6) had a mean vertical probing depth (vPD) reduction of 6.42 and a mean CAL gain of 6.17 mm. Mean radiographic bone fill was 2.14 mm. Furcation defects treated with rhPDGF-BB/DFDBA (n=5) exhibited mean horizontal and vertical PD reduction of 3.40 and 4.00 mm, respectively, and a mean CAL gain

of 3.2 mm. Histological evaluation revealed regeneration of a complete periodontal attachment apparatus, including new cementum, PDL, and bone coronal to the root notch in 4/6 interproximal and 4/4 furcation defects (1 not determined). In contrast, 2/4 defects treated with ABB demonstrated regeneration. No significant differences between the concentrations of rhPDGF were shown.

Discussion on clinical pharmacology

The last two studies provide the only histological data available with rhPDGF-BB, and they report periodontal regeneration. However, the data on dose selection are highly insufficient because the human data refer to different application conditions as rhPDGF-BB was used alone or with demineralised freeze-dried bone allograft which is able by itself to induce periodontal regeneration. Furthermore, no differences were seen between the various concentrations (0.5 to 5.0 mg/mL). Finally, no histological data are available for the combination with the β-TCP matrix used in Gemesis. Nevertheless they were used to guide the dose selection on the pivotal clinical study that included 1.0 mg/mL and 0.3 mg/mL rhPDGF-BB administration.

- Main study

The only pivotal trial performed was a double-blind, randomised, parallel group trial conducted in 11 US centres (Study Number BMPI-2001-01) which was monitored by a CRO.

METHODS

Study Participants

180 patients were enrolled and allocated to three different groups.
The mean age for the groups was 49.4, 50.4 and 52.8 years in Groups I, III and III, respectively; 20%, 31% and 20% of patients per group were smokers.
Demographic data for the 180 patient intent-to-treat population is provided in the table below:

Demographic characteristics

	GROUP I (N = 60)	GROUP II (N = 61)	GROUP III (N = 59)	P-VALUE
	N (%)	N (%)	N (%)	
Gender				0.074**
Female	31 (51.7%)	20 (32.8%)	21 (35.6%)	
Male	29 (48.3%)	41 (67.2%)	38 (64.4%)	
Race				0.387***
Caucasian	33 (55.0%)	37 (60.7%)	37 (62.7%)	
Hispanic	6 (10.0%)	4 (6.6%)	8 (13.6%)	
Asian	10 (16.7%)	13 (21.3%)	9 (15.3%)	
African American	11 (18.3%)	5 (8.2%)	5 (8.5%)	
Native American	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	0 (0.0%)	2 (3.3%)	0 (0.0%)	
Age (years)				0.222*
Mean ± SE	49.4±1.3	50.4±1.7	52.8±1.2	
Min – Max	27 - 67	23 – 73	29 - 71	
Weight (kg)				0.739*
Mean ± SE	78.0±2.9	79.4±2.7	80.9±2.2	
Min – Max	46.4 - 155.0	52.3 - 186.4	50.0 - 122.7	
Height (cm)				0.167*
Mean ± SE	169.5±1.1	172.6±1.2	170.1±1.3	
Min – Max	154.9 - 188.0	152.4 - 188.0	139.7 - 188.0	
Smoking History				
Current Smoker	12 (20.0%)	19 (31.1%)	12 (20.3%)	0.262*
Number of Years Smoking (Mean ± SE)	21.5±3.7	24.4±3.8	24.4±4.4	0.851*
Number of Cigarettes Smoked Daily (Mean ± SE)	11.6±1.6	9.5±1.5	8.2±2.0	0.429*
Number of Cigars Smoked Weekly (Mean ± SE)	0.0±0.0	0.0±0.0	0.1±0.1	0.438*
Number of Pipes Smoked Weekly (Mean ± SE)	0.0±0.0	0.0±0.0	0.6±0.6	0.281*

The main inclusion criteria of study BMPI-2001-01 were:

- 25-75 year old patient with advanced periodontal disease
- at least 1 site requiring surgical intervention to correct a bone defect
- pocket depth at least 7 mm at baseline
- after surgical debridement, 4 mm or greater vertical bone defect with at least 1 bony wall
- sufficient keratinised tissue to allow complete coverage of the defect
- radiographic base of defect at least 3 mm coronal to the tooth apex.

All groups were balanced for standard demographics and smoking history.

Treatments

Patients were randomly allocated to one of the following treatment groups:

- GROUP I: Gemesis , with sodium acetate buffer containing 0.3 mg/mL rhPDGF-BB;
- GROUP II : Gemesis, with sodium acetate buffer containing 1.0 mg/mL rhPDGF-BB;
- GROUP III: β-TCP with sodium acetate buffer alone (control).

Sterile β-TCP was provided in granular form (0.25 mL) and stored in glass vials. The test solution, approximately 0.25 mL sodium acetate buffer (alone, containing 0.3 mg/mL rhPDGF-BB or 1.0 mg/mL rhPDGF-BB) was provided in syringes.

The doses were selected on the basis of the proof of concept studies previously described and two dog studies, which used a concentration of 0.5 mg/mL.

Objective

The objective of the study was to demonstrate that Gemesis promotes greater periodontal regeneration than an osteoconductive scaffold alone (β-TCP) and historical controls.

Endpoints

Primary endpoint:

- Change in clinical attachment level (CAL) between baseline and 24 weeks post-surgery comparing Group I vs. Group III.
  CAL was defined as "the distance from the cemento-enamel junction (CEJ) or other fixed reference point, generally along the long axis of the tooth to the deepest extent of the periodontal pocket".

Secondary endpoints:

- CAL change between baseline and 24 weeks post-surgery (Group II vs. Group III).
- Change in pocket depth reduction (PDR) between baseline and 24 weeks with PD defined as the distance from the gingival margin generally along the long axis of the tooth to the deepest extent of the periodontal pocket (Group I and II vs. Group III).
- Change in gingival recession (GR) between baseline and 24 weeks with GR defined as the distance from the free gingival margin (FGM) to the CEJ (Group I and II vs. Group III).
- Wound healing (WH) during the first three weeks post-surgery. The scale ranged from 0 (absence of inflammation) to 4 (severe inflammation) (Group I and II vs. Group III).
- Radiographic assessment of linear bone growth (LBG) and % bone fill (%BF) from baseline to 24 weeks post-surgery; LBG was defined as the improvement in bone height.
- Area under the curve (AUC) of CAL change using 12- and 24-week time points (Group I and II vs. Group III).

Composite endpoint used for the post-hoc analysis:

- CAL change ≥ 2.7 mm and an LBG ≥ 1.1 mm at 24 weeks or CAL change ≥ 2.7 mm and a %BF ≥ 14.1 % (Group I and II vs. Group III).

All investigators had to have experience in periodontal regenerative procedures and were successfully calibrated prior to enrolment and during the follow-up period, ensuring the consistency and accuracy of the probing measurement technique. The CHMP regarded the proposed endpoints as adequate and in line with the recent literature.

Sample size

A total of 180 patients were randomly allocated to three groups (I, II and III).

The estimated sample size was calculated using CAL and relied on the normal deviate distributions for a one-sided t-test comparing two groups of independent and randomly allocated subjects. Each

participating individual contributed one osseous defect to the trial. The number of subjects needed per treatment group was calculated using the following assumptions:

- alpha = 0.05 (one-sided)
- beta = 0.20 (80% power)
- standard deviation (SD) of CAL change = 2.0 mm
- minimum detectable difference in CAL = 1.0 mm.

For the present study, in which the bulk of the changes in CAL measurements were expected to be in the 0.4 - 3.3 mm range, the best estimate of the standard deviation in CAL was conservatively estimated to be 2.0 mm. The minimum detectable difference was the minimum difference that is typically observed with currently available treatment for periodontal defects. When comparing to the control device, 50 subjects per group were required. Conservatively allowing for 15% attrition, each group was randomly allocated 60 subjects in order to allow for statistical power to be as calculated.

The CHMP noted that the Applicant only presented 60 patients treated with the proposed regimen for a group of indications that is quite common. Moreover, an alpha level of 0.05 in the context of a single pivotal trial is considered too high (reference is made to CPMP/EWP/2330/99).

Randomisation

The investigators used the randomization schedule based on variable block sizes of 3 and 6.
The randomisation procedure was considered appropriate by the CHMP.

Blinding (masking)

It was a randomised, double-blind, controlled, parallel-arm, pivotal human clinical trial. The syringes containing the solution of becaplermin or buffer were identical so that all study personnel and subjects were unaware of the treatment assignment.
The double blinding was deemed acceptable for this kind of study by the CHMP.

Statistical methods

The first analysis of the change in CAL for each group was a comparison to a historical benchmark of 1.5 mm. If this first step was successful, the primary efficacy analysis was the comparison of Group I (0.3 mg/mL rhPDGF-BB) with group III (buffer alone), to establish superiority of the low concentration over control. The comparison was to be made using a two-sample t-test and the result was to be considered positive if $p \leq 0.05$ (one-sided). It should be noted that this represents the amended statistical plan which according to the Applicant was solely motivated by the results of the pivotal study in dogs (BMPI 2003-004).

Among the three secondary endpoints listed in the original study protocol PDR and GR were both continuous variables to be analysed using two-sided t-tests; WH was to be analysed as a success (= score 0)/failure (= scores 1-4) endpoint using a chi-squared test. The amended protocol also established new secondary efficacy endpoints, namely radiographic assessments and the AUC for CAL changes. Other analyses added to the plan were comparisons to historical benchmarks of effectiveness for change in CAL, LBG, and %BF based on literature references.

The CHMP stated that the choice to use one-sided p-values is not appropriate. It would be conventional to consider the trial successful only if the two-sided p-value is <0.05, which means the one-sided p-value needs to be <0.025. Furthermore, since this is a single pivotal trial, the p-values should be even lower (reference is made to CPMP/EWP/2330/99).

Interim analysis
After 3-month follow-up was obtained on approximately one-half of the subjects (30 subjects per treatment group, 90 total), an analysis was performed to verify the assumptions used in the original sample size calculation and to examine trends in effectiveness and safety variables. No decisions were to be made concerning stopping the trial as a result of futility or better than expected effectiveness. Thus, the overall significance level of the final analysis (5% Type I error) was maintained.

RESULTS

Participant flow

An overall of 99% of subjects (178/180) completed the study. One subject was lost to follow-up and one subject refused to continue in the trial, but still agreed to return at the 6-month visit to provide efficacy measurements.
There were 174 patients (97%) that had complete sets of radiographic films (baseline and 6 months) and were included in the radiographic analysis; two patients were excluded because of study discontinuation, three because the radiographs were not evaluable, and one because the incorrect radiograph was received. No protocol deviations were considered able to affect the study outcome.
Periapical radiographs were taken at baseline, and at the 12 and 24 week post-surgery visits. Six of the 180 randomised patients were excluded from the radiograph analysis due to study discontinuation (n=2), radiograph not evaluable (n=3) and receipt of a non-legible radiograph (n=1).
All patients were followed for a minimum of 24 weeks (6 months) post-surgery.

Subject disposition

	Group I: β-TCP + 0.3 mg/mL rhPDGF-BB	Group II: β-TCP + 1.0 mg/mL rhPDGF-BB	Group III: β-TCP + buffer alone
Screened	195		
Randomised	60	61	59
Completed	60 (100%)	60 (98%)	58 (98%)
Lost to follow-up	*0*	*1*	*0*
Withdrew consent	*0*	*0*	*1*
Radiographic assessments	60 (100%)	58 (95%)	56 (95%)

The CHMP noted that the patients lost during the study were not significant and appropriate justification was given.

Recruitment
Patient recruitment was made by clinicians in eleven US centres.

The CHMP noted that despite this being a one country study the patient demographics showed that patients had different ethnic origins.

Conduct of the study

The study was conducted according the GCP as stated.

Baseline data

The baseline characteristics of the defects treated are summarised in the table below:

BASELINE CHARACTERISTICS & SURGICAL OUTCOMES		GROUP I N=60	GROUP II N=61	GROUP III N=59	P-VALUE
CAL (mm)	Mean ± SE	9.1±0.2	8.8±0.2	8.8±0.2	0.500*
	Range	7 to 14	7 to 13	6 to 13	
PD (mm)	Mean ± SE	8.6±0.2	8.2±0.2	8.3±0.2	0.167*
	Range	7 to 14	7 to 13	7 to 14	
GR (mm)	Mean ± SE	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.1	0.891*
	Range	-2 to 4	-2 to 5	-2 to 4	
Defect Location					0.612**
	MB	25 (41.7%)	27 (44.3%)	27 (45.8%)	
	B	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	DB	21 (35.0%)	17 (27.9%)	15 (25.4%)	
	ML	8 (13.3%)	14 (23.0%)	10 (16.9%)	
	L	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	DL	6 (10.0%)	3 (4.9%)	7 (11.9%)	
Defect Classification (Coronal Portion)					0.301**
	1 wall	20 (33.3%)	17 (27.9%)	19 (32.2%)	
	2 wall	26 (43.3%)	32 (52.5%)	26 (44.1%)	
	3 wall	5 (8.3%)	8 (13.1%)	11 (18.6%)	
	Circumferential	9 (15.0%)	4 (6.6%)	3 (5.1%)	
Defect Tooth					0.713**
Multi-rooted		35 (58.3%)	33 (54.1%)	30 (50.8%)	
Single-Rooted		25 (41.7%)	28 (45.9%)	29 (49.2%)	
Vertical Bone Defect Depth (mm)(Mean ± SE)		6.0±0.2	5.7±0.2	5.7±0.2	0.357*
Width of Osseous Defect (Mean ± SE)		3.7±0.2	3.5±0.1	3.7±0.1	0.606*
Primary Flap Closure		60 (100%)	60 (98.4%)	58 (98.3%)	0.773***
PDGF Solution dispensed		60 (100%)	61 (100%)	58 (98.3%)	0.328***
Bone Architecture (Normal)		60 (100%)	61 (100%)	59 (100%)	1.000***
Base of Defect to Root Apex (mm) (Mean ± SE)		6.5±0.3	7.0±0.3	7.7±0.4	0.044*

(MB= Mesiobuccal, B= Buccal, DB= Distobuccal, ML= Mesiolingual, L= Lingual, DL= Distolingual)

There were no statistically significant differences between the groups at baseline, except for "base of defect to root apex" (p=0.044), which was not considered clinically meaningful.
Most defects were 1- or 2-wall defects. The CHMP noted that the data presented did not distinguish between intrabony and furcation defects, the usual classification in clinical trials, which will have an impact on the wording of the indication.

Subgroup analyses
Descriptive subgroup analyses (no p values) were performed on data from the study BMPI-2001-01 to determine if there were any trends within demographic variables or baseline characteristics that could affect effectiveness outcomes. Improved effectiveness outcomes were seen in patients with baseline areas of defect >21 mm^2, and who were <50 years of age and non-Caucasian. Overall, increased LBG, improvements in %BF, and higher CAL gain were observed in non-smokers compared to smokers, and patients with three circumferential apical bone walls compared with patients with one or two apical bone walls. However, no special population requirements were identified.

Outcomes and estimation

Primary endpoints

All three treatment groups showed a significant gain in clinical attachment level at 24 weeks (3.7, 3.7, and 3.5 mm, respectively) over an established historical value of 1.5 mm.

Seventy-two percent (72%) of patients in Group I experienced complete wound healing at 3-weeks post-surgery compared to 60% in Group II and 55% in Group III. A statistically significant benefit was shown in Group I compared to Group III for clinical attachment level (CAL) gain and gingival recession at 12 weeks. By week 24 Group I results were numerically superior to Group III, but the difference was not statistically significant for CAL gain and gingival recession. Statistically significant benefit was also shown in Group I compared to Group III for linear bone growth, and percent bone fill at 24 weeks, as well as the composite analyses.
The following table summarizes the most relevant comparisons between Group I and Group III:

CAL: Change from Baseline to 12 and 24 Weeks Post-surgery Group I vs. Group III: Study Number BMPI-2001-01			
Time-point	**CAL Gain**	**Group I**	**Group III**
Week 12		**(N=60)**	**(N=58)**
	Mean ± SE [mm]	3.78 ± 0.19	3.31 ± 0.20
	Median [mm]	3.00	3.00
	Range [mm]	1.0 to 8.0	-1.0 to 6.0
	p-value vs. Group III one-sided two-sample t-test	0.041	
Week 24		**(N=60)**	**(N=59)**
	Mean ± SE [mm]	3.73 ± 0.22	3.49 ± 0.18
	Median [mm]	4.00	3.00
	Range [mm]	-2.0 to 7.0	0.0 to 7.0
	p-value vs. Group III one-sided two-sample t-test	0.200	

Although the Applicant claims that the data, when taken as a whole, clearly demonstrates an early beneficial effect of the 0.3 mg/mL rhPDGF-BB concentration, the study clearly fails the primary endpoint. In addition, the clinical relevance of the 12th Week result is questioned when this advantage disappears after 24 weeks as the main goal of these kind of treatments is the long-term results instead of the short term ones. In addition to the extremely short clinical program this is also a major issue of the dossier.

Although the Applicant states that Gemesis was statistically significantly better than the control at month 3 for both clinical attachment level gain and gingival recession gain, this is not correct. As 1-sided p-values have been presented the critical value is $p<0.025$ rather than $p<0.05$, even before we consider that this is a single pivotal trial (meaning the level should be even more extreme); $p<0.025$ is not achieved for either of these endpoints.

In summary, the study clearly fails the primary endpoint. Despite the Applicant's claims, when we note that 1-sided p-values were used, a statistically significant difference was not seen at week 12. In any case,

any advantage seen at week 12 on CAL was not sustained and disappears after 24 weeks. The long term results should be seen as more relevant than the short term ones as the ultimate goal is tooth preservation

Secondary Endpoints

CAL Gain Group II versus Group III
The comparison of CAL gain at 24 weeks between Groups II and III was made as a secondary endpoint to determine if there were differences in efficacy between the two rhPDGF-BB concentrations when compared to the control. There is no significant difference in CAL gain at either 12 (p=0.403) or 24 (p=0.287) weeks between Groups II and III.

AUC of CAL gain
The area under the curve (AUC) of CAL gain from baseline to 24-weeks post-surgery approached statistical significance in Group I compared to Group III (p=0.054). This analysis represents the gain in CAL between baseline and six months. The data for the analysis are displayed in the table below:

AUC of CAL Gain at 24 Weeks: Study Number BMPI-2001-01			
AUC of CAL Gain	**Group I N=60**	**Group II N=60**	**Group III N=59**
Mean ± SE [mm]	67.5 ± 3.2	61.8 ± 2.9	60.1 ± 3.2
Median [mm]	63.0	59.6	58.2
Range [mm]	11.5 to 140	0.5 to 117	0.1 to 112
p-value vs. Group III one-sided two-sample t-test	0.054	0.350	

CAL gain from baseline to 24 weeks post-surgery using a historically established level of clinical effectiveness of 1.5 mm showed that all 3 treatment groups had a CAL gain above this level (3.7 mm; 3.7 mm; and 3.5 mm in Groups I, II and III, respectively) that was statistically significant (p<0.001).

Pocket Depth Reduction (PDR)
There were no significant differences in probing pocket depth reduction (PDR) between the groups at either the 12 or 24-week time-points.

Gingival Recession (GR)
Gingival recession improved significantly in Group I as compared to Group III (p=0.041) at the 12-week time-point. No statistically significant differences were observed at the 24-week time-point. No statistically significant differences were observed for the comparison between Group II and Group III at both the 12 and 24-week time-points.

Wound Healing
Three weeks post-surgery, 72% of Group I patients experienced complete healing compared to 60% in Group II and 55% in Group III. The differences between the groups were not statistically significant (p=0.138 Group I vs. Group III; p=0.442 Group II vs. Group III).

Linear Bone Growth
Linear bone growth (LBG) was calculated as the difference between baseline and 24 weeks post-surgery in “cemento-enamel junction to base of defect”. A statistically significant increase in LBG was observed in Groups I and II as compared to Group III as shown in the table below:

Radiographic Assessment of Linear Bone Growth LBG at 24 Weeks Study Number BMPI-2001-01			
LBG	**Group I** **(N=60)**	**Group II** **(N=58)**	**Group III** **(N=56)**
Mean ± SE [mm]	2.52 ± 0.3	1.53 ± 0.2	0.89 ± 0.2
Median [mm]	2.17	1.15	0.70
Range [mm]	-0.22 – 9.36	-1.80 – 6.97	-6.66 – 5.06
p-value vs. Group III one-sided two-sample t-test	<0.001	0.021	

Percent Bone Fill (%BF)
Percent bone fill was defined as the percent of the original osseous defect filled with new bone as measured radiographically. At 24-weeks post-surgery, a statistically significant increase in %BF was observed in Groups I and II as compared to Group III:

Radiographic Assessment of Percent Bone Fill (%BF) at 24 Weeks Study Number BMPI-2001-01			
%BF	**Group I** **(N=60)**	**Group II** **(N=58)**	**Group III** **(N=56)**
Mean ± SE [mm]	56 ± 5.9	34 ± 4.2	18 ± 6.4
Median [mm]	49	33	20
Range [mm]	-4 to 255	-23 to 108	-235 to 86
p-value vs. Group III one-sided two-sample t-test	<0.001	0.019	

- Additional Statistical Analyses

Composite analysis
An analysis was performed to determine the percent of patients with a successful combined outcome for hard and soft tissue components of the periodontium.
When the composite endpoints were applied to the BMPI-2001-01 data, Group I demonstrated statistically significant differences when compared to Group III for both composite endpoints:

Composite Analysis of Success at 24 Weeks: Study BMPI-2001-01			
	Group I	**Group II**	**Group III**
CAL and LBG			
Composite analysis of success	**(N=60)**	**(N=58)**	**(N=56)**
	61.7%	37.9%	30.4%
p-value vs. Group III one-sided Chi-square test	≤ 0.001	0.197	
CAL and %BF			
Composite analysis of success	(N=60)	(N=60)	(N=59)
	70.0%	55.2%	44.6%

p-value vs. Group III one-sided Chi-square test	≤ 0.003	0.130	

Overall the results in Group I or II were not better than the results in Group III in 4 of the seven secondary endpoints. The secondary endpoints did not clearly favour the proposed therapeutic dose. None of them showed better results of Group I over Group II.
Although the comparison with the historical background is interesting it has obvious limitations.
In summary, it is difficult to consider, with the available data, that 0.3 mg/mL rhPDGF-BB when administered together with β-TCP improves the clinical results when compared with β-TCP alone. The concentration of rhPDGF as 0.3 mg/mL seems to perform better than the higher concentration when both are compared with the β-TCP alone on CAL gain, linear bone growth and percent bone fill.

Study extension
The primary focus of the extension study was to collect long-term radiographic (LBG and %BF) and clinical data (CAL, PD and GR). Results have been reported through 36 months for patients who continued for the duration of the extension trial. This study enrolled 135 of the 180 patients that completed the treatment and follow-up phases of the Pivotal study (Study BMPI-2001-01). 131 of the 135 patients enrolled in the extension study were evaluated at 12 months, 88 were evaluated at 24 months and 83 were evaluated at 36 months.
The analyses were only performed in the patients that completed the follow-up period in question and missing data were not taken into account. Three different patient sets were analysed for the results at 12, 24 and 36 months. The tests were one-sided, so p-values should be doubled to allow interpretation in accordance with conventional standards. Out of the 11 centres involved in the pivotal trial, 9 participated in the extension study up to 12 months and only 6 up to 36 months.

Few baseline characteristics were provided for the patient subsets studied, except for smoking status and type of bone defect (number of walls, vertical bone defect depth). There were slightly more severe defects in the control group than in the 0.3 mg/ml group. The Applicant also performed a comparison of these baseline characteristics as well as the 6-month results between the various patient subsets and the patients with no data available ("survivor analysis"). Overall, there were more 1-2 wall defects and the 6-month results tended to be less favourable in the patients with no follow-up data.

Table 31: Results of clinical measurements in study BMPI-2001-01-EXT			
Change from baseline	***GEMESIS* Group I**	**1.0 mg/mL rhPDGF-BB + ß-TCP Group II**	**B-TCP Alone Group III**
CAL gain [mm] (mean ± SD)			
	N=45	N=43	N=43
6 month	3.73 ± 1.56	3.72 ± 1.69	3.65 ± 1.46
12 month	3.76 ± 1.63	3.51 ± 1.65	3.60 ± 1.58
	N=29	N=30	N=29
6 month	4.14 ± 1.60	3.57 ±1.89	3.55 ± 1.64
12 month	4.04 ± 1.65[a]	3.43 ± 1.74	3.45 ± 1.74
24 month	4.07 ± 1.81	3.47 ± 1.96	3.28 ± 1.98
	N=27	N=28	N=28
6 month	4.00 ± 1.54	3.50 ± 1.71	3.68 ± 1.66
12 month	3.96 ± 1.68[b]	3.39 ± 1.62	3.68 ± 1.70
24 month	4.00 ± 1.81[b]	3.32 ± 1.76	3.39 ± 1.99
36 month	4.30 ± 1.79[c]	3.48 ± 2.00[c]	3.44 ± 1.94[c]
PD reduction [mm] (mean± SD)			
	N=45	N=43	N=43
6 month	4.44 ± 1.42	4.40 ± 1.38	4.21 ± 1.46
12 month	4.47 ± 1.44	4.16 ± 1.45	4.09 ± 1.44
	N=29	N=30	N=29
6 month	4.59 ± 1.62	4.27 ± 1.51	4.10 ± 1.61
12 month	4.48 ± 1.50[a]	4.07 ± 1.41	3.97 ± 1.59
24 month	4.48 ± 1.62	4.03 ± 1.75	3.79± 1.72
	N=27	N=28	N=28
6 month	4.41 ± 1.53	4.11 ± 1.20	4.18 ± 1.63
12 month	4.50 ± 1.53[b]	4.00 ± 1.39	4.07 ± 1.61
24 month	4.46 ± 1.63[b]	3.93 ± 1.49	3.86 ± 1.76
36 month	4.57 ± 1.70[c]	4.04 ± 1.43[c]	4.16 ± 1.60[d]
GR [mm] (mean ± SD)			
	N=45	N=43	N=43
6 month	0.71 ± 0.82	0.67 ± 0.94	0.56± 0.98
12 month	0.71 ± 0.99	0.65 ± 1.02	0.49 ± 1.12
	N=29	N=30	N=29
6 month	0.45 ± 0.83	0.70 ± 0.92	0.55 ± 1.02
12 month	0.44 ± 1.01[a]	0.63 ± 1.03	0.52 ± 1.30
24 month	0.41 ± 1.12	0.57 ± 0.86	0.52 ± 1.12
	N=27	N=28	N=28
6 month	0.41 ± 0.80	0.61 ± 0.88	0.50 ± 1.00
12 month	0.54 ± 0.99[b]	0.61 ± 0.92	0.39 ± 0.96
24 month	0.46 ± 1.07[b]	0.61 ± 0.83	0.46 ± 1.00
36 month	0.26 ± 1.01[c]	0.57 ± 1.27[c]	0.72 ± 1.34[d]
a N=27, b N=26, c N=23, d N=25			

Table 32: Results of radiographic measurements in study BMPI-2001-01-EXT			
Change from baseline	***GEMESIS*** **Group I**	**1.0 mg/mL rhPDGF-BB + ß-TCP Group II**	**B-TCP Alone Group III**
LBG [mm] (mean ± SD)			
	N=45	N=43	N=43
6 month	2.49 ± 1.73	1.56 ± 1.46[a]	1.14 ± 1.37[a]
12 month	2.88 ± 1.76	2.25 ± 1.60	1.42 ± 1.56
	N=29	N=30	N=29
6 month	2.74 ± 1.57	1.39 ± 1.43	1.16 ± 1.44[b]
12 month	3.05 ± 1.46[c]	2.23 ± 1.73[d]	1.72 ± 1.40
24 month	3.32 ± 1.66	2.40 ± 1.66	1.81 ± 1.40
	N=27	N=28	N=27
6 month	2.83 ± 1.68	1.36 ± 1.31	1.13 ± 1.46[c]
12 month	3.18 ± 1.53[d]	1.93 ± 1.41[c]	1.74 ± 1.41
24 month	3.25 ± 1.69[f]	2.06 ± 1.13[c]	1.89 ± 1.41[c]
36 month	3.45 ± 1.57	2.46 ± 1.30	2.74 ± 2.00
%BF [%] (mean ± SD)			
	N=45	N=43	N=43
6 month	53.9 ± 34.7	35.0 ± 31.5[a]	24.8 ± 33.3[a]
12 month	60.5 ± 33.5	53.7 ± 38.5	32.6 ± 38.9
	N=29	N=30	N=29
6 month	59.1 ± 33.8	29.4 ± 30.9	28.8 ± 31.8[b]
12 month	65.3 ± 30.6[c]	53.5 ± 43.4[d]	42.9 ± 31.2
24 month	68.3 ± 27.3	57.3 ± 32.8	41.5 ± 25.7
	N=27	N=28	N=28
6 month	60.8 ± 35.2	32.5 ± 34.1	28.5 ± 32.4[c]
12 month	67.6 ± 31.0[d]	49.5 ± 40.8[c]	43.5 ± 31.5
24 month	68.0 ± 28.8[f]	52.6 ± 29.9[c]	43.2 ± 25.7[c]
36 month	73.1 ± 26.4	63.0 ± 33.4	62.8 ± 32.6
A N=42, b N=28, c N=27, d N=29, e N=26, f N=25			

At 24 months, Gemesis patients showed the greatest clinical improvement in CAL gain, PD reduction and GR when compared to patients in the β-TCP alone group. For all other clinical measures, Gemesis patients maintained an overall level of clinical improvement that was superior to that of patients in the β-TCP group; however, the differences were not statistically significant. At 36 months all effects are no longer significant due to improvements observed for the patients who received β-TCP alone.

Inconsistent results were shown for the two composite endpoints. Only the endpoint using the linear bone growth (LBG) exhibited a significantly higher success rate with Gemesis (0.3 mg/ml) than with the matrix alone ($p<0.05$ with a two-sided test) at 12, 24 and 36 months (at 36 months: 87% vs. 54%, respectively). The difference in the endpoint using the percent bone fill (%BF) was not significant at any time point (at 36 months: 87% vs. 72%, respectively).

Subgroup analyses of radiographic outcomes according to the severity of the defect were performed although patient numbers were small in some of these groups; these analyses had not been conducted for

the pivotal trial. The effects of becaplermin 0.3 mg/ml were less pronounced in the most severe defects (1-2 walls, vertical depth <6mm).

Finally, these follow-up data confirmed that the high dose had only marginal effects, if any. Moreover, the long-term data does not add any support to the demonstration of a substantial benefit over the use of the matrix alone. On the contrary, these long-term data showed a decline of the benefit of Gemesis over time in terms of bone gain while this was the only statistically significant benefit reported in the short-term. Furthermore, no safety data were collected.

- Clinical studies in special populations

The only data available in at risk patients are those observed in smokers, which are not encouraging. Overall, there is a clear need for more data in patients with risk factors for impaired wound healing.

- Analysis performed across trials (pooled analyses AND meta-analysis)

The Company compared the results of study number BMPI-2001-01 with two sets of meta-analysis data that were independently collected and published in a peer-reviewed journal (Reynolds *et al*. 2003 and Giannobile *et al*. 2003). In addition a third analysis was conducted. A Bayesian model was used to perform this meta-analysis on 9 allograft studies and 8 *Emdogain* studies in comparison to *Gemesis* 0.3 mg/mL Group I of study number BMPI-2001-01 (Schoenfeld 2004).

The historical comparison with other available alternatives seems to favour the Gemesis treatment. Nevertheless these comparisons have strong methodological problems. The β-TCP results in such comparisons seem to be better or equivalent to other historical controls raising concerns about the reliability of such comparisons. Hence, these comparisons do not allow overcoming the clinical insufficient program and results provided.

- Supportive study(ies)

Upon request on Day 120 of the procedure the Applicant submitted a summary, reports and publications of six additional studies.

The additional studies are tabulated in the following table:

Protocol No.	Title	Design	Treatment	Duration	Journal Article
BMPI-2002-01-Study 1	Histologic Evaluation of β-TCP plus rhPDGF-BB in the treatment of Human Periodontal Osseous Defects	Single-centre, randomised, evaluator blinded At least 2 teeth scheduled for extraction and prosthetic replacement	N=8 (16 sites; 19 defects) Per patient: 1 tooth: β-TCP + 0.3 mg/mL rhPDGF-BB 1 tooth: β-TCP+ 1.0 mg/mL rhPDGF-BB	6 months	Int J Periodontics Restorative Dent 2008;28:171-179
BMPI-2003-01-Study 3	A Single Centre, Controlled, Parallel-arm, Human Clinical Trial to Compare the Safety and Effectiveness of GEM 21S and Demineralized Freeze-dried Bone Allograft (DFDBA), in Combination with a GTR Membrane, for the Treatment of	Randomised, evaluator blinded Advanced intra-osseous defects	Group I: β-TCP + 0.3 mg/mL rhPDGF-BB N=11 Group II: β-TCP + 1.0 mg/mL rhPDGF-BB N=10 Group III	12 months	Not published
	Periodontal Bone Defects		(active control): DFDBA With bioresorable membrane N=11		
BMPI-2002-02-Study 4	A Blinded Human Clinical Trial to Evaluate the Clinical Utility of GEM 21S for the Treatment of General Bone Defects: A Case Series in Periodontally-Related Defects	Single-centre, evaluator blinded Bone void or gap requiring surgical intervention and grafting	Both groups were treated with β-TCP and/or other bone void filler + rhPDGF-BB Group I: 0.3 mg/mL rhPDGF-BB N=7 Group II: 1.0 mg/mL rhPDGF-BB N=6	6 months	Int J Periodontics Restorative Dent 2007;27:421-427
BMPI-2002-02-Study 5	A Blinded Human Clinical Trial to Evaluate the Clinical Utility of GEM 21S for the Treatment of General Bone Defects	Single-centre, randomised by tooth, single blind At least 2 recession defects requiring surgical intervention and grafting	Per patient: 1 tooth: β-TCP + 0.3 or 1.0 mg/mL rhPDGF-BB + resorbable collagen membrane Control tooth: subepithelial connective tissue graft N=9 (18 sites)	6 months	Int J Periodontics Restorative Dent 2006;26:127-133
Luitpold Study No. 1GEM04001	A Single-Blind, Controlled, Split-Mouth, Single-Center Clinical Trial to Evaluate the Safety and Effectiveness of GEM 21S Associated with an Absorbable Collagen Wound Dressing Compared to Subepithelial	Single-centre, single-blind, randomised, controlled, split mouth study Recession-Type Periodontal Defects	Per Patient Treatment A: GEMESIS + absorbable collagen wound dressing Treatment B (control): subepithelial CTG	6 months	Accepted for publication Int J Periodontics Restorative Dent Jan, 2009

	Connective Tissue Graft (CTG) for the Treatment of Recession-Type Periodontal Defects		N=32 (64 sites)		
BPI-2000-01-Brazil	Clinical, Radiographic and Histologic Evaluation of rhPDGF-BB Delivered in Bone Allograft for the Treatment of Periodontal Defects in Humans	Single-centre, open label 2 Class II furcation defects/dose level and 2 angular, intrabony, interproximal lesions/dose level in ascending dose order [Study was conducted in Brazil. Biopsied sites were reconstructed to allow successful implant supported prosthetic reconstruction.]	Group 1: 500 µg/ml rhPDGF-BB + Grafton N=5 sites Group 2: 1000 µh/ml rhPDGF-BB + Grafton N=5 sites Group 3: 5000 µg/ml rhPDGF-BB + Grafton N=5 sites	9 months	J Periodontol 2003;74:1282-1292 Int J Periodontics Restorative Dent 2003;23:213-225

- Discussion on clinical efficacy

The clinical development plan for the efficacy of Gemesis in the treatment of periodontally related defects includes only one pivotal trial (BMPI-2001-01). The primary endpoint for this study was the change from baseline to month 6 in clinical attachment level (CAL), comparing the low dose of Gemesis (0.3 mg/mL) to the β-TCP matrix control (after amendment of the study protocol). No statistically significant differences were observed in this study concerning the primary efficacy analysis. The bone gain analysis did have positive results, but the remainder of the secondary endpoints also failed to show a difference. Moreover, the bone gain achieved in the control group was especially poor and was not consistent with the results of several other trials with hydroxyapatite ceramics. In view of these results there was a lack of internal consistency with all important endpoints.
An interim analysis after 3 months revealed that Gemesis lead to better results in the primary endpoint clinical attachment level (CAL) and the secondary endpoint gingival recession (GR). The level of significance reached was in both cases $p=0.041$, however as these were 1-sided p-values the critical value is $p<0.025$ rather than $p<0.05$. Moreover, this non-significant advantage disappeared after 6 months and long-term follow-up data of 36 months showed no difference for Gemesis compared to the β-TCP matrix alone. This raised additional doubts about the long term efficacy of Gemesis.
Moreover, results from the single pivotal trial were better for the low concentration (0.3 mg/mL) than for the high concentration (1.0 mg/mL) and the true significance of this finding remained unknown.
Overall, it is not considered that this study has provided robust evidence of efficacy to the standards required for a marketing authorisation as the Applicant failed to demonstrate that adding becaplermin to the calcium phosphate matrix increases the performance of the device in terms of both clinical and radiographic measurements.

Concerning supportive studies, in the summary provided by the Applicant, CAL gain outcomes were presented for all studies. It is noteworthy that all three phase II (small) studies comparing the two

concentrations of becaplermin associated with β-TCP showed better results with the higher dose. Thus, the rationale for the change to the statistical plan of the pivotal trial by the Applicant in favour of the lower dose remains unclarified.
Histological evidence of true regeneration has been provided for the association of becaplermin with β-TCP matrix. Nevertheless the provided histological information in humans does not allow concluding that there is a gain in adding becaplermin to β-TCP as no direct comparisons were made, i.e., β-TCP with or without becaplermin. The results of the dog study, although useful, are difficult to extrapolate due to the lack of comparative binding affinity data of rhPDGF-BB to animal and human target receptors.
Therefore the CHMP concluded that the additional results are not sufficient to further support a marketing authorisation for Gemesis.

Clinical safety

Data for the evaluation of safety of the combination of β-TCP with rhPDGF-BB were derived from the randomised, controlled pivotal study. Following surgery for periodontal disease and implantation of the study article, the patients were observed regularly up to the end of the follow-up period of 24 weeks.

- Patient exposure

A total of 178/180 patients were followed clinically for 24 weeks. For the two patients that did not complete the 24-week follow-up, safety was collected up to the time of discontinuation.

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Active –controlled	180	120	60	60

The number of patients exposed to the proposed dose range is only 60. This figure is very low for such frequent clinical setting.

Upon request after the Day 120 questions the Applicant provided additional information that can be summarised as follows:

- Of the 204 patients (212 treatment sites) who received rhPDGF-BB in the Pivotal study and the five additional periodontal studies; 116 treatment sites received the *Gemesis* configuration (0.3 mg/mL rhPDGF-BB + β-TCP); 83 treatment sites received 1.0 mg/mL rhPDGF-BB + the *Gemesis* β-TCP; and 13 treatment sites received a combination of rhPDGF-BB + DFDBA or DFDBA/Xenograft. The 1.0 mg/mL treatment represents a greater than three fold dose compared to *Gemesis*.
- Greater than 70,000 units of *Gemesis* have been sold in the US and Canada since 2005 with no adverse events reported through the Medical Device Reporting system.
- More than 600 patients have been enrolled in orthopaedic studies, adding substantially more safety data on the 0.3 mg/mL dose of rhPDGF-BB in combination with β-TCP. Given that patients can receive up to 9 mLs of rhPDGF-BB (0.3 mg/mL) in the orthopaedic studies; this represents a potential 18-fold increase in patient exposure to rhPDGF-BB compared to treatment with *Gemesis*. The summary of the results of both ongoing and completed orthopaedic clinical trials provide additional data regarding the safe clinical use of rhPDGF-BB in musculoskeletal applications.
- There were no serious surgical complications observed with rhPDGF-BB, and no serious adverse events that were considered related to study treatment. The rates and types of adverse event occurrence were as expected for subjects undergoing ankle or hindfoot fusions or distal radius fracture repair procedures, respectively.

- Adverse events

The most frequently reported adverse event was study site pain (102/270; 38%), followed by headache (15/270; 6%) tooth disorder (12/270; 4%), tooth pain (11/270; 4%), backache (8/270; 3%), and flu syndrome (8/270, 3%).

The adverse events distribution per group is summarised in the next table:

Incidence of Adverse Events			
	Group I N=60	Group II N=61	Group III N=59
Number of patients with at least 1 AE	44 (73.3%)	42 (68.9%)	39 (66.1%)
Number of patients with at least 1 SAE	1 (1.7%)	1 (1.6%)	2 (3.4%)
Number of AEs	88	93	89
Number of SAEs	1	1	2
Number of AEs likely or definitely related	7	6	5

The adverse events were mostly mild to moderate (99%), and were balanced among groups; with the sole exception of "tooth disorder" (primarily comprised of patients reporting "tooth sensitivity"), which was more commonly noted in the groups that included rhPDGF-BB (6.7% and 11.5%) compared to β-TCP alone (1.7%).

Adverse events with incidence ≥ 5%

Event	Group I	Group II	Group III
Back Pain	5 (8.3%)	2 (3.3%)	1 (1.7%)
Flu Syndrome	2 (3.3%)	3 (4.9%)	3 (5.1%)
Headache	5 (8.3%)	3 (4.9%)	7 (11.9%)
Surgical Site Reaction[1]	35 (58.3%)	35 (57.4%)	32 (54.2%)
Tooth Disorder[2]	4 (6.7%)	7 (11.5%)	1 (1.7%)
Tooth Pain[3]	3 (5.0%)	4 (6.6%)	4 (6.8%)
Muscle Pain	3 (5.0%)	1 (1.6%)	0 (0.0%)
Respiratory Disorder	2 (3.3%)	1 (1.6%)	3 (5.1%)
Ref.: Statistical Table 13c, Data Listing 19			

1 Includes bleeding, bruising, pain, swelling, and tenderness of the treatment site following surgery. All are expected sequelae from periodontal surgical grafting procedures.
2 Includes disorders (e.g. sensitivity) at a location other than the surgical site.
3 Includes pain unrelated to the surgical procedure and at a location other than the surgical site.

Adverse events reported by the investigator as likely related to study article included study site pain (n=16) and loss of interdental papilla (n=1; Group II patient). One adverse event for study site pain was judged by the investigator as definitely related to the study article (n=1; Group III patient).

There were no significant differences in AE reporting between the treatment groups. Analysis by Organ System or Syndrome was not performed as a systemic effect is not anticipated.

The Applicant has provided efficacy results up to 36 months. However, the safety issues (especially with regard to repeated applications, risk of malignancy and immunogenicity) have not been addressed and the Applicant has not provided any plan for collecting such data.

- Serious adverse events and deaths

There were 4 serious AEs, none of which was judged as being study article related. These were spine surgery requiring hospitalisation (n=1), complication of diabetes (n=1), bronchitis requiring hospitalisation (n=1), and operative removal of a skin cancer (n=1). There were 4 severe AEs, none of which was judged as being study article related. These were back pain (n=1), stomach ulcer (n=1), headache (n=1), and surgical site reaction (n=1).
There were no deaths during the observation period post-surgery.

The safety profile of Regranex, which contains the same active substance as Gemesis and is authorised in the EU and many other countries outside the EU since 1998, was described in a review of 6 controlled clinical studies in patients with lower extremity diabetic neuropathic ulcers (Smiell, 1998). Among 538 patients that received becaplermin gel (30 µg/g or 100 µg/g) erythematous rash occurred in 2% of the patients with suspected wound infections vs. 1% in the patients treated with placebo gel; none was observed in patients treated with good ulcer care alone. The incidence of infections, cardiovascular, respiratory, musculoskeletal, and central and peripheral nervous system disorders were similar across all treatment groups.

It is acknowledged that the reference to Regranex may bring some useful information since it is obvious that the exposure to becaplermin through a daily topical application for up to 20 weeks with a gel dosed at 100µg/g of becaplermin must be much higher than a single dose of 0.15 mg. However, repeated application of Gemesis is possible to some extent as some patients may be submitted to several surgical procedures at different sites. No studies have been conducted, and no Pharmacovigilance data is available, in patients having several surgical procedures utilising Gemesis at different sites. Nevertheless none of those patients treated at multiple sites during a single procedure in the periodontal clinical studies received more than the maximum dose of Gemesis allowed (0.15 mg rhPDGF-BB).
A warning was issued by the FDA March 2008 regarding the possibility of an increased risk of death from cancer in patients who had repeated treatments with Regranex. In addition, a recent paper suggests that periodontal disease itself may be associated with a small, but significant, increase in overall cancer risk, even in never-smokers. By cancer site, significant associations were found for lung (probably because of residual confounding by smoking since the association was not noted in never-smokers), kidney, pancreas, and haematological cancers. Currently, it is not known whether periodontal disease is a marker of a susceptible immune system or might directly affect cancer risk through systemic inflammation, pathogenic invasion into the blood stream, or immune response to periodontal infection (Michaud *et al.*, 2008).
Overall, there is a clear need for a long-term observational study in order to assess the long-term safety and effectiveness of Gemesis, including the effects of repeated applications on safety and immunogenicity. As already mentioned earlier, Gemesis is proposed to be contraindicated in patients with tumours.

- Laboratory findings

Study protocol did not include clinical laboratory evaluations.

- Safety in special populations

No data were provided. According to the Applicant there are no intrinsic ethnic differences associated with the use of rhPDGF-BB in humans. Descriptive subgroup analyses were performed to determine if there were any trends within demographic variables or baseline characteristics that could increase effectiveness outcomes. A trend toward improved effectiveness outcomes were seen in patients with baseline areas of defect >21 mm^2, and who were $\leq$50 years of age and non-Caucasian. Overall, increased LBG, improvements in %BF, and higher CAL gain were observed in non-smokers compared to smokers, and patients with three circumferential apical bone walls compared with patients with one or two apical bone walls. However, no special population requirements were identified.

Pregnant women and women intending to become pregnant were excluded from the clinical study. No studies have been conducted for Gemesis on the effect of rhPDGF-BB on human reproductive toxicity. Until relevant data are available, Gemesis is not considered suitable for use during pregnancy or lactation. Therefore, Gemesis is contraindicated for use in pregnant women.

- Immunological events

No antibody measurement has been performed in patients treated with Gemesis. A literature search on the clinical use of rhPDGF-BB and the risk of an immunologic response has been provided by the Applicant. Repeated daily applications on neuropathic or pressure ulcers for up to 20 weeks resulted in a low incidence of anti-PDGF antibodies (0.4 to 6%). No neutralising antibodies to PDGF have ever been detected.

- Safety related to drug-drug interactions and other interactions

As *Gemesis* is not administered systemically but is delivered locally and is implanted in a single dose containing 0.15 mg rhPDGF-BB, the clinical programme did not include testing of rhPDGF-BB for drug interactions. PDGF is a naturally occurring protein that is released from platelets at the site of an injury. Additionally, patients enrolled in the pivotal clinical study took a variety of concomitant medications, including drugs to treat pain, depression/anxiety, hypertension, diabetes, asthma/allergies, hyperthyroidism, arthritis, seizures, gastric reflux, birth control, sexual dysfunction, and post-menopausal symptoms (hormone replacement and osteoporosis). No adverse events related to drug interactions were reported in the study.

- Discontinuation due to AES

Not reported.

- Discussion on clinical safety

The available safety data is derived from one clinical trial with a total of 121 patients exposed to two different doses of Gemesis for 6 months. A low rate of associated adverse events and no serious or unanticipated adverse events attributable to Gemesis were observed. The most frequently reported adverse events were study site pain followed by headache, tooth disorder, tooth pain, backache and flu syndrome. Four serious adverse events were reported but none could be attributed to the treatment with Gemesis. These results suggest that a single treatment with β-TCP, with and without the adjunctive use of rhPDGF, is reasonably safe in periodontal procedures. However, the number of subjects treated in this trial is rather limited (121 patients). In fact only 60 patients were exposed to the actual proposed dose of 0.3 mg/ml and the patients were only followed for six months and no long-term safety follow-up data is available in order to detect unanticipated adverse effects. In view of the wide potential target population for Gemesis the size of the safety database was not considered sufficient without long-term post-marketing observational studies. Furthermore, a slight concern remained with regards to potential risks associated with possible repeated applications of Gemesis, such as carcinogenicity and immunogenicity, in patients with several surgical procedures at different sites.

Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.5 Overall conclusions, risk/benefit assessment and recommendation

Quality

Although to some extent the data submitted provide evidence with respect to the quality of Gemesis, major issues related to the quality of the product and their potential impact on efficacy and safety were identified by the CHMP as follows:

Comparability of the drug product

The company did not present convincing characterisation data to support the comparability of the drug product before and after the changes to the manufacturing process (i.e. change of site and scale) in relation to those forms that have a decreased biological activity. The method used for retrospective analysis of released batches does not distinguish between forms with reduced potency. Nevertheless the company presented an extensive characterisation for the qualification of reference standards. This was the only study presented where the content of forms with reduced potency were performed using another method and demonstrated to be equivalent. In the absence of data analysing the previous clinical lots in terms of quantification of forms by this other method, it can not be concluded that no significant changes on the quality attributes occurred between the clinical batches and the commercial product.

Forms with reduced potency

The occurrence of high levels of forms with reduced bioactivity raises several concerns with respect to the consistency of the quality of the product and its uniform clinical performance.

First, the company was not able to demonstrate that there is no partition effect on product related impurities upon interaction with the β-TCP component. Results using the bioassay to quantify other forms and to demonstrate that there is no partition effect are not convincing given the wide variability of this bioassay and given that results are inconsistent with other results provided in the application. Therefore, a more direct quantification of the other forms is required to unequivocally demonstrate that no partition occurs favouring the presence of less potent forms.

Second, there are high levels of forms of reduced potency in the drug substance and drug product which are not appropriately controlled. The company proposed to tighten the limit of the specification for other forms in drug substance lots based on the claimed positive outcome of non-clinical and clinical data. The proposed reduction does not constitute a significant reduction of other forms and it is not validated in light of the inconclusive clinical results. Also, the possibility that the forms of reduced potency may also be a degradation impurity has not been adequately investigated and addressed. Since the possible partition effect cannot be ruled out, a significant reduction and adequate control of the other forms at the level of the drug product is important to ensure consistent product production and since these forms may have a detrimental impact on the uniform clinical performance of the product. It is possible that this will only be possible by making significant changes such as including additional purification steps for the drug substance.

Non-clinical pharmacology and toxicology

The non-clinical part of the dossier for Gemesis is not entirely satisfactory. There is a rationale for the inclusion of rhPDGF-BB in the scaffold, but the only proof of concept study which is meaningful for the periodontal indication applied gave moderate evidence of efficacy and it is not clear whether a lower dose can be used. In addition, no studies were performed by the Applicant to study the affinity and interaction pattern of rhPDGF-BB to the human receptors as compared to human PDGF, and to the target receptors in the species used for pharmacology and toxicology studies. This reduces the value of the results of the safety studies performed and again questions the basis for clinical dose selection. The application of

rhPDGF-BB will be local, but a leakage from the site of application into periodontal tissue, namely the gingiva, might be possible and the consequence is not clearly defined. Given the clinical experience with the matrix scaffold, no additional studies were deemed necessary. However, several concerns related to the safety of rhPDGF-BB were not sufficiently clarified by the Applicant.

Efficacy

The clinical development plan for the efficacy of Gemesis in the treatment of periodontally related defects includes only one pivotal trial which failed its primary endpoint. Even though the use of Gemesis led to significant improvements in the secondary endpoints linear bone growth (LBG) and % bone fill (% BF) at 6 months (radiological secondary outcomes), it failed to show a significant difference in terms of other secondary endpoints. Therefore a general lack of consistency between important endpoints was recognised. Furthermore, long term data of up to 36 months showed that the claimed initial bone gain obtained with Gemesis as compared to the β-TCP matrix alone was not maintained further questioning the long-term benefit of the product. Moreover, the reason for the better outcomes for the low concentration of Gemesis compared to the high concentration was not sufficiently explained by the Applicant and its importance remains unknown. The data from the additional phase II trials and the supportive data were insufficient to compensate for the deficiencies of the pivotal trial. Overall, the Applicant failed to provide convincing evidence of efficacy and therefore the benefits of adding becaplermin to the β-TCP matrix were not confirmed.

Safety

The available safety data derived from the only clinical study performed suggests that the single application of β-TCP, with and without the adjunctive use of rhPDGF, was reasonably safe in periodontal procedures with a low rate of associated adverse events (AEs) and no serious or unanticipated AEs attributable to Gemesis. However, the number of subjects treated in this trial is rather limited (121 patients). In fact only 60 patients were exposed to the actual proposed dose of 0.3 mg/ml and the patients were only followed for six months and no long-term safety follow-up data is available in order to detect unanticipated adverse effects. In view of the wide potential target population for Gemesis the size of the safety database was not considered sufficient without long-term post-marketing observational studies. Furthermore, a slight concern remained with regards to potential risks associated with possible repeated applications of Gemesis, such as carcinogenicity and immunogenicity, in patients with several surgical procedures at different sites.

Risk-benefit assessment

The rationale of Gemesis is based on the addition of a growth factor to a matrix in order to enhance its capacity for tissue regeneration since periodontal regeneration is a fundamental therapeutic objective for the maintenance of teeth in health and function.
Although the product seems to have a low rate of associated AEs, the safety database from controlled studies on the proposed indications is small. In addition the patients were only followed for six months concerning safety.
It is considered that the addition of the growth factor must improve the efficacy of the matrix in order to justify the authorisation of the combination. This potential has been insufficiently supported by the provided clinical data as the only clinical study failed the primary endpoint. The supportive studies are clearly insufficient to compensate the pivotal trial results. In addition, it is not proven that the potential treatment benefit is sustained over a year or more as compared to β-TCP alone. There is evidence that the claimed initial gain over the β-TCP was not maintained beyond 6 months.
It is not considered that historical comparisons showing similar efficacy of the combination to other graft materials is sufficient to grant a marketing authorisation for Gemesis.
Overall, the results of the single pivotal trial do not show convincing evidence that adding becaplermin to the matrix is of any benefit.

The lack of substantial efficacy of the combination as compared with the matrix alone cannot outweigh the low risk of adverse reactions. There is a slight concern about potential carcinogenicity.

Conclusions

In conclusion, the CHMP considers that, following review of the data provided, there are major concerns with respect to the risk-benefit of Gemesis in the treatment of periodontally related defects on the following grounds:

- Efficacy has not been demonstrated for the proposed indications as the single pivotal trial failed the primary end point. The data from other phase II trials are insufficient to compensate for the deficiencies of the pivotal trial. In addition, the long term data showed that after 36 months the initial bone gain claimed with Gemesis as compared to the β-TCP matrix alone was no longer observed.

- The binding affinity and interaction pattern of recombinant human PDGF to the human receptors and to the receptors in the animal species used for the pharmacology and toxicology studies as compared to human PDGF was not sufficiently clarified.

- The comparability of product used in clinical studies and product intended to be placed on the market had not been demonstrated.

- The levels of forms with reduced potency in the active substance/finished product are not appropriately controlled. The levels must be greatly reduced to ensure consistent product production and accurate measure of becaplermin-specific biological activity. It has not been unequivocally demonstrated that there is no partition effect upon interaction with the β-TCP component favouring the presence of the less potent forms.

- Due to the aforementioned concerns, a satisfactory summary of product characteristics, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Gemesis in the treatment of periodontally related defects was unfavourable and therefore did not recommend the granting of the marketing authorisation.

3. RE-EXAMINATION OF THE CHMP OPINION

At the July 2009 CHMP meeting, the CHMP concluded that the risk-benefit balance of Gemesis, that is intended for the following indications:

- For bone and periodontal regeneration in adult patients only.
- To treat periodontally related defects, including:
    - Intrabony/Infrabony periodontal defects; and
    - Furcation periodontal defects; and
    - Gingival recession associated with periodontal defects,

was unfavourable and therefore did not recommend the granting of the marketing authorisation.

On 22 September 2009, the applicant submitted the detailed grounds for the re-examination of the grounds for refusal listed above.

Ground for Refusal 1
The comparability of product used in clinical studies and product intended to be placed on the market had not been demonstrated.

- Company ´s response

BioMimetic Therapeutics, Inc. (BMTI) acknowledges that a direct comparison of rhPDGFBB Drug Product lots was not performed during the transition from the production of clinical materials to the manufacture of commercial product. However, analytical data are available for a retrospective comparison of the characteristics of one clinical lot, filled at Chesapeake Biological Laboratories, with the initial commercial batches, filled at Patheon, and product manufactured in 2005, 2006, and 2007 for commercial distribution.

The rhPDGF-BB Drug Product is produced by a simple dilution of the Drug Substance in an aqueous sodium acetate buffer. The buffer composition is identical to the buffer used to prepare the Drug Substance. The preparation of the Drug Product is performed in a controlled environment following a validated production process to reduce the potential for introducing changes. BMTI acknowledges that changes in the characteristics of rhPDGF-BB (such as an increase in the percentage of two forms) can affect the biological activity of rhPDGF-BB since both variants have a reduced potency. However, the fact that the content of one form is consistently below the limit of quantitation – also during long term stability – makes it unlikely to impact the biological activity. Furthermore, BMTI proposes to tighten the specification of this form.

Previous work suggests that the intact and one variant of rhPDGF-BB have similar biological activity, while another variant of rhPDGF-BB has reduced biological activity. The different variants have been isolated by high temperature HPLC and assayed in a bioassay used for release of drug substance and drug product.

The bioassay is able to detect differences in product potency. When intact (IN) rhPDGF-BB is spiked with a known amount of the other species, two bioassays were sufficiently sensitive to detect a decline in bioactivity in response to an increasing proportion of the variant with reduced bioactivity.

A revised specification has been established for the level of the reduced-potency form acceptable in the rhPDGF-BB DS.
The variants of the material differ substantially in the test profile of one method indicating the appropriate use of this method to show changes in the variants although direct measurement of the variant is best achieved by another method.

Data obtained from testing clinical and commercial batches of Drug Product are presented. These data demonstrate the consistency of the manufacturing process for the transition from production of clinical materials to the manufacture of Drug Product for commercial distribution.

- CHMP conclusion

The data package provided by the Applicant on the comparability between the product used for phase III clinical trial and the product intended for the market, has been reviewed. No new information is presented; the Applicant's opinion is based on the same evaluation as was submitted during the original assessment

A number of changes in the manufacturing process have taken place both for the drug substance and for the drug product between phase III clinical studies and the initial commercial manufacturing process., Considering the heterogeneity of the drug substance, with emphasis on the forms with significantly

reduced biological activity, and the nature of the changes introduced to the manufacturing process, a comprehensive evaluation would be required in order to satisfactorily demonstrate comparability between the product used in late clinical trials and the product intended for the market. No direct comparison is however available.

For qualification of reference standards, the Applicant provides a characterisation analysis including determination of different rhPDGF-BB forms. The results suggest similar degree of the different forms in the three standard batches analysed. The batch results included for one clinical batch, three initial commercial batches, and for commercial batches produced in 2005, 2006, and 2007, do not confirm the level of forms with the reduced-potency as the method in use is unable to separate the forms with normal biological bioactivity and reduced bioactivity. This is a major deficiency, which cannot be compensated by the potency data as proposed by the Applicant. The differences in the potency test results for protein preparations with differing ratios of forms are very small and they are further diluted by the high variability of the cell-based potency assays. The main problem, however, is the lack of data on forms with reduced bioactivity in the clinical DP batches, which hampers the comparability assessment between the clinical and commercial lots.

As a conclusion, the reassessment of the comparability data provided leads to the same conclusion as in the original evaluation, i.e. comparability between the product used for clinical trials and the current commercial material, has not been properly demonstrated.

Ground for Refusal 2

The levels of forms with reduced potency in the active substance/finished product are not appropriately controlled. The levels must be greatly reduced to ensure consistent product production and accurate measure of becaplermin specific biological activity. It has not been unequivocally demonstrated that there is no partition effect upon interaction with the β TCP component favouring the presence of the less potent forms.

- Company´s response

There are two molecular variants of becaplermin that demonstrate reduced activity. However, the fact that the content of one form is consistently below the limit of quantitation – also during long term stability – makes it unlikely that this form will impact the biological activity. The other variants have been isolated under high temperature and assayed in the bioassay used for release of drug substance and drug product.
The content of forms of reduced potency in the Drug Substance originates from the biosynthesis in yeast and the fermentation process. During product development in the 1990s the yeast cell construct was changed in order to achieve a reduction in material with reduced bioactivity. The current yeast construct has been shown to produce rhPDGF-BB with a consistent and decreased amount of material with reduced bioactivity, and this active drug substance is the basis for both Regranex and *GEMESIS*. According to the Applicant, a further reduction of the content of material with reduced bioactivity would only be possible either by developing a new engineered yeast strain for production or by eliminating the cleavage site by recombinant technology. Attempts to separate the variants using chromatography have not been successful either.
According to the Applicant, Drug Substance lots used by the company for all non-clinical, clinical and commercial scale DP lots have had the same specifications for material with reduced bioactivity. The revised specifications for the respective forms were set by evaluation of the manufacturing variability of Commercial lots. While the first method is used to analyze the rhPDGF-BB DS, the second method is used for analysis of both the DS and the DP, and can be used to quantify the percentage of the protein that is cleaved. The Applicant has provided retrospective characterisation data using the first method; however the batches studied do not contain the clinical lots.

Although the potency material with reduced bioactivity is decreased, the overall potency of the Drug Product, as measured by the bioassay that uses a working standard calibrated against the WHO rhPDGF-BB International Standard 94/728 and expressed in International Units per mg protein, is still considered adequate to exert a biological action. This is evidenced by the body of non-clinical and clinical data on safety and efficacy of rhPDGF-BB.

Mixing and elution kinetics of rhPDGF-BB from the β-TCP component of *GEMESIS* have been studied. The interaction of the rhPDGF-BB with the β-TCP ceramic material is minimal with no adsorption of the protein to the β-TCP, but rather, physical entrapment of the liquid containing the protein between the β-TCP particles. Analysis of the eluted rhPDGF-BB has shown that the eluted protein is chemically identical to the protein present in the starting material. The results demonstrate that the ratio of variants is not affected by the β-TCP matrix, and hence there is no partition effect on the variants of rhPDGF-BB.
Although the first method was performed to directly quantify the variant, the profiles of the second method showed that the overall amount of variants was consistent.

- CHMP conclusion

The overall content of truncated forms in the DS is very high. At release and during stability studies, the Applicant has followed truncated DP variants by the second method, which unfortunately is not able to separate the variants. The first method has been used as part of retrospective characterisation to verify the amount of forms with reduced potency in the commercial batches and the levels. The original specification set by the company for all forms for individual batches exceed the specification for all batches.
The statement about the variants occurring during the fermentation only is not substantiated by data. In the study report, the Applicant mentions "partial nicking" occurring during fermentation, which could mean that part of the variant occurs later during the process. It cannot be also excluded that part of the enzyme responsible could be co-purified with the drug substance. Since data obtained with the first method for the forms with reduced potency is not available for process validation, stability evaluation, nor for DP batch release, the company's claims cannot be endorsed. It is also unclear; why the Applicant has restricted the purification attempts to chromatography and not tried other possibilities to reduce the level of the form.
The acceptable level for forms with reduced potency in the final product should be justified by functional, non-clinical and clinical data. The functionality of the recombinant PDGF is clearly impaired by the missing parts of the Beta-strand and the reason to allow administration of significant amounts of forms with reduced potency into the patients is questionable. The correlation between heterogeneity of the rhPDGF and the potency of the product has not been demonstrated; the differences between spiked materials are very small and should be considered negligible as the variability of the cell-based potency assays is high. Neither are the signals from non-clinical and clinical studies supporting the view of adequate, controlled biological activity for the product.
Regarding the partition effect, the Applicant has, again, studied this possibility using analytical chromatography. As this method does not separate the forms with reduced potency, it is impossible to draw any firm conclusions whether either of the forms could be superseding the other in the final combination.

Ground for Refusal 3
The binding affinity and interaction pattern of recombinant human PDGF to the human receptors and to the receptors in the animal species used for the pharmacology and toxicology studies as compared to human PDGF was not sufficiently clarified.

- Company's response

A review of receptor binding data for human recombinant PDGF-BB both for human receptors and rat receptors demonstrates that the affinity of the human protein is similar in both species. As previously stated the primary amino acid sequence of PDGF is highly conserved across species, with the lowest level of amino acid identity being 91% comparing the rat and human proteins and other relevant species

comparisons having higher levels of identity between 92-98% that of human. On the basis of the conservation of PDGF sequence across species, it is expected that the binding affinities of the human PDGF protein would be similar for receptors on cells from species relevant to the pivotal toxicology studies discussed in the *GEMESIS* submission to EMEA. As requested by CHMP reviewers, the data in Table 1 summarize the available binding data for human PDGF, derived from recombinant sources, with receptors from human and rat.

Table EPAR-EMA/CHMP/791565/2009-1: Summary of Published Binding Data for Recombinant Human PDGF-BB with PDGF receptors of Human and Rat Origin

Literature Source	Species origin of cells or receptors	Source of purified human PDGF	Cell Type or Purified Receptor	Half-Maximal Binding (nM ^{125}I-PDGF)	Apparent Dissociation Constant (K_d, nM)
[1]	Human	Yeast recombinant, pure BB	Skin fibroblasts (SK5) and osteosarcoma cells (U-2 OS)	0.050	ND
[2]	Rat	*E. coli* recombinant, pure BB	Liver fat-storing cells	0.15-0.18	0.023
[3]	Human	*E. coli* recombinant, pure BB	Purified *E.coli* recombinant PDGF β and β-receptor	ND	0.50

Prior to the availability of purified recombinant PDGF-BB, binding studies were conducted using crude preparations of human PDGF purified from platelets when less was understood regarding the multiplicity of isoforms of the PDGF protein (i.e. AA, AB and BB) or that two receptors for PDGF existed. Since the preparations used in these studies did not consist of homogeneously purified proteins, there is greater variability in the data from one study to the next. However, if data are compared within a single study so that a single PDGF preparation is compared against itself on multiple cell types from different species, there is value in showing that similar binding affinities were measured. The data from these studies is summarized in Table 2. For example, the study conducted by Bowen-Pope and Ross (1982) included comparisons of binding data for crude human PDGF preparations isolated from platelets to cells from mouse, human and monkey (macaque) species. The binding data were similar (approximately 10 pM) for each of the cell lines tested, suggesting that the binding affinities of human PDGF across these species is very similar.

Table EPAR-EMA/CHMP/791565/2009-2: Summary of Published Binding Data for Human PDGF Partially Purified from Human Platelets with Cells or Crude Receptor Preparations

Literature Source	Species origin of cells or receptors	Source of purified human PDGF	Cell Type or Purified Receptor	Half-Maximal Binding (nM ^{125}I-PDGF)	Apparent Dissociation Constant (K_d, nM)
[4]	Human	human platelets, crude	Foreskin fibroblasts	2-3	0.10
[5]	Mouse	human platelets, crude	3T3 cells	0.0065	0.0086
	Mouse		3T3 cells, high-binding	0.0075	0.0122
	Monkey (macaque)		Smooth muscle cells	0.0105	0.017
	Human		Foreskin fibroblasts	0.0060	0.0077
	Human		Smooth muscle cells	0.0085	0.0108
	Human		A431 carcinoma cells	0	0
	Mouse		3T3 variant clone PF 2	0.0107	0.010
[6]	Mouse	human platelets,	3T3 cells	0.17	ND

	Mouse	crude	3T3 cell membranes	0.20	ND
	Rat		Liver cell membranes	0.080	ND
[7]	Mouse	human platelets, crude	Purified receptors	ND	0.10
[8]	Rabbit	Human platelets, purified AB isoform	Renal papillary and cortex fibroblasts	ND	0.20-0.80

A significant portion of the published studies on the function of PDGF in wound healing have focused on soft tissue and skin lesions in a variety of species. There are also a sizeable number of nonclinical studies published that demonstrate the *in vitro* and *in vivo* activity of PDGF for osteoblasts, osteoclasts, and chondrocytes, supporting the role of rhPDGF-BB as a therapeutic treatment for bone regeneration and repair in a variety of species. Along with dermal and bone tissue indications, Table 3 summarizes non-clinical studies that demonstrate the efficacy of human PDGF for eliciting biological responses in a wide variety of cells, tissues and organs in species used for toxicity testing. The literature is rich with examples of human recombinant PDGF eliciting biological responses in cells and tissues from mouse, rat, rabbit, dogs, monkeys and other species that support using them as relevant analogs to humans for toxicity testing.

Table EPAR-EMA/CHMP/791565/2009-3: PDGF published non-clinical studies: soft and hard tissue	
In vitro studies	
Primary mouse cells	[9] (fibroblasts) [10] (bone)
Primary rat cells	[2] (liver) [11] (bone) [12] (kidney) [13] (kidney) [14] (bone) [15] (bone) [16] (bone) [17] (bone) [18] (cardiovascular)
Primary rabbit cells	[8] (kidney)
Primary canine cells	[19] (kidney)
Primary equine cells	[19] (kidney)
Primary bovine cells	[20] (cartilage)
Table EPAR-EMA/CHMP/791565/2009- is continued on the following page	

Table EPAR-EMA/CHMP/791565/2009-3: PDGF published non-clinical studies: soft and hard tissue (continued)	
***In vivo* studies**	
Mice	[21] (developmental) [22] (bone)
Rats	[23] (cartilage/bone) [24] (dermal) [25] (cardiovascular) [26] (bone) [27] (kidney) [28] (bone) [29, 30] (bone) [31] (bone)

	[32] (bone) [33] (bone) [34] (bone, cementum) [35] (bone)
Rabbits	[36] (dermal) [37] (dermal) [38] (bone) [39] (cornea) [40] (dermal)
Dogs	[41] (periodontal) [42] (periodontal) [43] (periodontal) [44] (periodontal) [45] (periodontal) [46] (periodontal) [47] (periodontal)
Pigs	[48] (dermal)
Monkeys	[49] (periodontal) [50] (periodontal)

The data from the literature provided demonstrate the range of binding affinities for PDGF to human, mouse, rat, rabbit and monkey receptors on various cell types. The binding affinity data vary depending on the preparation of PDGF used (recombinant or purified from human platelets), and the cell types or purified receptors under study. In the majority of cases, the apparent dissociation constant (K_d) for human PDGF preparations binding to PDGF receptors, either purified or on human cells, range from 0.10 to 0.50 nM. In comparison, K_d's for various species were 0.023 nM for rat liver cells, 0.10 nM for purified mouse PDGF receptors, and 0.20-0.80 nM for rabbit renal cells. Thus, on the basis of apparent K_d's, the binding affinity of human PDGF for cells and receptors from pivotal species used for toxicology studies lie in a similar range to those of human. The human PDGF preparation evaluated by Bowen-Pope and Ross (1982) exhibited binding affinities (K_d) that were an order of magnitude lower than most other studies reporting this type of data. In this study, human PDGF purified from human platelets bound to human cells with K_d's ranging from 0.0077 to 0.0108 nM compared to 0.0086 to 0.0122 nM for mouse cells and 0.017 nM for monkey cells. Considered alone, the study by Bowen-Pope and Ross demonstrated that binding affinities of human PDGF for cells from pivotal animal species used for toxicity testing are very similar to those for PDGF receptors on human cells.

The company is conducting laboratory studies to further characterize the binding of yeast-derived rhPDGF-BB to cell lines from human, rat, mouse and rabbit to provide additional data in this regard. A report on the findings from these studies will be submitted to EMEA upon completion.

The CHMP reviewers have requested that we calculate safety margins for the various safety data submitted in support of the approval of *GEMESIS*. The maximum human clinical dose of *GEMESIS* is one (1) kit per patient, which is equivalent to a total dose of 0.15 mg of rhPDGF-BB. For a patient having a mass of 70 kg, this is equivalent to a dose of 2.1 µg rhPDGF-BB per kg body weight. As an example, the safety margin in the studies conducted to evaluate systemic toxicity in mice involved extraction of 1.0 mg/ml rhPDGF-BB combined with β-TCP in vehicles such as 0.9% saline or cottonseed oil. The extraction procedure led to dilution of the rhPDGF-BB by a 10-fold factor yielding about 0.1 mg/ml rhPDGF-BB in the extracts. Mice were dosed at 50 ml extract/kg body weight intraperitoneally and as a result they received a dose of rhPDGF-BB equivalent to 5 mg/kg body weight. Thus, mice received a dose that exceeded the maximum human clinical dose (2.1 µg/kg body weight) by approximately 2,381-fold for the evaluation of systemic toxicity. This clearly represents a massive dose of the protein especially considering that, as discussed previously, the

binding affinity of human PDGF appears to be similar for mouse PDGF cell-surface receptors compared to human. No acute toxic outcomes were observed in the mice over a 7 day period following dosing in any of the studies conducted. For some of the ISO 10993 studies submitted to EMEA to provide safety data for *GEMESIS*, extractions of the formulated product were conducted in a standard fashion that led to a final rhPDGF-BB concentration of approximately 0.1 mg/ml in the various extraction vehicles.

An exception to this included the procedure for conducting intramuscular implantations of rhPDGF-BB combined with β-TCP in rabbits. These studies were designed to implant the formulated product, undiluted, into four intramuscular sites in the paravertebral muscles of rabbits. A total of 0.1 ml of 1.0 mg/ml rhPDGF-BB combined with β-TCP was implanted per IM site on each rabbit. This was equivalent to implanting approximately 50 µg of rhPDGF-BB per site for a total of 0.2 mg per animal. The animals had masses of about 4 kg each such that the dose received was 50 µg rhPDGF-BB/kg body weight. In comparison to the maximum clinical dose received by patients treated with *GEMESIS* (2.1 µg/kg), the dose administered to rabbits exceeded the maximum human dose by approximately 24-fold. The *GEMESIS* test article in these studies was evaluated histopathologically and found to be a slight irritant in comparison to controls 4 weeks after implantation.

Similarly, a neat preparation of 0.3 mg/ml rhPDGF-BB that had been aged for >12 months at 30°C was injected in 0.2 ml aliquots intracutaneously and paravertebrally in five locations in rabbits to evaluate the test article for dermal reactions. Thus, a total of 0.3 mg of rhPDGF-BB was delivered to rabbits weighing approximately 4 kg. The total dose delivered was, therefore, 75 µg/kg body weight which represents a dose exceeding the maximum human clinical dose for *GEMESIS* of approximately 36-fold. The conclusion from the study was that the test article was a non-irritant following intracutaneous injection in rabbits.
Thus, in the preclinical studies submitted in support of the safety of *GEMESIS*, there was a large safety margin built into the studies to ensure the outcomes were relevant to humans.

- CHMP conclusion

The Applicant has provided literature data on the binding properties of hPDGF onto receptors of several experimental species. Overall the binding affinity of hPDGF to receptors of rat, rabbit and dog seems to be very similar to that of binding to the human receptors. The source of PDGF and methods of binding analysis differ between the available literature data. However, when comparing data within each study the equivalent cross-species binding of hPDGF seems valid. Also, the Applicant is conducting studies to generate rhPDGF binding.

The applicant has provided literature data addressing the binding properties of rhPDGF to human and rat receptors. It is difficult to conclude based on the limited and variable data provided, maximal binding (nM ^{125}I-PDGF) and apparent dissociation constant (K_d, nM), from different assays.

The applicant has also provided published binding data for human PDGF with cells or crude receptor preparations from human, mice or monkey (macaque). Only one study including different species receptors (mouse, monkey and human) has been submitted (Bowen-Pope and Ross, 1982). Half-maximal binding values obtained were similar among species, and around 8 pM. However, it should be considered that the test item was purified human PDGF and not the rhPDGF under assessment in this procedure.

The applicant also provided literature references regarding human PDGF biological responses in a wide variety of cells, tissues and organs in species used for toxicity testing. However, these data do not specifically address the aforementioned concern. In addition, it should be considered that effects on the periodontium were mainly observed after co-administration of PDGF and IGF-1.

The applicant stated several assays were performed to specifically address the CHMP concern. However, the only information provided is six figures. This information cannot be assessed since its origin is

uncertain and the relevant study reports have not been submitted during the procedure. In addition, it remains unknown if human PDGF was also tested in these assays and if results from both substances were compared.

For future marketing authorisation applications it is noted that the issue could be reconsidered if the applicant provides a) sufficient results of rhPDGF binding studies, b) full study reports of the 6 assays stated to have been performed to address the CHMP concern and c) an updated critical appraisal of these data, specifically addressing the CHMP concern.

In conclusion, the Applicant has shown that hPDGF has similar binding to human, rat, rabbit and dog receptors. It should be considered that the test item was purified human PDGF and not the rhPDGF under assessment in this procedure and therefore, the ground for refusal has not been sufficiently addressed.

Ground for Refusal 4

Efficacy has not been demonstrated for the proposed indications as the single pivotal trial failed the primary end point. The data from other phase II trials are insufficient to compensate for the deficiencies of the pivotal trial. In addition, the long term data showed that after 36 months the initial bone gain claimed with Gemesis as compared to the β-TCP matrix alone was no longer observed.

- Company's response

The Applicant argues that the body of evidence demonstrates the clinical safety and effectiveness of Gemesis. This pivotal trial used the most rigorous and sensitive scientific methods available for large randomized clinical trials, to analyze the data which support these claims. The studies referenced provide the highest levels of evidence, including clinical, radiographic, and histological evidence of efficacy, which has not been demonstrated by other regenerative therapeutics. As such, the Company feels that the risk to benefit profile of Gemesis is favourable and warrants strong consideration from the EMEA for marketing approval.

The applicant further states that:

Gemesis is an established, marketed combination product for the treatment of severe periodontal disease requiring regenerative procedures. This combination product has an excellent track record of safety and efficacy in its many years of commercial distribution in the U.S. and Canada.

Periodontal disease is a common and serious medical condition with an increasing prevalence with age. It can be debilitating if not properly treated resulting in poor nutrition and social isolation. There is substantial evidence documented in published papers in peer reviewed journals that severe periodontal disease may increase a patient's risk for coronary artery disease, stroke, bacterial infections including endocarditis, respiratory infections, diabetes, impaired fertility, premature births, low birth weight babies and preeclampsia. The condition requires improved treatment modalities and represents an unmet medical need. Further, there are currently no fully synthetic treatment options in the EU that have demonstrated the level of evidence (i.e. efficacy and safety) as Gemesis, which includes, clinical, radiographic, and histological evidence of periodontal regeneration.

While the single, pivotal efficacy trial presented in the application for marketing authorisation did not demonstrate statistical efficacy for the designated primary efficacy endpoint of clinical attachment level at 24 weeks this endpoint is only one of several clinically reasonable surrogate endpoints for the definitive one of histological evaluation, which is not possible for large clinical trials such as this.

In addition to the Pivotal study, a long-term (12, 24 and 36 month) follow-up report of a subset of patients enrolled in the Pivotal study was completed (Study BMPI-2001-EXT), and as well as five additional

periodontal study reports (BMPI-2002-01-Study 1; BMPI-2003-01- Study 3; BMPI-2002-02-Study 4; BMPI-2002-02-Study 5; and Luitpold Study No. 1GEM04001).

It should be noted that while the CHMP has criticized the study for not achieving its primary endpoint, the Sponsor would like to point out that the primary endpoint of CAL gain was achieved at an earlier time point than expected (12 weeks) and thus a statistically significant improvement in CAL between baseline and 24 weeks was demonstrated. The pivotal study achieved statistically significant results for many other end points including secondary efficacy endpoints of linear bone growth at 24 weeks, percent bone fill at 24 weeks, composite effectiveness using CAL and LBG(%) at 24 weeks and composite effectiveness using CAL and BF(%) at 24 weeks. The significant results for LBG and BF indicate a strong regenerative promoting affect on bony tissue and the significant composite results indicate a clinically meaningful dual affect on soft and bony tissues. There was also a significant effect on wound healing at the 3 week time point which along with the positive result for CAL at 12 weeks and the significant affect on Area Under the Curve (AUC) for CAL indicate that *GEMESIS* accelerates the rate of tissue regeneration resulting in a better outcome more quickly. This enhancement of the healing and regenerative processes is a desirable effect which can mitigate the risk of infection and promote patient comfort and compliance with good oral hygiene, and has not been demonstrated by another synthetic product to date. In the extension study LBG was statistically superior in both active groups at 12, 24 and 36 months. BF was statistically superior in both active groups at 12 and 24 months. The composite endpoint of CAL & LBG achieved statistical significance at 12 months (1 mg/mL group), at 24 months (both active groups) and at 36 months (0.3 mg/mL group). In addition, the composite result of CAL and BF showed numerically superior results at 12, 24 and 36 months. Finally, for the primary efficacy endpoint of CAL there were numerically superior results which increased in magnitude over time at 6, 12, 24 and 36 months. These data support the long-term effectiveness of GEMESIS. It should be noted that while the other treatment groups continued to demonstrate improvements at later time points, this is an expected outcome, as the β-TCP control is CE-marked as a bone void filler and is commonly used to enhance periodontal repair. The assertion that the beneficial results of Gemesis were not sustained during the extension study does not seem to be supported by the actual data [cross ref data in dossier/responses].

The Gemesis pivotal trial is highly regarded by the medical professionals that specialise in treatment of periodontal disease. The trial is by far the largest randomized controlled clinical trial ever conducted on a grafting material in periodontal bone defects. The difficulties in conducting large scale periodontal clinical studies are well recognised, meta-analysis within the field generally includes studies with an average sample-size of 20-30 patients.

In total, two hundred four (204) patients (212 treatment sites) received rhPDGF-BB in the Pivotal study and the five additional periodontal studies; 116 treatment sites received the Gemesis configuration (0.3 mg/mL rhPDGF-BB + β-TCP); 83 treatment sites received 1.0 mg/mL rhPDGF-BB + the Gemesis β-TCP; and 13 treatment sites received a combination of rhPDGF-BB + DFDBA (demineralised freeze-dried bone allograft) or DFDBA/Xenograft, which are commonly used matrices in the subject indications. Additionally, a study was conducted in Brazil (BPI-2000-01-Brazil) where 11 out of 15 treatment sites (in 9 patients) received 0.5 mg/mL-, 1.0 mg/mL- or 5.0 mg/mL- rhPDGF-BB combined with DFDBA. This was the initial human clinical trial utilising rhPDGF-BB to treat periodontal defects and involved the taking of human biopsies of jaw bone and gum tissue to assess on a cellular level the safety and efficacy of the product. This study is highly significant as it was the first time true periodontal regeneration had been demonstrated histologically using recombinant growth factor technologies. Except for BMPI-2003-01-Study 3, results of all of these studies have been published in internationally recognised peer-reviewed periodontal journals. Theses periodontal clinical studies are previously summarised and assessed, see above. In addition, data from seven studies using 0.3 mg/mL rhPDGF-BB for orthopaedic indications were provided to support the safety of Gemesis.

- CHMP conclusion

No additional analyses of the data were provided by the Applicant. The major clinical concern regarding the benefit-risk of Gemesis in the treatment of periodontically related defects remains.

The CHMP is of the opinion that the available data do not provide sufficient evidence of the efficacy of Gemesis in the treatment of the claimed indications. In a single pivotal study, results must be robust and consistent in order to support efficacy.

This view is based on:

The added benefit of the growth factor (0.3 mg/mL rhPDGF-BB), to the matrix (β-TCP) is not considered sufficiently demonstrated.

- *The primary endpoint, CAL gain at week 24 compared to controls, was not achieved in the single pivotal study.*
- *There is a lack of consistency in secondary endpoints.*
- *Only two (linear bone growth (LBG) and % bone fill (BF) of the five secondary endpoints comparing group I with group III at week 24 (wound healing was assessed three weeks post surgery) demonstrated statistical superiority for Gemesis.*
- *The better result in CAL gain in the test group demonstrated at 3 months post surgery is not considered clinically relevant as this advantage of the addition of the growth factor did not sustain at 6 months or later.*
- *The rational for the selected becaplermin dose, 0.3 mg/mL is highly incomplete:*
  - *No specific dose-finding studies were performed.*
  - *The selected dose (0.3mg/ml) is not supported by the additionally submitted phase 2 studies. In all three phase 2 studies comparing two concentrations of rhPDGF-BB (0.3 mg/mL and 1 mg/mL) in combination with β-TCP (Study 1, Study 3 and Study 5) the groups receiving the higher dose, 1.0 mg/mL rhPDGF-BB, performed numerically but not significantly better for the endpoint CAL gain compared to those receiving 0.3 mg/mL rhPDGF-BB. In addition, in study 1 regeneration was more pronounced in subjects receiving the higher dose, and in study 5 100% root coverage was achieved at 6 months for the 1.0 mg/mL treatment compared to 54% in subjects receiving 0.3 mg/mL.*
- *No significant difference between the test group and controls in wound healing three weeks post surgery could be demonstrated. This is a short term efficacy parameter of importance for patients' comfort and compliance with oral hygiene and risk of infection.*
- *Long-term follow-up data (up to 36 months) do not convincingly support any sustained benefit of the addition of the growth factor over the use of the matrix alone. Importantly, missing data was not taken into consideration in the assessment of long-term efficacy.*
- *Comparison with historical data is not considered sufficient to support weak results in the pivotal study.*

Although the product seems to have a low rate of associated AEs, the safety database from controlled studies on the proposed indications is very small.

- *Currently available safety data are deemed insufficient to justify a positive benefit – risk balance for Gemesis, due to the limited population of target patients exposed for Gemesis, the lack of long-term safety data and data on repeated use.*

- Oral clarification during the BWP meeting on 9th November, 2009

During the oral explanation the Applicant presented data that was also included in the re-examination response package. No new information was provided concerning the level of forms with reduced potency in the Drug Product to demonstrate the comparability of the batches used in the clinical studies and those intended for commercial use. The Applicant confirmed that both beta-strands alter the 3D structure of the

PDGF molecule and thus reduces the capability of the molecule to bind its receptor. Glycosylation was not considered to be an issue for the activity of the PDGF molecule. During the discussion it was noted that the level of forms with reduced potency in the final product could be reconsidered if the clinical risk/benefit for such product is clearly positive and provided that the product is adequately controlled with regards to the product forms with reduced activity.
The BWP endorsed the conclusions drawn by the Rapporteur and the Co-Rapporteur. Based on the review of the quality grounds for re-examination and on the explanations given by the Applicant during the oral clarification in front of BWP, the BWP considers that the application for Gemesis is not approvable, as major deficiencies remain precluding a recommendation for a marketing authorisation. The remaining major quality issues pertain to 1) the comparability of the materials produced for clinical studies and for commercial use and to 2) the uncontrolled level of the form with reduced potency in the final product and lack of demonstration that there is no partition effect upon interaction with the β TCP component favouring the presence of the less potent forms.

Views of the clinical ad hoc expert group on Gemesis

For the evaluation of the grounds for re-examination, the CHMP decided to consult an *ad hoc* expert group for Gemesis consisting of experts with expertise in the treatment of periodontally related defects. The ad hoc expert group met on 10 November 2009.
The group first discussed the List of Questions to be addressed by the experts. In relation to this, current clinical practice and issues when treating periodontally related defects were discussed.
The Applicant gave an oral clarification at the *ad hoc* expert meeting. The following questions were to be addressed by the Applicant in their presentation:

- Efficacy has not been demonstrated for the proposed indications as the single pivotal trial failed the primary end point. The data from other phase II trials are insufficient to compensate for the deficiencies of the pivotal trial. In addition, the long term data showed that after 36 months the initial bone gain claimed with Gemesis as compared to the β-TCP matrix alone was no longer observed.

- In relation to this, the following clinical issues should be addressed:

- Clinical relevance of different endpoints, in short-term and long-term perspectives, in particular:
    - The clinical relevance of the composite endpoints; Clinical attachment level (CAL) ≥ 2.67 mm plus linear bone growth (LBG) ≥ 1.1 mm; and CAL ≥ 2.67 plus % bone fill (BF) ≥ 14.1 mm, at 24 weeks post-surgery.
    - Importance of soft tissue related endpoints, such as gingival recession and wound healing.

The experts then discussed and concluded on their views on the major concerns. There was a consensus between experts to support the following clinical major concerns raised by the Rapporteurs in their Joint Assessment Report:
-The Rapporteur considers that, following review of the data provided, efficacy of Gemesis has not been convincingly demonstrated and that the potential benefits of the addition of becaplermin to β-TCP compared to the matrix alone were not justified by the submitted documentation. There is a lack of robust efficacy data and the clinical development plan is considered insufficient. This specifically relates to lack of consistency in primary and secondary endpoints and the weak rationale for the selected target dose.

Overall conclusions on grounds for re-examination

Quality issues

With their grounds for re-examination, the Applicant provided in writing data that they subsequently presented at an oral clarification meeting held on 9 November 2009.

The grounds for refusal relating to 1) the comparability of the materials produced for clinical studies and for commercial use and to 2) the level of rh-PDGF forms with reduced potency in the final product and the lack of demonstration that there is no partition effect upon interaction with the β-TCP component favouring the presence of the less potent forms were not satisfactorily addressed by the Applicant and therefore remain. It is noted that the level of rh-PDGF form with reduced potency in the final product could be reconsidered if the clinical benefit/risk for such product is clearly positive and provided that the product is adequately controlled with regards to the product forms with reduced bioactivity.

Non-clinical issue

The Applicant has shown that hPDGF has similar binding to human, rat, rabbit and dog receptors. However, the test item was purified human PDGF and not the rhPDGF under assessment in this procedure, and therefore the ground for refusal has not been sufficiently addressed.

Efficacy issue

The rationale for Gemesis is based on the addition of a growth factor to a matrix in order to enhance its capacity for tissue regeneration which is considered clinically reasonable and supported by some of the preclinical models and in minor phase 2 studies. Histological evidence of true regeneration in humans has been provided for the association of becaplermin with β-TCP matrix, although no direct comparisons were made, i.e, β-TCP with or without becaplermin.

In the present application, efficacy of Gemesis has not been convincingly demonstrated. The single pivotal study failed its primary endpoint and there was an inconsistency in the outcomes of important secondary endpoints. The rationale for the selected dose is unclear and seems not to be supported by clinical data. Furthermore, long-term follow up data did not demonstrate any sustained benefit of Gemesis compared to the matrix alone.

GROUNDS FOR REFUSAL

Whereas

- The comparability of product used in clinical studies and product intended to be placed on the market had not been demonstrated.

- The levels of forms with reduced potency in the active substance/finished product are not appropriately controlled. It has not been unequivocally demonstrated that there is no partition effect upon interaction with the β-TCP component favouring the presence of the less potent forms. It is noted that the level of rh-PDGF form with reduced potency in the final product could be reconsidered if the clinical benefit/risk for such product is clearly positive and provided that the product is adequately controlled with regards to the product forms with reduced bioactivity.

- The binding affinity and interaction pattern of recombinant human PDGF to the human receptors and to the receptors in the animal species used for the pharmacology and toxicology studies as compared to human PDGF was not sufficiently clarified.

- Efficacy of Gemesis has not been convincingly demonstrated. The potential benefits of the addition of becaplermin to β-TCP compared to the matrix alone were not justified by the submitted documentation. There is a lack of robust efficacy data and the clinical development plan is considered insufficient. This specifically relates to lack of consistency in primary and secondary endpoints and the weak rationale for the selected target dose.

– Due to the aforementioned concerns, a satisfactory summary of product characteristics, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

The benefit-risk balance of Gemesis cannot be considered positive, and therefore the CHMP has recommended the refusal of the granting of the Marketing Authorisation for Gemesis.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit-risk balance of Gemesis, that is intended for the following indications:

- For bone and periodontal regeneration in adult patients only.
- To treat periodontally related defects, including:
    - Intrabony/Infrabony periodontal defects; and
    - Furcation periodontal defects; and
    - Gingival recession associated with periodontal defects,

was unfavourable and therefore did not recommend the granting of the marketing authorisation.