SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Regranex. This scientific discussion has been updated until 1 October 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Regranex 0.01 % gel contains becaplermin, recombinant human platelet-derived growth factor (rh-PDGF-BB), at a concentration of 100 µg/g (0.01 %). It is supplied in multi-use tubes as a non-sterile, preserved colourless to straw coloured gel for topical use, containing 15 g of gel.

Regranex 0.01 % gel is intended for topical use only, to promote the granulation and thereby the healing of full thickness chronic diabetic ulcers less than or equal to 5 cm², in association with 'good wound care'. Good wound care consists of initial debridement (to remove all the necrotic and/or infected tissues), additional debridement as necessary and a non-weight-bearing regimen to alleviate pressure on the ulcer. Wound-related infections should be identified and treated with appropriate antimicrobial therapy prior to the use of Regranex.

Chronic, full-thickness diabetic ulcers are currently treated with wound care practices which include debridement, frequent dressing changes, infection control and a non-weight-bearing regimen. When this standard therapy fails, alternative treatment regimens for chronic ulcers are limited to rigorous treatment modalities (e.g. skin-grafting or total contact casting). For patients not responding to these treatments, long standing diabetic ulcers often are complicated by infections which will eventually result in a need for amputation.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition and product development

Regranex is provided as a gel. The composition is the following: becaplermin (active ingredient, 0.100 mg/g), sodium carboxymethyl-cellulose, sodium chloride, sodium acetate trihydrate, glacial acetic acid, methylparahydroxy benzoate, propylparahydroxy benzoate, m-cresol 99%, L-lysine hydrochloride, water for injections.

Methylparaben, propylparaben and m-cresol are included as preservatives because Regranex is presented as a non-sterile multidose gel product. The combination of these preservatives is based on the experimental data for preservative efficacy (USP and BP acceptance criteria for topical products) and is optimal for the requisite biological activity. The company provided data proving that the finished product is adequately preserved. The sodium chloride content and pH are chosen to resemble physiological salt concentrations and to establish maximal stability of the active substance respectively. L-lysine hydrochloride concentration has proven to stabilise the protein in the gel formulation.

The gel is filled into laminated aluminium tubes with a polyethylene liner. Full specifications of the primary packaging and full justification for its use have been satisfactory addressed with respect to minimisation of potential interactions between the active ingredient and metal ions.

The formulation used in Phase I/II has not substantially changed, with the exception of the amount of active ingredient used where two new strengths (100 and 300 µg/g) were introduced into the Phase II studies.

In vitro release characteristics and in vivo preclinical data indicate that the becaplermin is available from the gel formulation.

A report has been submitted to simulate the in-use situation of the product by patients. The data provide reassurance that the in-use product is adequately preserved.

As a post authorisation commitment, the company investigated the development of a sterile formulation, which was to replace the present preserved formulation. The company submitted progress reports, indicating that the sterile formulation failed to demonstrate adequate evidence of clinical

efficacy in 2 controlled studies of large sample size. The CPMP concluded that the failure to develop an efficacious sterile unpreserved product was disappointing, but did not impact on the favourable benefit/risk balance previously demonstrated for the marketed product formulation. The CPMP considered that the company should be released from this post marketing commitment.

Active substance

Becaplermin has a molecular weight of approximately 24.5 kDa and is composed of two identical polypeptide chains, each composed of 109 amino acids, bound together by an inter-chain disulphide bridge. The molecule is produced by Saccharomyces cerevisae in which a plasmid encoding the sequence for the human B-chain of platelet derived growth factor (PDGF-B) is inserted.

Plasmid identity is tested by restriction profile analysis and the sequence of the expression cassette (including regulatory regions) is adequately controlled.

Adequate cell banks have been established and adequate cell bank characterisation has been performed. Stability of the cell banks during storage has been addressed with respect to purity, viability and retention of the expression plasmid. Maintenance and storage conditions of the cell banks have been detailed.

The cells are expanded through three different stages in a shake flask, batch seed fermentor and fed-batch production fermentor. In-process controls are in place, including checks for sterility, culture purity, restriction endonuclease mapping (plasmid identification) and PDGF-BB content by ELISA. Consistency of the fermentation process has been demonstrated. Quantitative and qualitative genetic stability has been shown.

The sterilisation of the culture media was adequately validated. The only animal derived reagent used in the fermentation process is hydrolysed casein, produced from milk from Australia or New Zealand, countries that have no reported cases of BSE.

The downstream processing of the active substance is a sequence of validated standard chromatographic and ultrafiltration steps. The company has provided the procedure for the performance and maintenance of the purification systems.

The routine tests ensure quality and consistency of the active substance.

The mature rhPDGF-BB is composed of 2 identical antiparallel glycosylated polypeptide chains of 109 amino acids with two interchain disulphide bonds between cysteine 43 and 52. Three intrachain disulphide bonds are also present in each monomeric rhPDGF-B molecule. Post-translation modification of the active substance results in a mixture of related species of the homodimer rhPDGF-BB molecule. The active substance has been characterised adequately.

The company provided substantiation that the quality of the pre-clinical/clinical batches and the commercial batches are comparable.

Excipients and packaging material

All excipients and the packaging material (tubes) are adequately controlled.

Finished product

The active substance, manufactured by Chiron, USA is transported to OMJ Pharmaceuticals Inc., San German, Puerto Rico, where the finished product is manufactured. Packaging and labelling is performed in the Cilag manufacturing plant in Schaffhausen, Switzerland. The manufacturing process has been validated in accordance with the pre-set acceptance criteria.

Routine test ensure the quality of the finished product. All control tests have been adequately validated. Three conformance batch analyses have been provided. Reasonable batch consistency has been demonstrated.

Stability

The stability of the rhPDGF-BB active substance (ultrafiltrate after purification) has been adequately investigated and established.

The stability protocol for the finished product was designed to provide information of the finished product at 2 – 8 °C in inverted tube position. A shelf life of 12 months at 2 – 8 °C was granted. In addition, a simulated patient use study was performed to evaluate the stability of the multi-dose preserved drug product after opening. An in-use stability after opening of 6 weeks has been granted.

3. Part III: Toxico-pharmacological aspects

The estimated maximum exposure to becaplermin is 14 µg/kg/day, based on the treatment of diabetic ulcer with 700 µg/ulcer (100 cm² ulcer receiving 7 µg becaplermin/cm²) or 700 µg/50 kg patient. The duration of the treatment can be up to 20 weeks.

Pharmacodynamics

Platelet derived growth factor (PDGF) consists of 2 peptide chains (A and B). Platelets contain all 3 isoforms (AA, AB and BB). PDGF is produced in low or undetectable levels in normal cells, but its production can be increased by factors released at the site of injury (e.g. TGF-ß, TNF-a, thrombin).

PDGF receptors are found on mesenchymal cells, including fibroblasts, osteoblasts, chrondroblasts, smooth muscle cells, glial cells and some leukocytes and endothelial cells. A wide range of neoplastic cells also express the PDGF receptor.

PDGF may have a direct mitogenic effect on cells or it may induce the target cell to produce a second factor that is mitogenic. In addition to mitogenesis, other properties of PDGF include cell-directed migration, chemotaxis, modification of cellular matrix constituents and vasoconstriction. PDGF activates mesenchymal cells to secrete collagen and collagenase, thus mediating processes such as wound healing and tissue repair.

A large number of studies using the guinea pig partial thickness wound excision model were performed, using various formulations, treatment schedules, concentrations and volumes. Becaplermin increased granulation, but not epithelialisation or wound contraction at concentrations ≥ 3 µg/g.

PDGF-B (100 µg/g) also increased granulation tissue in full and partial thickness pig wound model and the full thickness diabetic (db/db) mouse wound model. Other parameters (epithelialisation and contraction) were generally unaffected. In the hairless guinea pig full thickness wound model, PDGF-B increased granulation but tended to inhibit wound contraction and epithelialisation. Absorbent wound dressing applied over the PDGF-B gel appeared to reduce the granulation response. Overall wound strength was unaffected by PDGF-B treatment. Yorkshire pigs with partial thickness burns or excisions showed a reduction in the wound healing time when treated with PDGF-B compared to controls.

In general, the only data that were presented that would indicate that PDGF-B is likely to influence wound healing was an increase in granulation tissue thickness; other parameters (epithelialisation, wound contraction or strength) were not influenced. The majority of wound models investigated effects on normal wound healing and consequently there was little change in overall wound healing.

The enhanced granulation tissue produced by PDGF-B is probably sufficient to indicate that becaplermin may be efficacious in the treatment of diabetic ulcers.

Secondary pharmacology: Doses up to 45 µg/kg, s.c. had no significant effect on cardiovascular parameters. No other secondary pharmacological studies were presented. This was considered to be acceptable for a topical product with little absorption.

Interactions: Drug interactions were conducted with other growth factors. Interactions with other drugs likely to be administered topically (e.g. antibiotics) were not performed.

Pharmacokinetics

Table 1 : Overview of pharmacokinetic studies.

Species/ Strain/Sex	Dose µg/kg/day x days, route	C_{max} pg eq/ml	T_{max} h	$AUC_{0-(h)}$ ng eq.h/ml	$T_{1/2}$ (ß) Min	Comments
Rat, Fisher, M	127 x 1, FTW* (20.1 µg/cm²)	53.6	8-24	655.6	-	ELISA, Mean untreated control plasma level = 37.3 pg/ml
Rat, Fisher, M	1.15 x 1; i.v.	4158.6	0	218.7	2.5	ELISA
Rat, Fisher, M	181.4 x 5, FTW* (17.2 mg/cm²)	17.5	8 (Day 5)	-	-	Only 1/36 samples were above the LOQ
Anaesthetised dog	45 x 1, s.c.	282.4	3	-	-	ELISA
Monkey, cynomolgus, M + F	15 x 1, s.c. 1.5 x 1, i.v.	125.6 1462	1 0	375.8 177.2	- 4.2	ELISA ; pretreatment control plasma levels were 0 pg/ml
Monkey, cynomolgus, M + F	30 x 1, s.c. 100 x 1, s.c. 300 x 1, s.c.	140.6 309 495.7	2 2 2	- - -	- - -	ELISA ; only two time points : 0.5 and 2 h.
Monkey, cynomolgus, M + F	1.5 x 92, s.c. 15 x 92, s.c. 150 x 92, s.c.	42 87.1 >250	2 2 2	- - -	- - -	Corrected for endogenous PDGF-B (74.1 pg/ml). 2 h last time point.

* FTW = Full Thickness wound application

The only pharmacokinetic study that was conducted to GLP standards was the 13 week monkey study. Levels of PDGF-B were determined by a double antibody capture ELISA with a quantification limit of 62.5 pg/ml and was specific to PDGF-BB and demonstrated no cross-reactivity for PDGF-AA and 3 % with PDGF-AB.

In rats the amount of PDGF-B absorbed from a full thickness wound was about 3 % compared to intravenous injection and plasma levels were no much greater than those of untreated controls. Repeat dosing in monkeys (s.c.) did not indicate accumulation after 13 weeks treatment at doses < 15 µg/kg but there was evidence of accumulation at 150 µg/kg as both trough and peak PDGF-B values were > 250 µg/kg. Available kinetic data are presented in the table above.

The likely route of absorption of becaplermin when applied topically is by lymphatics; becaplermin possibly binds to α-macroglobulin, which appears to prevent its binding to cell surface mitogenic receptors. No data were presented regarding the distribution, metabolism and excretion of PDGF-B. Due to the lack of the ADME data, exposure in the toxicological studies is best expressed on a mg/kg/day basis, on the assumption that absorption by the routes of administration used in animals will be far greater than that by the topical route used clinically.

Toxicology

Single dose toxicity

Acute toxicity studies were performed using mice, rats and monkey, 3 mg/kg s.c. and/or i.v. PDGF-B had no effect on mortality and the only evidence of toxicity was in the mouse i.v. study in which this dose produced a decrease in spontaneous activity and hunched posture for 1 hour after dosing. Intravenous doses up to 100 µg/kg resulted in two deaths. No target organs were identified and effects were limited to reversible peripheral vasodilatation and CNS depression. These data indicate a huge margin of safety.

Repeated dose toxicity

None of the repeated dose toxicity studies showed evidence of systemic toxicity except a mouse intravenous study where doses ≥ 1 mg/kg/day produced clinical signs (vasodilatation and CNS depression). In a dermal rabbit study, becaplermin (100 µg/ml) was applied to intact and abraded skin and the only finding was dermatitis, which was attributed to the excessive hydration of the skin by the vehicle, and was not becaplermin related. However, as the formulation used in this study was not the same as that intended for marketing, the significance of this finding is unknown.

In the pivotal 13 week monkey study, becaplermin (1.5 to 150 µg/kg/day, s.c.) resulted in injection site reactions (fibroplasia with mixed chronic perivascular inflammation and/or diffuse eosinophilic infiltration) which were considered to be related to the pharmacology of PDGF. From this pivotal safety study there is little evidence that would indicate that PDGF is likely to be carcinogenic.

In the 13 week monkey study, antibodies to PDGF-B were detected in all treatment groups from week 5 to 15; only in 1 of the 20 animals neutralising antibodies (inhibited mitogenesis) were demonstrated at a concentration of becaplermin of 625 ng/ml. Antibodies were also detected in the 1 month rat, s.c. study : the higher the dose, the greater the antibody titre and affinity and only rats (4/15) from the high dose (150 µg/kg) produced neutralising antibodies (30-60 % inhibition) against a concentration of 62.5 ng/ml becaplermin.

The formulation of all the becaplermin preparations used in the toxicological studies was dissimilar to that intended for marketing (becaplermin produced by means of other plasmid and a gel formulation including preservative could not be used for the i.v. and s.c studies and was not even used in the rabbit dermal study). The main point arising from the animal studies is that becaplermin has no systemic toxicity. The lack of systemic toxicity could be due to the production of antibodies that are capable of neutralising the concentrations that were found in the plasma of animals or due to plasma components (possibly α-macroglobulin) which prevent the binding of PDGF-B to its cell surface mitogen receptors.

The applicant has presented, as a response to questions raised, a 28 day dermal rabbit toxicity study with the formulation intended for marketing. This study reaffirms the lack of toxicity observed in the previous 21 day study. This study also addresses the contribution of the other components (parabens...) to the toxicity and percutaneous absorption of Regranex.

Reproductive toxicology

No studies have been performed, which was justified on the basis that PDGF-B is an endogenous protein with a short half life, is applied topically and is poorly absorbed. The lack of reproductive studies is acceptable, however use of the product during pregnancy and lactation is not recommended.

Mutagenicity

The mutagenicity of becaplermin was studied in the following assay systems: Ames test, CHO/HGPRT, mouse lymphoma L5178Y $TK^{+/-}$ assay, CHO chromosome aberration assay, unscheduled DNA synthesis in primary rat hepatocytes and in vivo mouse bone marrow micronucleus assay. All studies were negative.

Carcinogenicity

Carcinogenicity studies have not been performed. This is justified because becaplermin is an endogenous protein with a short half life, it is applied topically and is poorly absorbed, it is negative in the mutagenicity testing, long term s.c. administration of rodents/non rodents to a protein would elicit a significant immune response that would compromise such a study and conventional bioassays are not deemed appropriate for biotechnology products with immunogenic properties.

As it is possible that becaplermin could be administered to a patient with newly formed tumour thereby accelerating the tumour growth, the applicant has contraindicated the use of becaplermin in patients with known neoplasms at the site of application and advised cautious use in patients with known malignancies. The duration of the treatment should also be limited to 20 weeks.

Other studies

Various irritancy tests in rabbits did not indicate that becaplermin gel is irritant to intact or abraded skin when applied for 14 days or to the eye after a single application. These data would seem of minimal value to the intended indication. Becaplermin produced delayed contact hypersensitivity following intradermal challenge in the guinea pig using the maximisation method and the Landsteiner/Draize test, which is not unexpected for a large MW protein injected with and without Freund's complete adjuvant. Topical challenge resulted in an equivocal hypersensitivity reaction. Administration of becaplermin as near to a bone surface as possible resulted in accelerated bone remodelling. This finding could be relevant in certain clinical situations.

Summary and conclusion on preclinical pharmacology and toxicology

The majority of the studies to investigate the effect of becaplermin on wound healing were in normal animals and consequently it was difficult to show improvement in healing other than an increase in granulation tissue thickness. Pharmacokinetic data were very limited, but this is considered acceptable bearing in mind the very limited absorption in man. The toxicological studies did not raise any concerns; it was apparent that animals do produce antibodies to PDGF-B which could be neutralising at the plasma levels of PDGF-B found in these studies. The toxicological studies were short (max. 13 weeks) and the number of animals used was small, however for a topical product the data was considered sufficient. Mutagenicity studies gave no causes for concern and the lack of carcinogenicity and reproductive studies was considered acceptable due to the very limited absorption, the production of neutralising antibodies in animals and the fact that PDGF-B is an endogenous protein. The potential concern of the possible carcinogenic potential of PDGF could be considered resolved if the treatment is to be limited to 20 weeks and to small ulcers.

The applicant discussed during the oral presentation what further pre-clinical studies could be undertaken to research the tumorigenic potential of becaplermin. From the information provided, it seems that there are no suitable tests that the applicant could employ that would produce unequivocal evidence that becaplermin is or is not carcinogenic. Human data to date has produced no indication that becaplermin is tumorigenic at the site of application.

4. Part IV: Clinical aspects

REGRANEX is indicated, in association with other good wound care measures, to promote granulation and thereby the healing of full-thickness, neuropathic, chronic, diabetic ulcers less than or equal to 5 cm^2.

Human pharmacology

Pharmacodynamics

No studies in humans formally researching the effect of becaplermin on the growth of granulation tissue have been undertaken. The potential of the product to cause skin irritancy has, however, been assessed in 3 small studies on a total of 45 male volunteers (Studies 90-22120-A, 90-22120-B and 90-22120-C). At a concentration of 30µg/g, becaplermin gel appears non irritant to normal human skin.

Pharmacokinetics

No conventional pharmacokinetic studies have been performed, but 3 trials (Studies PDGF-PH10-005, PDGF-PH1-007 and 90-22120-E) are included which have assessed whether significant systemic absorption of becaplermin takes place when the product is used in its clinical setting, which is as a topical agent to ulcerated skin. In addition to these, a study is included which assesses the longevity of the active ingredient in the presence of wound fluid (Study PDGF-WFA-001).

When applied topically to diabetic ulcers, becaplermin does not appear, on the evidence presented, to be significantly systemically absorbed at a dose concentration up to 100 µg/g.

The active ingredient has a longevity in the presence of wound fluid, of at least 12 hours in vivo and 48 hours in vitro, which support the once daily dosing frequency proposed.

Table 2: Overview of the efficacy trials in the indication of diabetic foot ulcers.

Study	Study design	Number of patients	Duration of treatment	Dosage regimen	Objectives/Endpoints
92-22120-K Pivotal study	Phase 3, double blind randomised, parallel group, vehicle controlled efficacy and safety study	382 Diabetic ulcers	20 weeks	Once daily Vehicle or becaplermin gel 30 µg/g or 100 µg/g	Efficacy : complete healing, time to healing, relative ulcer area at endpoint Safety : AEs, lab values, vital signs
90-22120-F	Phase 2, double blind randomised, parallel group, vehicle controlled efficacy and safety study	118 Diabetic ulcers	20 weeks	Once daily Vehicle or becaplermin gel 30 µg/g	Efficacy : complete healing, time to healing, relative ulcer area at endpoint Safety : AEs, lab values, vital signs
PDGF-DBFT-001	Phase 2, third-party-blind randomised, parallel group, vehicle controlled, vehicle-effect study	172 Diabetic ulcers	20 weeks	Once daily Vehicle, becaplermin gel 100 µg/g or standard therapy	Efficacy : complete healing, time to healing, relative ulcer area at endpoint Safety : AEs, lab values, vital signs
PDGF-DBFT-002	Phase 3, third-party-blind randomised, parallel group, controlled, safety and efficacy study	250 Diabetic ulcers	20 weeks + 16 weeks standard therapy	Once daily Becaplermin gel 100 µg/g or standard therapy	Efficacy : complete healing, time to healing, relative ulcer area at endpoint Safety : AEs, lab values, vital signs

Table 3 : Overview of the pharmacodynamic studies

Study	Study design	Number of patients	Duration of treatment	Dosage regimen	Objectives/Endpoints
90-22120-A	Phase 1, randomised, open label, local irritation study in healthy volunteers	10	10 days	Once daily Becaplermin gel 30 µg/g	Safety : local skin irritation, AEs, lab values, vital signs
90-22120-B	Phase 1, randomised, open label, local irritation (chamber scarification) study in healthy volunteers	10	3 days	Once daily Becaplermin gel 30 µg/g	Safety : local (scarified) skin irritation, AEs, lab values, vital signs
90-22120-C	Phase 1, randomised, open label, local irritation (Maximisation Test) study in healthy volunteers	25	10 days	Single topical dose of Becaplermin gel 30 µg/g or vehicle following application of sodium lauryl sulphate	Safety : local skin irritation and sensitisation, AEs, lab values, vital signs

Table 4 : Overview of the pharmacokinetic studies

Study	Study design	Number of patients	Duration of treatment	Dosage regimen	Objectives/Endpoints
PDGF-PH10-005	Phase 1, open label pharmacokinetic (absorption) study	10 Diabetic ulcers	14 days	Once daily Becaplermin gel 100 µg/g	Absorption : ELISA determination of plasma PDGF-BB levels, AUC. Safety : AEs, lab values, vital signs
PDGF-PH1-007	Phase 1, open label pharmacokinetic (absorption) study	10 Diabetic ulcers	14 days	Once daily Becaplermin gel 100 µg/g	Absorption : Immunoassay determination of plasma PDGF-BB levels, AUC. Safety : AEs, lab values, vital signs
90-22120-E	Phase 1, open label pharmacokinetic (absorption) study	17 Pressure ulcer	7 days	Once daily Becaplermin gel 30 µg/g	Absorption : Immunoassay determination of plasma PDGF-BB levels, AUC. Safety : AEs, lab values, vital signs
PDGF-WFA-001	Phase 1, double-blind, randomised, parallel group, vehicle controlled wound fluid analysis	12 Diabetic or pressure ulcer	Single dose	Becaplermin gel 100 µg/g or vehicle	Wound fluid analysis : quantity, immunoreactivity, biological activity of becaplermin in wound fluid. Safety : AEs and vital signs

Efficacy

Choice of dose

The presented data are heterogeneous and, with the exception of studies 92-22120-M and 92-22120-K, are from small trials in patients with a different disease (i.e. decubitus ulceration) from that requested in the marketing authorisation application, or utilising formulations different from that requested for marketing.

On basis of the data provided in diabetic ulcers, 100 µg/g once daily appeared to be the optimum dose concentration of those studied.

Efficacy studies

The clinical studies 92-22120-K, 90-22120-F, PDGF-DBFT-001 and PDGF-DBFT-002 (see table 2) employed a similar design (i.e. a multicentre, blinded, parallel group design). In particular, the recruitment criteria, treatment schedules and evaluation criteria were similar. All employed a 20 week treatment phase. Patients recruited were adult diabetics. The target ulcer was required to have a target limb transcutaneous partial pressure of oxygen ($TcpO_2$ of ≥ 30 mm Hg), suggesting that the pathogenesis of the ulcers was of neuropathic and not ischaemic aetiology. Efficacy endpoints were similar; the primary one being complete ulcer healing without drainage or the need for a dressing. These studies recruited some 920 patients in toto. The applicants have combined data from these four studies and have undertaken an efficacy "meta-analysis" on this combined group.

(a) Pivotal Study (Study 92-22120-K)

The primary objectives of this study were to demonstrate the safety and efficacy of two different doses (30 and 100 µg/g) of becaplermin gel compared with vehicle in the healing of chronic, lower extremity, diabetic ulcers during a 20-week treatment period. 395 diabetic patients from 24 centres with an ulcer area between 1.0 and 40 cm^2 were recruited and were randomised 1:1:1 to be treated with one of the following modalities: vehicle gel (n=127), becaplermin gel 30 µg/g (n=132) or becaplermin gel 100 µg/g (n=123). Wounds were dressed twice daily, but the test product was applied once daily. Ulcers received "good wound care" in addition to the study medication which included debridement and systemic antibiotics, if and when necessary, together with a non - weight bearing regimen and dressings appropriate to maintain a moist wound environment.

The chief efficacy endpoint was the frequency of complete ulcer healing. Other endpoints were the time to healing, relative ulcer area at endpoint and weekly healing rate. The groups appear to be comparable at baseline with regard to age, ulcer area etc. 49.6% of patients treated with becaplermin 100 µg/g achieved ulcer healing at endpoint, compared to 36.4% treated with becaplermin 30 µg/g and 34.6% on vehicle alone. The 1 sided p value for the 100 µg/g: vehicle difference is stated as 0.007. Becaplermin appeared particularly effective in healing smaller ulcers.

Days to healing are expressed in percentiles. For the 25th percentile, the time to healing was 79 days for vehicle alone, 91 days for becaplermin 30 µg/g and 71 days for becaplermin 100 µg/g. For the 35th percentile, the time to healing was 127 days for vehicle alone and 86 days for becaplermin 100 µg/g.

The relative ulcer area (i.e. ulcer area at endpoint/ulcer area at baseline) was not significantly different between the groups, nor was the weekly ulcer healing rate.

(b) Supporting Studies

(i) Study 90-22120-F

The objective of this study was to evaluate the efficacy of becaplermin 30 µg/g in the treatment of lower extremity diabetic ulcers by examination of the proportion of subjects with completely healed target ulcers, compared with vehicle treatment. A similar design was used to the pivotal study, but the concentration of becaplermin proposed for marketing (i.e. 100 µg/g) was not evaluated. 118 patients were recruited and were randomised to receive either placebo (n=57) or becaplermin gel 30 µg/g (n=61). 47.5% of patients receiving becaplermin 30 µg/g achieved healing at 20 weeks compared with 24.6% on vehicle alone. (p = 0.016 by logistic regression analysis).

(ii) Study PDGF-DBFT-001

This trial also employed a similar design to the pivotal trial. 172 patients with diabetic ulcers were recruited and were randomised to receive either standard therapy (n=68), vehicle alone (n=70) or becaplermin gel 100 µg/g (n=34). The purpose of this study was to determine whether the vehicle gel had any untoward effect on wound healing relative to standard wound care. Therefore the becaplermin group in this study is smaller than the two other treatment groups.

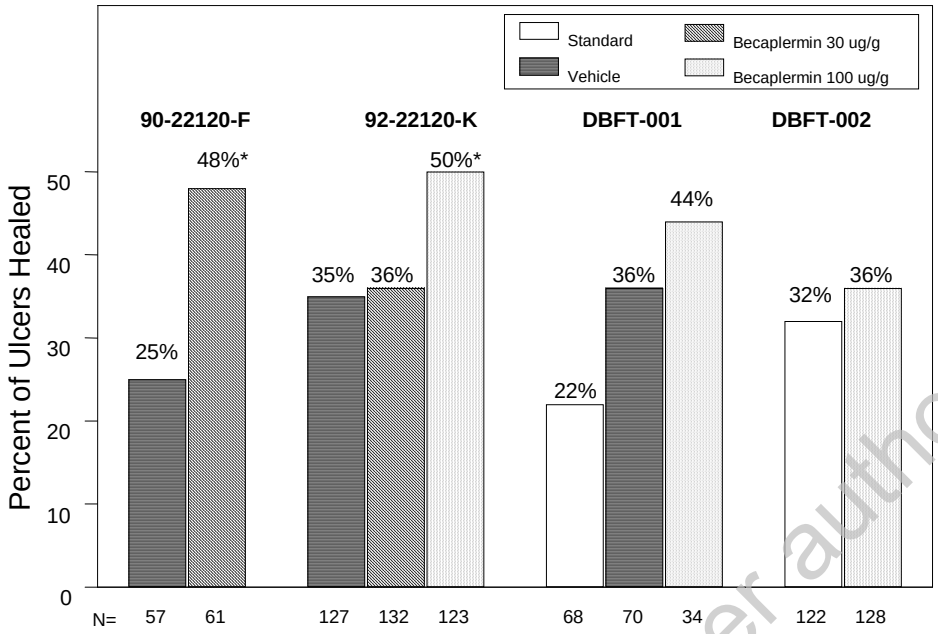
After 20 weeks, 44.1% of patients on becaplermin gel 100 µg/g achieved healing, compared to 35.7% who were treated on vehicle alone and 22.1% who received standard therapy. These results show that the vehicle gel formulation does not adversely affect wound healing. In this study, the number of patients healed on becaplermin gel treatment was not statistically different from treatment with vehicle gel or standard treatment.

(iii) Study PDGF-DBFT-002

The primary objective of study PDGF-DBFT-002 was to evaluate the efficacy of becaplermin gel 100 µg/g as compared to standard therapy when applied topically to chronic, lower extremity diabetic ulcers for up to 20 weeks. A similar study design to that in the pivotal trial was employed. 252 patients with diabetic ulcers were recruited and were randomised to receive standard therapy (n=122) or becaplermin gel 100 µg/g (n=128). 35.9% of patients achieved healing at endpoint on active treatment compared with 32% on standard therapy. This difference was not statistically significant. One centre achieved no healers on standard therapy.

The incidence of complete healing in the 4 efficacy studies is shown in figure 1.

Figure 1: Incidence of Complete Healing
(Intent-to-Treat Patients in Four 20-Week Diabetic Ulcer Studies)



* Significantly different than vehicle group.

Combined Analysis

A "meta-analysis" using combined data from these four studies has been performed. In this analysis, a modest dose response relationship for becaplermin over vehicle alone is apparent. The 100 µg/g concentration heals about 10% more ulcers at 20 weeks than vehicle alone. Becaplermin 100 µg/g appears more efficacious for small ulcers than for larger ones.

The integrated analysis was judged to be valid (despite the use of different comparators in the 4 efficacy trials): the combining of the 4 efficacy studies is justified since the study endpoints were similar and the relative treatment effect across the studies homogeneous.

There was concern regarding the observed variability with regard to the primary efficacy endpoint of complete ulcer healing for vehicle alone, the 30µg/g dose concentration of becaplermin and the 100µg/g dose concentration of becaplermin in the clinical trials. In the view of the CPMP the causes for this variability observed in the clinical trials remain hypothetical apart from the effect of unbalanced infection control and ulcer size across the database.

Further analyses of the efficacy were conducted, utilising the endpoint of complete ulcer healing for the following cohorts based on baseline ulcer area of less than or equal to 5 cm², of more than 5 but less or equal to 10 cm² and of more than 10 cm². In the cohort of ulcer size ≤ 5 cm², complete healing rates after 20 weeks of treatment were 30 % on standard therapy, 35 % on vehicle gel, 42 % on becaplermin 30 µg/g gel and 47 % on becaplermin 100 µg/g gel. The p-values of complete healing on becaplermin 100 µg/g gel versus vehicle gel and on becaplermin 100 µg/g gel versus standard therapy were $p = 0.012$ and $p = 0.001$ respectively.

There does not appear to be any relative increase in the incidence of healing in the becaplermin 100 µg/g treatment group for ulcers > 5 cm² at baseline. It should be pointed out, however, that the data are relatively sparse for ulcers > 5 cm² and the true healing rate for larger ulcers may be obscured by the 20 week limitation for the four studies.

The company provided a further analysis to determine to what extent the efficacy of the product depends upon the duration of existence of the ulcer treated.

For ulcer sizes with a baseline wound area of ≤ 10 cm² using all four efficacy studies combined, the difference in complete wound healing between the 100 µg/g becaplermin gel and vehicle gel diminished slightly from 13.0 % for ulcers existing for 8 weeks to 11.7 % for ulcers existing for 188 weeks. Thus, although the analysis showed that the duration of the target ulcer had a negative association with the outcome (ulcers of longer duration ware less likely to heal), the efficacy of Regranex compared to control treatments was shown similarly superior regardless of the duration of the ulcer prior to treatment.

The choice of standard therapy including most saline gauze appeared outdated. The company provided expert depositions to refute this contention and to advise against the use of the product with occlusive dressings. The standard therapy (moist saline gauze dressings) as used by the applicant was considered appropriate and section 4.2 of the SPC was modified to include statements that Regranex and moist saline dressings should be applied once daily, together with a statement to advise against the use of the product in conjunction with occlusive dressings.

Significant longterm safety and efficacy data in excess of a 20 week treatment phase were not available, nor were data concerning the repeated use of the product. However, data were provided to demonstrate that ulcers healed with the aid of this product remain healed. There appears to be no significant difference in ulcer recurrence frequency or in the time to recurrence following the use of either Regranex or comparator therapy in the first 3 months following wound healing. A number of patients received treatment with Regranex for longer than 20 weeks in open label extensions of the double-blind efficacy studies; but is it the CPMP's view that the treatment by Regranex should be limited to 20 weeks in any individual until significant additional data become available. Additional data are also necessary before any retreatment with Regranex can be allowed.

Conclusions on efficacy

Following the assessment of the dossier submitted by the company, and the assessment of the responses to the list of questions, the company was asked to present further explanations to outstanding efficacy questions during an oral explanation, held at the December CPMP meeting. The issues listed below were discussed, and the CPMP conclusions are given:

The appropriateness of moist saline gauze as a standard reference therapy and as a dressing regimen is resolved, and appropriate amendments to the SPC have been made in this area.

The frequency of wound breakdown is not different from the reference therapies.

The issue on the justification of the dose concentration (100 µg/g) was discussed and is resolved. Additional support for the efficacy of the 100 µg/g concentration of becaplermin was provided from studies in patients with pressure ulcers. Pressure ulcer trial PDGF-PULC-001 also included a 300 µg/g treatment arm, which did not show greater efficacy than the becaplermin 100 µg/g treatment arm.

The data presented are considered adequate to demonstrate the efficacy of the product. The product possesses modest efficacy. Over a 20 weeks treatment course, Regranex heals some 10-15 % more ulcers than a placebo gel. The efficacy database in excess of 900 patients is of an adequate size. A further randomised study in this indication would provide no significant clarification of our knowledge concerning efficacy in this indication.

The validity and relevance of the combined analysis was discussed. Combining the 4 efficacy studies was found justified.

The concerns raised regarding the observed variability with regard to the primary efficacy endpoint of complete healing for vehicle alone, the 30 µg/g and the 100 µg/g becaplermin concentration in the clinical trials were discussed by the applicant. Study-to-study results and the differences among treatment groups are more consistent when only ulcers with sizes ≤ 5 cm² are included in the analysis. Furthermore, for ulcers > 5 cm² at baseline, no valid conclusion could be drawn from the clinical studies: the subgroup of patients with ulcers > 5 cm² was too small and the limitation of the treatment to 20 weeks may have influenced the rate of complete healing (primary endpoint of all efficacy studies) of these larger wounds. Restriction of the use of Regranex to ulcers with a baseline area ≤ 5 cm² is therefore included in the SPC and PL.

In absence of sufficient long-term data in excess of a 20 week treatment phase and in absence of data on retreatment, the treatment duration was limited to 20 weeks in any individual patient. The company will provide further long term efficacy and retreatment data as a post licensing commitment.

Safety

Safety data is available on 1016 subjects from completed clinical trials. Of these, 697 were treated for diabetic neuropathic ulcers, of whom 538 received becaplermin. A further 218 patients were treated for pressure ulcers of whom 164 received becaplermin. 308 subjects treated for diabetic ulcers received becaplermin at the dose concentration proposed for marketing (i.e. 100 µg/g).

Adverse events

66% of patients with diabetic ulcers, treated with becaplermin reported at least one adverse event, compared to 67% on vehicle alone and 81% on standard therapy.

The most frequently reported adverse events to becaplermin were infection (18 %), skin ulceration (12 %), cellulitis (10 %), osteomyelitis (7 %), upper respiratory tract infection (5 %), pain (6 %) and bullous eruption (5 %).

The quality and frequency of reported adverse events is similar between becaplermin treated and the control groups. The applicants argue that these events are related to the underlying disease condition.

Infection

The frequency and nature of the infectious events appears similar in both becaplermin treated and control groups. Analysis for time to first infection reveals no difference between becaplermin and vehicle treated groups. Compared to patients who received standard therapy, infections tended to occur later in the gel treated groups.

There was concern that the product is presented in a multi-use tube. In view of the potential use of this product on a certainly infected ulcer base, and the potential therefore for contamination of the contents of the tube, and the possibility of cross infection between patients, the company committed to modify the product presentation as soon as possible to a single-use presentation. A statement has been included in the SPC and package leaflet stating that a tube should be used on a single patient only.

Application Site Reactions

The observed frequency of application site reactions was around 1% in all groups. Allergy was not reported as a significant adverse reaction. Rash occurred in 1% of treated patients; bullous eruption in <1%.

It should be noted that some of the excipients in the product, such as m-cresol and parabens, are associated with skin reactions. The preservatives in questions have been used in all the clinical studies.

The company committed to provide a single dose sterile formulation to replace the current product. Removal of the preservatives may enhance the local tolerability of the product. The company is encouraged to introduce a sterile formulation as soon as possible.

Neoplasms

12 neoplasms were reported in patients recruited into the clinical trials. 6 occurred in becaplermin treated individuals and 6 in the control groups. The nature of these neoplasms is listed in table 5.

Table 5: Nature of neoplasms reported in the clinical trials *.

	Control Gel or Standard Therapy n=468	Becaplermin 30 µg/g or 100 µg/g n=520
Carcinoma (unspecified)	1	2
Skin neoplasm malignant	0	2
Basal cell carcinoma	0	1
Benign breast tumours	1	1
Lipoma	1	0
Bronchial Carcinoma	1	0
Neoplasm NOS	2	0
Neoplasm malignant	1	0

* Two additional cases were reported post study therapy (becaplermin 100 µg/g): one case of basal cell carcinoma and one case of adenocarcinoma.

Although the numbers are small, the slightly higher number of skin cancer in patients exposed to becaplermin gave rise to concern. It should be noted that the SPC urges caution to prescribers when using Regranex in patients known to have tumours.

The company provided information regarding the relationship between these skin tumours and the length and extent of exposure to becaplermin: in the randomised clinical trials 3 skin tumours were reported in patients receiving Regranex. All these neoplasms were remote from the ulcer site and were detected between 16-36 days after the commencement of the therapy. One skin neoplasm and 4 other tumours have been reported following treatment with becaplermin. Seven other tumours were reported in patients receiving reference treatments other than Regranex. Once again, these tumours were all remote from the site of the ulcer. This clarification was reassuring.

Long-term follow up data concerning the development of neoplasms after exposure to this product are very limited. A post-marketing follow-up will be conducted by the company (at least 1 year) to obtain additional long term safety data with particular emphasis on the incidence of tumour formation.

Cardiovascular Events

45 patients (8%) who received becaplermin suffered a cardiovascular event compared to 33 (7%) in the control groups. This was not a significant difference. 7 patients suffered from cerebrovascular disorders in the becaplermin treated group compared with 2 patients in the control group. However, 5 of the cases in the becaplermin treated group were in patients treated at the 30 µg/g dose concentration. There were only 2 cases in patients who received 100 µg/g.

The numbers of these cases are too small for any conclusion to be drawn concerning the effect of becaplermin on this disorder. However, the lack of significant absorption of the active ingredient results in a difficulty in providing a biologically plausible hypothesis for the relationship between exposure to becaplermin and the development of cerebrovascular disorders.

Serious Adverse Events

The adverse events which have been classified as serious are generally those which are commonly associated with the diabetic condition or with ulceration. There are no significant differences between the becaplermin treated and the control treated groups.

Deaths

37 patients died in the clinical trial programme, 18 of whom had received becaplermin. The causes of death are generally those associated with diabetes. There are no appreciable differences in the causes of death between becaplermin treated and control treated patients.

Withdrawals

20% of patients on standard therapy withdrew from the clinical trials compared to 18% on vehicle alone and 15% on any dose concentration of becaplermin. The reasons for discontinuations due to adverse events appeared similar across the groups.

Laboratory Monitoring

No significantly different frequencies in abnormal haematological, biochemical or urinalysis results in post treatment readings compared to pre-treatment values were observed between becaplermin and control treated groups.

Antibody Formation

475 becaplermin treated patients in the diabetic ulcer studies were investigated for antibody development. 2 patients only are said to have developed positive titres, and these were of low affinity, suggesting that topically applied becaplermin has no significant propensity to induce a systemic antibody response.

Conclusions on safety

Topical becaplermin at a dose level of 100 µg/g applied to diabetic ulcers is associated with no significant excess of adverse reactions overall compared to the placebo gel vehicle.

Some of the excipients in the product, such as m-cresol and parabens, are associated with skin reactions. The use of these preservatives is not considered justified.

The product is currently presented in a multi-use tube. In view of the potential use of this product on a certainly infected ulcer base, and the potential therefore for contamination of the contents of the tube, and the possibility of cross infection between patients, the company was encouraged to introduce a sterile formulation as soon as possible. The company submitted progress reports, indicating that the sterile formulation failed to demonstrate adequate evidence of clinical efficacy in 2 controlled studies of large sample size. The CPMP concluded that the failure to develop an efficacious sterile unpreserved product was disappointing, but did not impact on the favourable benefit/risk balance previously shown for the marketed product formulation.

The data which appear to show an excess of skin tumours in exposed individuals gave rise to concern, but the company provided evidence that:

- there is no temporal relationship between the exposure and the development of the malignancy ;
- there was no relation of the anatomical proximity of the tumours to the exposed area.

There was concern that the long term data supporting this application (i.e. beyond 20 weeks in any individual) were inadequate; in particular with regard to a possible association with the use of Regranex in the development of skin tumours (theoretical carcinogenic potential of growth factors). There are also no data available concerning the repeated use of Regranex.

The duration of use of Regranex has therefore been limited to 20 weeks in any individual ; the SPC has been amended to include statements contraindicating use in those patients with tumours at the application site and urging caution in those with remote malignancies. As there are no data concerning the repeated use of Regranex and limited long term safety and efficacy data, a statement is included in the SPC to limit the total exposure to treatment with Regranex to 20 weeks. The company will provide further long term safety data and data on repeated use of Regranex as post-licensing commitments.

Post marketing

In the assessment of the fourth PSUR it was found that in the Regranex post-marketing database there were 37 reports coded as skin hypertrophy. On further review, 2 cases of the 37 appeared to possibly represent hypertrophic changes at the margins of the treated ulcer.

Of the rest, 29 described cases that have hypergranulation in the base of the ulcer, 3 others are described as hypertrophic granulation or hyperkeratinisation. Two others reported callus formation, 1 distant from the treated lesion and 1within the treated lesion.

Hypertrophic granulation tissue formation or hypergranulation was defined by the finding of granulation tissue extending beyond the periwound area. There was no reported association of hypertrophic granulation to hypertrophic scarring or hypertrophic skin.

Risk / Benefit Assessment

The CPMP requested the company to provide a further analysis of the efficacy, utilising the primary endpoint of complete healing, for cohorts based on baseline ulcer area of ≤ 5 cm² and > 5 cm². For ulcers ≤ 5 cm² a dose related increase in the incidence of healing was demonstrated, with the greatest efficacy with becaplermin 100 µg/g gel: from data combined from the 4 clinical trials conducted over a 20 week treatment phase for ulcers ≤ 5 cm², 47 % of the ulcer treated with becaplermin 100 µg/g gel completely healed, compared with 35 % which were treated with gel alone.

The CPMP considered that the efficacy was proven for diabetic ulcers ≤ 5 cm².

The indication was restricted to full-thickness, neuropathic, chronic diabetic ulcers less than or equal to 5 cm².

The adverse events reported in the clinical trials were similar across all treatment groups and include infection, skin ulceration, skin disorder including erythema, pain and rarely bullous eruption and oedema. These application site reactions were ≤ 1 % in all groups. The company addressed the concerns on the possible tumorigenic action of becaplermin. The CPMP agreed that the risk of skin tumours or other malignancies was limited, although a theoretical concern remains, the active substance being a growth factor. The SPC contraindicates use the product if there are known neoplasms at or near the site of application (Section 4.3: Contraindications), and urges caution in the use the product in patients with known malignancies (section 4.4).

Regranex is indicated for neuropathic diabetic ulcers: In section 4.2 and 4.4 of the SPC is mentioned that underlying conditions such as osteomyelitis and peripheral arteriopathy should be excluded or treated if present.

As the analysis of the clinical trials demonstrated that infection of the wounds negatively influence the healing process, additional statements were included in sections 4.2 and 4.4 (special warnings) of the SPC to recommend the identification and treatment of infections prior to the use of Regranex and if a wound becomes infected to discontinue treatment.

At present, insufficient efficacy and safety data are available for reassurance concerning the longterm use or repeated use of Regranex. A clinical trial studying this will be initiated. Therefore, the SPC includes statements limiting the use of Regranex to a maximum of 20 weeks in any individual patient, and that Regranex is not intended for retreatment.

It was the opinion of the CPMP that a positive risk/benefit was demonstrated for Regranex for the indication as included in the SPC.

5. Conclusion

In view of the positive risk/benefit ratio, the CPMP adopted a positive opinion for Regranex.
The approved indication for Regranex is: Regranex is indicated, in association with other good wound care measures, to promote granulation and thereby the healing of full-thickness, neuropathic chronic diabetic ulcers less than or equal to 5 cm².