Report on the Deliberation Results

August 17, 2016

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Regroth Dental Kit 600 μg
	Regroth Dental Kit 1200 μg
Non-proprietary Name	Trafermin (Genetical Recombination) (JAN*)
Applicant	Kaken Pharmaceutical Co., Ltd.
Date of Application	October 1, 2015

Results of Deliberation

In its meeting held on August 4, 2016, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 6 years. This product is not classified as a poisonous drug, a powerful drug, a biological product, or a specified biological product.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

July 15, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name	Regroth Dental Kit 600 μg Regroth Dental Kit 1200 μg
Non-proprietary Name	Trafermin (Genetical Recombination)
Applicant	Kaken Pharmaceutical Co., Ltd.
Date of Application	October 1, 2015
Dosage Form/Strength	Lyophilized product for reconstitution: Each kit contains 0.81 mg (972,000 international units [IU]) or 1.41 mg (1,692,000 IU)[1)] of Trafermin (Genetical Recombination)
Application Classification	Prescription drug, (3) Drug with a new route of administration
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug I

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of alveolar bone defect due to periodontitis and show acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following condition.

Indication

Alveolar bone defect due to periodontitis

Dosage and Administration

Administer an appropriate amount of the product that fills the alveolar bone defect during a flap operation.

Condition of Approval

1) The drug substance is overfilled so that the labeled dose of 600 μg or 1200 μg can be administered when reconstituted with the accompanying diluent.

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

June 3, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Regroth Dental Kit 600 μg Regroth Dental Kit 1200 μg
Non-proprietary Name	Trafermin (Genetical Recombination)
Applicant	Kaken Pharmaceutical Co., Ltd.
Date of Application	October 1, 2015
Dosage Form/Strength	Lyophilized product for reconstitution: Each kit contains 0.81 mg (972,000 international units [IU]) or 1.41 mg (1,692,000 IU)[1)] of Trafermin (Genetical Recombination)
Proposed Indication	Regeneration of periodontal tissues destroyed by periodontitis
Proposed Dosage and Administration	Reconstitute the lyophilized product with the diluent, and administer an appropriate amount of the reconstituted solution that fills the alveolar bone defect.

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[1)] The drug substance is overfilled so that the labeled dose of 600 μg or 1200 μg can be administered when reconstituted with the accompanying diluent.

List of abbreviations

Adverse drug reactions	Adverse events associated with the study drug
ALP	Alkaline phosphatase
AUC	Area under the curve
bFGF	Basic fibroblast growth factor
C_{max}	Maximum concentration
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
EMD	Enamel matrix derivative
FAS	Full analysis set
FGF	Fibroblast growth factor
FOP	The flap operation alone group
GTR	Guided tissue regeneration
HPC	Hydroxypropylcellulose
HPLC	High performance liquid chromatography
LOCF	Last Observation Carried Forward
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum concentration
UV-VIS	Ultraviolet-visible spectrum

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Periodontitis is an inflammatory disease caused by plaque that accumulates in the junction of tooth and gingiva, with gingival inflammation spreading into the deep periodontal tissues such as tooth cementum, periodontal ligament, and alveolar bone. As periodontitis progresses, morphological changes occur in periodontal tissues (e.g., deepening of periodontal pockets, alveolar bone absorption, and root exposure due to gingival recession), thereby reducing the ability of periodontal tissues to support teeth, ultimately resulting in tooth loss. Tooth mobility and loss not only cause disorders of oral function but also pose a risk of cardiac diseases and diabetes (*J Periodontol.* 2013;84:S24-29; *J Periodontol.* 2013;84:S106-112).

Basic periodontal therapy to improve the oral environment (e.g., plaque control) is the first-line therapy for periodontitis. After basic periodontal therapy, periodontal surgery may be performed for severe cases of periodontitis. Periodontal surgery includes tissue attachment therapies and periodontal tissue regeneration therapy. Flap operation is an example of tissue attachment therapies. A flap operation consists of the following procedures: (1) the tooth root and alveolar bone are exposed by detaching the gingiva from the tooth; (2) infected granulation tissues are eliminated; and (3) accumulated plaque, dental calculus, and contaminated pathological cementum are removed from deep periodontal pockets (plaque etc. in deep periodontal pockets cannot be removed by basic periodontal therapy). The purpose of these procedures is to eliminate or reduce periodontal pockets. Periodontal tissue regeneration therapies include autologous bone grafting, guided tissue regeneration (GTR), and application of enamel matrix derivative (EMD) (Guidelines for test, diagnosis, and treatment plan for periodontal diseases 2008, The Japanese Society of Periodontology). However, there are challenges such as the high invasiveness of autologous bone grafting, the difficulty of performing GTR procedures, and the use of swine-derived biological materials in EMD (Guidelines for regeneration therapy in patients with periodontal diseases 2012, The Japanese Society of Periodontology).

Regroth Dental Kit 600 μg and 1200 μg (hereinafter referred to as Regroth) are solutions containing the active ingredient of Trafermin (Genetical Recombination) (hereinafter referred to as trafermin), a recombinant human basic fibroblast growth factor (bFGF). When trafermin is administered to a periodontal tissue defect during a flap operation, it promotes proliferation of undifferentiated mesenchymal cells in the periodontal tissue defect. Undifferentiated mesenchymal cells differentiate into osteoblasts, cementoblasts, and periodontal ligament cells, thereby generating new alveolar bone and cementum, resulting in reformation of connective tissue attachment. This process promotes periodontal tissue regeneration.

The applicant conducted Japanese clinical studies in patients with periodontitis. The studies showed the efficacy and safety of Regroth. The applicant therefore submitted an application for marketing approval.

In Japan, Fiblast Spray 250 and 500 were approved as topical drugs containing trafermin for the indication of “pressure ulcers, skin ulcers (burn ulcers, leg ulcers)” in April 2001. Trafermin has not been approved as a dental drug in any foreign country.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance trafermin is the same drug substance used in the approved products Fiblast Spray 250 and 500.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a topical solution prepared by reconstituting the lyophilized product with the accompanying diluent. Each cartridge contains 0.81 or 1.41 mg of the drug substance. The drug product contains excipients: disodium edetate hydrate, [redacted], [redacted], [redacted], and sucrose.

The accompanying diluent (0.27 mL or 0.47 mL) contains hydroxypropylcellulose (HPC) and water for injection.

The drug substance is overfilled so that the labeled amount 600 or 1200 μg can be administered after reconstitution with the accompanying diluent.

The drug product is a single-use combination product composed of (a) a solution preparation/dosing unit and (b) an applicator needle. The solution preparation/dosing unit contains a glass cartridge filled with a lyophilized product containing the drug substance and with the accompanying diluent. The solution preparation/dosing unit [redacted]. The applicator needle is registered as a medical device in Japan (Registration number: [redacted]).

2.2.2 Manufacturing process

The manufacturing process of the drug product is as follows: preparation of the drug solution; filtration and filling; lyophilization; storage; packaging and labeling; and testing and storage. [redacted] has been defined as a critical step. Process validation of the manufacturing process has been performed on a commercial scale.

The manufacturing process of the accompanying reconstitution diluent is as follows: preparation of the drug solution; filtration and filling; [redacted]; storage; packaging and labeling; and testing and storage. Process control items have been established for [redacted], which has been defined as a critical step. Process validation of the manufacturing process has been performed on a commercial scale.

2.2.3 Manufacturing process development

During the development of the drug product, no change was made to the manufacturing process, drug formulation, or manufacturing site. The drug product used in the clinical studies, the drug product used to determine specifications, and the drug product subjected to stability testing were all produced in the same manufacturing process and are identical to the to-be-marketed drug product.

2.2.4 Control of drug product

The proposed specifications for the drug product consist of content, description [redacted], identification (UV-VIS, [redacted]), pH, purity (clarity and color of solution, related substances [SDS-PAGE, [redacted], [redacted]]), water content, uniformity of dosage units (content uniformity [[redacted]]), [redacted], and assay (protein [[redacted]], potency).

The proposed specifications for the accompanying diluent consist of description, identification (qualitative reaction), and viscosity.

2.2.5 Stability of drug product

Table 1 shows the main tests used to verify the stability of the drug product.

Table 1. Summary of main stability tests of the drug product

	No. of batches	Storage condition	Storage container	Storage period (month)
Long-term	**3[a)]**	**5°C ± 3°C**	**[redacted], [redacted], [redacted] and a glass cartridge (primary package)**	**36**
Accelerated	**3[a)]**	**25°C ± 2°C**		**6**
Stress	**1[b)]**	**−20°C ± 5°C**		**1**
		50°C ± 2°C		
Photostability	**1[c)]**	**25°C ± 2°C, total illuminance 1,200,000 lx•h and total near-ultraviolet radiation energy ≥200 W•h/m^2**		**-**
	1[b)]		**Primary packaged product + paper box**	

a) Three batches each of 0.2 and 0.4 mL formulations
b) One batch each of 0.2 and 0.4 mL formulations
c) One batch of 0.2 mL formulation

In the long-term testing, accelerated testing, and stress testing (−20°C), no obvious change was noted in the quality characteristics throughout the test periods.

In the stress testing (50°C), related substances tended increase.

The photostability testing showed increases over time in related substances in the primary package. The drug product was stable to light when the primary packaged product was packed in a paper box.

The accompanying reconstitution diluent was subjected to a 36-month long-term testing (5°C) and a 6-month accelerated testing (25°C). The diluent was stable for 36 months when stored at 5°C.

Based on the above findings, the shelf-life of the drug product was determined to be 36 months when the primary packaged product was loaded in the solution preparation/dosing unit, packaged in [redacted] and polyethylene terephthalate (PET) blister tray, protected from light in a paper box, and stored at 2°C to 8°C.

The post-reconstitution stability testing was performed after re-reconstitution with the accompanying diluent. Related substances increased over time at [redacted]°C and [redacted] for [redacted] hours and under [redacted] ([redacted] lx) for [redacted] hours. Therefore, the reconstituted solution should be used immediately.

2.3 Reference material

The reference material used to assay Regroth was trafermin reference standard, the same substance used to assay the approved product, Fiblast Spray 250 and 500.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance, drug product, and solution preparation/dosing unit are adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Primary pharmacodynamic studies were conducted to evaluate the actions of trafermin, including how the drug promotes periodontal tissue regeneration. Although this is an application for a new route of administration, no new pharmacological safety data have been submitted because the general pharmacology studies submitted as part of the application for the approval of Fiblast Spray 250 and 500 (which contain the same active ingredient) had evaluated the effect on the central nervous, respiratory, and cardiovascular systems following intravenous and subcutaneous administration of trafermin, and the exposure demonstrated in the studies is sufficient in relation to blood levels after administration to a periodontal tissue defect in clinical practice.

3.1 Primary pharmacodynamics

3.1.1 Evaluation of mechanism of action

3.1.1.1 Cell proliferation-promoting activity and differentiation-inducing activity in rat bone-marrow-derived mesenchymal cells (CTD 4.2.1.1-5; Study KP[redacted]0107)

Trafermin 0.5, 2.5, or 12.5 ng/mL was added to rat bone-marrow-derived mesenchymal cells. Differentiation to osteoblasts was induced in the absence of trafermin on Day 7 of incubation, to determine the DNA amount (index of cell proliferation), ALP activity (index of osteoblast differentiation), and deposited calcium content in the extracellular matrix (index of calcification) until Day 21 of incubation. The DNA amount showed concentration-dependent increases at all time points. The ALP activity showed concentration-dependent increases after differentiation induction (Days 11 to 21 of incubation). In the trafermin groups, the deposited calcium content in the extracellular matrix increased at several time points of each incubation day, compared with that in the control group. All treatment groups showed increases in the deposited calcium content over time.

3.1.1.2 Cell proliferation-promoting activity, differentiation-inducing activity, and migration-promoting activity in human periodontal ligament cells (CTD 4.2.1.1-6, 4.2.1.1-7, 4.2.1.1-8; Studies P[redacted]0401, P[redacted]0402, P[redacted]0502)

Trafermin 0.3, 1, 3, 10, or 30 ng/mL was added to human periodontal ligament cells, and the DNA amount (index of cell proliferation) was determined 3 days after incubation. The DNA amount showed concentration-dependent increases.

Human periodontal ligament cells incubated for 3 days after addition of trafermin 10 ng/mL or untreated human periodontal ligament cells were induced to differentiate into hard tissue-forming cells (cementoblasts and osteoblasts). The ALP activity 14 days after differentiation induction and the deposited calcium content in the extracellular matrix 24 days after differentiation induction were determined, to evaluate the effect of trafermin on the differentiation potency of human periodontal ligament cells. The trafermin and untreated groups showed similar ALP activities and similar increases in calcium content.

Trafermin 0.01, 0.1, 1, 10, or 100 ng/mL or control medium was added to human periodontal ligament cells, to evaluate trafermin concentration gradient-dependent migration (chemotaxis) and random migration (chemokinesis). Compared with the vehicle group, the trafermin 1 and 10 ng/mL groups showed significant increases in migratory cell count due to chemotaxis, and the trafermin 10 and 100 ng/mL groups showed significant increases in migratory cell count due to chemokinesis. According to the applicant, the trafermin 100 ng/mL group showed no chemotaxis-related significant increase in the migratory cell count, for the following reason: The continuous action of trafermin at high concentrations might have induced down regulation of FGF receptors expressed in human periodontal ligament cells, causing reduced sensitivity to trafermin.

3.1.2 Periodontal tissue regeneration promoting activity (CTD 4.2.1.1-1 to 4; Studies KP[redacted]0401, P[redacted]0501, P[redacted]0504, P[redacted]0401)

Trafermin 0.03%, 0.1%, or 0.3% or vehicle ([redacted]% HPC solution) was administered as a single dose to a periodontal tissue defect of a dog 2-wall periodontal tissue defect model.[2)] Table 2 shows the bone mineral content (BMC) in the defect part and results of morphometry (new bone tissue area, new cementum length, new periodontal ligament length) of tissue samples at Month 3.

The trafermin ≥0.1% groups showed significant increases in BMC in the defect part, new bone tissue area, new cementum length, and new periodontal ligament length, compared with the vehicle group.

2) [redacted]

Table 2. Bone mineral content and morphometry using tissue samples in the defect part in a dog 2-wall periodontal tissue defect model

	BMC in the defect part (total mm Al equivalent)	New bone tissue area (mm^2)	New cementum length (mm)	New periodontal ligament length (mm)
Vehicle	**20,095 ± 4159**	**10.620 ± 1.453**	**2.097 ± 0.793**	**1.990 ± 0.717**
Trafermin 0.03%	**22,970 ± 3556**	**12.014 ± 2.618**	**2.286 ± 1.191**	**2.107 ± 0.914**
Trafermin 0.1%	**26,371 ± 3226*** **	**14.470 ± 1.713*** **	**3.119 ± 0.934** **	**2.762 ± 0.611***
Trafermin 0.3%	**26,902 ± 2856*** **	**15.819 ± 1.750*** **	**3.157 ± 0.971** **	**2.752 ± 0.846***

n = 14 to 18, mean ± standard deviation (SD)
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (vs. vehicle group, Dunnett's multiple comparison test)

Trafermin 0.3% or vehicle ([redacted]% HPC solution) was administered as a single dose to a periodontal tissue defect of a dog 2-wall periodontal tissue defect model.[2)] At Month 13, when BMC stabilized, the following were evaluated: the new cortical bone volume; microstructure (trabecular volume fraction, trabecular thickness, trabecular separation, trabecular number) of cancellous bone trabecula in new bone; and morphometry (new bone tissue area, new bone height, new cementum length, new periodontal ligament length, distance to inner marginal epithelium) of tissue samples from the defect part.

The new cortical bone volumes (mean ± SD) at Month 13 were 3.93 ± 1.44 mm^3 in the vehicle group and 6.31 ± 2.13 mm^3 in the trafermin group; the trafermin group showed significant increases in new cortical bone volumes, compared with the vehicle group.

The trafermin and vehicle groups had similar microstructure (trabecular volume fraction, trabecular thickness, trabecular separation, trabecular number) of cancellous bone trabecula in new bone.

In morphometry of tissue samples, new bone tissue area, new bone height, new cementum length, new periodontal ligament length, and distance to the inner marginal epithelium were significantly greater in the trafermin group than in the vehicle group (Table 3). The new bone height was similar to the new periodontal ligament length. The gingival inner marginal epithelium was maintained on the crown side, showing no down growth.

Table 3. Morphometry of the defect part using tissue samples at Month 13 in a dog 2-wall periodontal tissue defect model

	New bone tissue area (mm^2)	New bone height (mm)	New cementum length (mm)	New periodontal ligament length (mm)	Distance to inner marginal epithelium (mm)
Vehicle	**11.1 ± 4.5**	**2.39 ± 1.02**	**2.86 ± 1.25**	**2.37 ± 1.06**	**3.06 ± 1.23**
Trafermin 0.3%	**16.1 ± 3.3** **	**3.38 ± 0.49** **	**4.02 ± 0.61** **	**3.55 ± 0.56** **	**4.08 ± 0.58***

n = 14, mean ± SD
* $P < 0.05$; ** $P < 0.01$ (vs. the vehicle group, t-test)

3.R Outline of the review conducted by PMDA

The applicant's explanation on the pharmacological effect of trafermin:
Periodontal tissues that support teeth are composed of soft tissues of gingiva and periodontal ligament, and hard tissues of cementum and alveolar bone. The periodontal ligament, mainly made up of collagen fibers, attaches the cementum (which covers the tooth root surface) to the alveolar bone. This is called

connective tissue attachment. Regeneration of alveolar bone and reconstruction of connective tissue attachment are essential for regeneration of periodontal tissues destroyed by periodontitis. Alveolar bone is formed by osteoblasts differentiated primarily from bone marrow-derived undifferentiated mesenchymal cells. The cementum and periodontal ligament, which form connective tissue attachment, are formed by cells derived from existing periodontal ligament tissues (*J Periodontal Res*. 1988;23:107-117; *J Clin Periodontol*. 1982;9:257-265, etc.).

In the submitted *in vitro* primary pharmacodynamic studies, trafermin promoted bone marrow-derived mesenchymal cell proliferation and periodontal ligament cell proliferation and migration, and the proliferated cells retained the ability to differentiate into osteoblasts and cementoblasts [see Sections 3.1.1.1 and 3.1.1.2].

Furthermore, the *in vivo* evaluation of periodontal tissue regeneration-promoting activity showed that administration of trafermin to the alveolar bone defect increased the new bone tissue area, new cementum length, and new periodontal ligament length [see Section 3.1.2], and promoted regeneration of alveolar bone and connective tissue attachment.

Based on the submitted results of primary pharmacodynamic studies and the applicant's explanation, PMDA considers that trafermin may be an effective treatment for periodontal tissues lost as result of periodontitis.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The serum trafermin concentrations were determined by ELISA, with a lower limit of quantitation (LLOQ) of 0.01 ng/mL in dogs and 0.1 ng/mL in rats. Gamma counter and autoradiography were used to determine radioactivity after administration of [^{125}I]-labeled trafermin. SDS-PAGE was used to analyze metabolites. Male animals were used in the following studies unless otherwise specified.

4.1 Absorption

4.1.1 Administration to periodontal tissue defect and intragingival administration in dogs (CTD 4.2.2.2-1, 4.2.2.2-2, 4.2.2.2-3; Studies M[redacted]0204, M[redacted]0203, M[redacted]0104)

Table 4 shows serum pharmacokinetic (PK) parameters of trafermin after the following treatment in dogs.

- Two periodontal tissue defects were prepared and 500 µg of trafermin 0.8% (vehicle, HPC) was administered to each defect.
- A single intragingival dose of trafermin 0.1% (vehicle, HPC) at 200 µg was administered to dogs.
- A single intravenous dose of trafermin 0.04% (vehicle, water) at 200 µg/kg was administered to dogs.

Table 4. Serum pharmacokinetic parameters of trafermin after administration to periodontal tissue defect, intragingival or intravenous administration in dogs

Administration route	Test substance (vehicle)	Dose	N	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng•h/mL)	t_{max} (h)	$t_{1/2}$ (h)
Periodontal tissue defect	Trafermin 0.8% (HPC)	1 mg (500 µg/site)	3	0.01 ± 0.01	0.07 ± 0.09	-[a)]	-[a)]
Intragingival	Trafermin 0.1% (HPC)	200 µg	2	0.06, 0.09	0.43, 0.36	0.25, 0.50	5.67, 2.86
Intravenous	Trafermin 0.04% (water)	200 µg/kg	3	326.5 ± 64.9	164.0 ± 2.6	-	7.8 ± 0.6

Mean ± SD or individual values of 2 dogs; -, not calculated
a) Not calculated as values were below LLOQ at many time points.

4.1.2 Intragingival, intravenous, and oral administration to rats (CTD 4.2.2.2-4, 4.2.2.2-5, 4.2.2.2-6; Studies M[redacted]0106, M[redacted]0105, M[redacted]0102)

Table 5 shows the serum PK parameters after the following treatments in male and female rats.

- A single intragingival dose of trafermin 0.1% at 100 µg/kg, trafermin 0.2% at 200 µg/kg, and trafermin 0.4% at 400 µg/kg was administered to male rats (vehicle, HPC in all treatment groups).
- A single intragingival dose of trafermin 0.2% (vehicle, HPC) at 200 µg/kg was administered to female rats.
- A single intravenous dose of trafermin 0.02% (vehicle, water) at 200 µg/kg was administered to male rats.

Table 5. Serum pharmacokinetic parameters of trafermin after intragingival or intravenous administration to rats

Administration route	Test substance (vehicle)	Dose	Sex	N	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng•h/mL)	t_{max} (h)	$t_{1/2}$ (h)
Intragingival	Trafermin 0.1% (HPC)	100 µg/kg	Male	3	2.29 ± 0.92	4.49 ± 1.53	0.22 ± 0.24	1.64 ± 0.33
Intragingival	Trafermin 0.2% (HPC)	200 µg/kg	Male	3	4.16 ± 0.64	10.52 ± 0.97	0.08 ± 0.00	3.04 ± 0.92
Intragingival	Trafermin 0.4% (HPC)	400 µg/kg	Male	3	8.84 ± 3.37	20.95 ± 3.86	0.14 ± 0.10	2.75 ± 0.22
Intragingival	Trafermin 0.2% (HPC)	200 µg/kg	Female	3	6.22 ± 0.77	11.96 ± 0.54	0.08 ± 0.00	2.92 ± 0.27
Intravenous	Trafermin 0.02% (water)	200 µg/kg	Male	3	296.7 ± 41.8	105.2 ± 10.6	-	1.3 ± 0.1

Mean ± SD; -, not calculated

Following a single oral administration of trafermin 0.4% (vehicle, HPC and water) at 2 mg to rats, all values were below LLOQ at all time points

4.2 Distribution

4.2.1 Tissue distribution after administration to periodontal tissue defect in rabbits (CTD 4.2.2.3-1, 4.2.2.3-2; Studies M[redacted]0101, M[redacted]0106)

Tissue distribution was evaluated for 21 days after a single administration of [^{125}I]-labeled trafermin 0.3% (vehicle, HPC) at 30 µg to a periodontal tissue defect in rabbits. The residual radioactivity levels in the administration site decreased over time: 97.7% ± 3.7% at 30 minutes postdose, 73.4% ± 3.4% at 24 hours postdose, 21.2% ± 5.2% at 7 days postdose, and 0.2% ± 0.1% at 21 days postdose. The

radioactivity levels in tissues[3)] peaked between 6 hours postdose and 3 days postdose, and then decreased over time (except for the administration site). As for the distribution of radioactivity (in tissues except for the administration site and the thyroid gland, where the free [^{125}I]-form of [^{125}I]-labeled trafermin accumulates), oral distribution of radioactivity peaked at 0.6% at 6 hours postdose, and decreased to ≤0.1% at 24 hours postdose and thereafter. Hepatic and gastric distribution of radioactivity was also high (maximum, 0.6% at 3 days postdose), but decreased to 0.3% at 7 days postdose and 0% at 21 days postdose. The applicant explained that the radioactivity recovered in the liver, kidneys, lungs, adrenal glands, and spleen was due to inactive metabolites of trafermin.

4.2.2 Tissue distribution after intragingival administration to rats (CTD 4.2.2.3-5, 4.2.2.3-6; Studies M[redacted]0101, [redacted])

Tissue distribution was evaluated for 7 days after a single intragingival administration of [^{125}I]-labeled trafermin 0.2% (vehicle, HPC) at 200 μg/kg to rats. The residual radioactivity level at the administration site decreased over time: 88.3% ± 10.2% at 15 minutes postdose, 45.2% ± 6.3% at 24 hours postdose, 16.9% ± 2.7% at 3 days postdose, and 7.7% ± 1.8% at 7 days postdose. The radioactivity levels in tissues[4)] peaked at 6 or 24 hours postdose, and then decreased over time (except for the administration site). In tissues other than the administration site, the liver showed the highest distribution of radioactivity at 9.4% at 6 hours postdose, but the level reduced to 1.0% at 3 days postdose.

Autoradiography was performed to evaluate tissue distribution for 7 days after a single intragingival administration of [^{125}I]-labeled trafermin 0.2% (vehicle, HPC) at 200 μg/kg to rats.

The administration site and thyroid gland (where the free [^{125}I]-form of [^{125}I]-labeled trafermin accumulates) showed higher radioactivity, compared with other sites at all time points, followed by the liver, kidneys, and adrenal glands. The radioactivity decreased over time in all tissues. The applicant explained that the radioactivity recovered in the liver, kidneys, and adrenal glands was due to inactive metabolites of trafermin.

4.2.3 Tissue distribution after administration to periodontal tissue defect in rats (CTD 4.2.2.3-3, 4.2.2.3-4; Studies M[redacted]0103, M[redacted]0103)

Autoradiography was performed to evaluate radioactivity distribution at the administration site for 14 days after a single administration of [^{125}I]-labeled trafermin 0.3% (vehicle, HPC) at 30 μg to a periodontal tissue defect in rats. At 15 minutes and 6 hours postdose, high levels of radioactivity were noted in the periodontal ligament, and distribution of radioactivity was also noted on the surface of the defect part of the alveolar bone, dentine, and gingival connective tissues. The radioactivity present in the periodontal ligament and gingival connective tissues largely disappeared at 3 days postdose. Negligible radioactivity was noted in the alveolar bone and dentine at 14 days postdose. Inflammatory cell invasion was noted at 6 hours postdose and thereafter, and radioactivity was aggregately distributed

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3) Liver, kidneys, lungs, adrenal glands, spleen, thyroid gland, stomach, esophagus, oral cavity

4) Brain, liver, kidneys, lungs, heart, spleen, pancreas, adrenal glands, pituitary gland, testes, prostate gland, eyeballs, harderian gland, cervical lymph nodes, thymus gland, submaxillary gland, bone marrow, muscles, white fat, artery, abdominal lymph nodes, skin, thyroid gland, stomach, small intestine, large intestine

in the invasion site of inflammatory cells at 24 hours postdose. At 7 days postdose and thereafter, the radioactivity in the invasion site of inflammatory cells decreased over time.

A single dose of trafermin 0.3% (vehicle, HPC) at 30 μg was administered to a periodontal tissue defect in rats. At 6 and 24 hours postdose and 3, 7, and 14 days postdose, the administration site was isolated, and immunostaining was performed using goat anti-human bFGF antibodies. At 6 and 24 hours postdose, tissues in periodontal tissue defect (e.g., the periodontal ligament, alveolar bone, dentine, and gingival connective tissues) tested positive for anti-human bFGF antibody. At 3 days postdose, the alveolar bone, dentine, and gingival connective tissues tested positive for the antibody, but the periodontal ligament did not. At 7 days postdose, only the alveolar bone tested positive, but the positive reaction disappeared at 14 days postdose.

4.3 Metabolism

4.3.1 Metabolism in the administration site after administration to periodontal tissue defect in rabbits (CTD 4.2.2.3-1; Study M[redacted]0101)

Metabolites of trafermin in soft tissues at the administration site were evaluated for 7 days after a single administration of [^{125}I]-labeled trafermin 0.3% (vehicle, HPC) at 30 μg to a periodontal tissue defect in rabbits.

Protein (B-1), which corresponds to the molecular weight of unchanged trafermin, and 3 low-molecular metabolites (B-2, B-3, and B-4) were recovered in soft tissues at the administration site. While B-1 to B-4 are heparin binding, B-1 and B-2 are bioactive forms (see the Review Report of Fiblast Spray 250 and 500, February 2, 2001). B-1 accounted for the highest percentage of radioactive proteins at all time points during 7 days after administration. B-2 to B-4 were recovered at 24 hours and 3 days postdose. The percentages of bioactive forms (the sum of B-1 and B-2) were 66.7% at 30 minutes postdose, 37.9% at 24 hours postdose, and 6.9% at 7 days postdose.

4.3.2 Metabolism at the administration site after intragingival administration to rats (CTD 4.2.2.3-5; Study M[redacted]0101)

Metabolites of trafermin in the administration site were evaluated for 7 days after a single intragingival administration of [^{125}I]-labeled trafermin 0.2% (vehicle, HPC) at 200 μg/kg to rats.

B-1 (corresponding to unchanged trafermin), B-2, B-3, and B-4 were recovered in the administration site. B-1 accounted for the highest percentage of radioactive proteins until 24 hours postdose. B-2 to B-4 were recovered at 6 hours postdose and thereafter. The percentage of B-1 decreased with increases in the percentages of B-2 to B-4 from 24 hours postdose to 7 days postdose. The percentage of bioactive forms was 58.6% at 15 minutes postdose, 21.4% at 24 hours postdose, and 3.6% at 7 days postdose.

4.4 Excretion

4.4.1 Excretion after intragingival administration to rats (CTD 4.2.2.5-1; Study M[redacted]0108)

Excretion in urine and feces was evaluated for 7 days after a single intragingival administration of [^{125}I]-labeled trafermin 0.2% (vehicle, HPC) at 200 μg/kg in rats.

The cumulative urinary and fecal excretion rates at 24 hours postdose were 44.8% ± 2.8% and 0.9% ± 0.6%, respectively. The cumulative urinary and fecal excretion rates at 7 days postdose were 78.8% ± 2.1% and 6.1% ± 1.0%, respectively. The cumulative urinary excretion of radioactivity in the urinary trichloroacetic acid precipitate fraction was 0.1% at 7 days postdose; this suggests that low-molecular trafermin was primarily excreted in urine.

4.R Outline of the review conducted by PMDA

The applicant's explanation on the PK of trafermin after administration to a periodontal tissue defect:
In dogs receiving trafermin administered to a periodontal tissue defect, the systemic uptake rate of trafermin was low at 0.1% [see Section 4.1.1]. This suggests that trafermin, administered to a periodontal tissue defect, is distributed in only negligible amounts throughout the body. In rats given oral trafermin, the serum trafermin concentrations were below LLOQ, without systemic uptake by gastrointestinal absorption [see Section 4.1.2].

The residual radioactivity levels in the administration site after administration of [^{125}I]-labeled trafermin to a periodontal tissue defect in rabbits decreased over time: 97.7% at 30 minutes postdose, 21.2% at 7 days postdose, and 0.2% at 21 days postdose. This suggested that most of the radioactivity was eliminated from the administration site. The oral distribution peaked at 0.6% at 6 hours postdose, and decreased to ≤0.1% at 24 hours postdose and thereafter. Therefore, the amount of trafermin leaked into the mouth was considered to be small [see Section 4.2.1]. The results after administration of [^{125}I]-labeled trafermin to a periodontal tissue defect in rabbits suggested that B-1 (corresponding to the unchanged trafermin) and B-2 (a metabolite), both bioactive, primarily existed at the administration site [see Section 4.3.1]. The results after intragingival administration of [^{125}I]-labeled trafermin to rats showed that urinary excretion of the high-molecular form was negligible at 0.1%; this suggested that trafermin metabolites transferred into blood were decomposed into low molecular weight compounds and excreted in urine [see Section 4.4.1].

PMDA's view:
There is no specific problem in the applicant's explanation of the PK after administration of trafermin to a periodontal tissue defect.

The systemic uptake rate after administration to a periodontal tissue defect was lower than that after administration of the approved product Fiblast Spray 250 and 500 to the wound surface (4.2%). No problematic trend was noted in distribution, metabolism, or excretion at this point, compared with those of the approved route of administration (see the Review Report of Fiblast Spray 250 and 500, February 2, 2001).

5. Toxicity and Outline of the Review Conducted by PMDA

The toxicity study data of trafermin, the active ingredient of Regroth, were evaluated at the initial approval application (see the Review Report of Fiblast Spray 250 and 500, February 2, 2001). The applicant submitted data from new toxicity studies (local irritation studies, i.e., oral mucosa irritation study in rats and primary gingival irritation study in dogs) for the present application. All these studies used an HPC solution as a vehicle.

5.1 Local irritation

5.1.1 Oral mucosal irritation study in rats (CTD 4.2.3.6-1; Study S[redacted]T001)

Trafermin 0.3% HPC formulation 1.5 mg/kg/day or vehicle was intraorally administered for 14 days to male and female rats. No finding suggestive of local damage were found in the oral mucosa, tongue, larynx, esophagus, or trachea.

5.1.2 Primary gingival irritation study in dogs (CTD 4.2.3.6-2; Study [redacted]T007)

A single dose of trafermin 0.1% and 0.8% HPC formulations, vehicle, saline (negative control), or 0.425% and 1.7% acetic acid (positive control) were administered at 500 μL/site to alveolar submucosa in female beagle dogs. A histopathological examination of the administration site was performed on Days 2 and 14. The trafermin 0.1% and 0.8% groups showed administration site swelling, outgrowth of periosteal osteoblast-like cells, angiogenesis of the lamina propria, and migration of fibroblast-like cells. Thickening of alveolar submucosal tissues and small round cell infiltration of the lamina propria were noted in the trafermin 0.8% group.

An alveolar bone defect was created at least 1 month after extraction of the third and fourth lower premolars in female beagle dogs. A single dose of trafermin 0.1% and 0.8% HPC formulations, vehicle, or saline (negative control) were administered at 250 μL/site to the defect part, and a histopathological examination of the administration site was performed on Days 7 and 28. The trafermin 0.1% and 0.8% groups showed outgrowth of fibroblast-like cells in alveolar bone, outgrowth of mesenchymal cells, cancellous bone formation, and outgrowth of osteoblast-like cells.

The applicant's explanation:
All histopathological findings in the trafermin groups were associated with the pharmacological effect of trafermin, and were not indicative of primary irritation.

5.R Outline of the review conducted by PMDA

5.R.1 Proliferative changes in periosteal osteoblast-like cells

In the primary gingival irritation study in dogs, proliferative changes in periosteal osteoblast-like cells were noted. PMDA requested the applicant to explain whether overgrowth of tissues could be a concern in the clinical use of trafermin.

The applicant's explanation:
Trafermin is unlikely to exert a prolonged pharmacological effect at the administration site because trafermin is eliminated by metabolism at the administration site after administration [see Section 4.3]. Outgrowth of fibroblast-like cells was observed in alveolar bone in the primary gingival irritation study in dogs. This finding, however, is a transient tissue regeneration reaction that induces new bone formation (this is the pharmacological effect of trafermin), and is not indicative of continuous cellular overgrowth. An evaluation of periodontal tissue defects in dogs showed that, at 13 months after trafermin administration, new bone did not outgrow the superior border of alveolar bone with no abnormal gingival findings [see Section 3.1]. This indicates that administration of trafermin to a periodontal tissue defect induces regeneration of periodontal tissue but is unlikely to cause its overgrowth.

PMDA considered that the use of trafermin in humans would not raise significant safety concerns from a toxicological perspective, and accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The serum trafermin concentration and serum anti-trafermin antibody were determined by ELISA. In the Japanese pharmacology study (Study 1D-04), the LLOQ of serum trafermin concentrations was 0.001 ng/mL.

6.2 Clinical pharmacology

6.2.1 Japanese pharmacology study (CTD 5.3.3.2-1; Study 1D-04, [redacted] to [redacted] 2010)

A multicenter, open-label, parallel-group study was performed at 6 Japanese sites to evaluate the PK and safety of trafermin in patients with periodontitis aged ≥20 years who required flap operation.

A single dose of trafermin 0.3% was administered at 0.2 or 0.6 mL to the alveolar bone defect in the test tooth during a flap operation. Serum trafermin concentrations were determined at 1, 2, 4, and 24 hours postdose, to assess the PK of trafermin.

All 25 subjects (0.2 mL, 8 subjects; 0.6 mL, 17 subjects) treated with trafermin were included in the PK analysis set and safety analysis set.

In the 0.2 mL group, the serum trafermin concentration (corresponding to endogenous bFGF concentration at baseline) (mean ± SD) was 0.004 ± 0.005 ng/mL at baseline, and ranged between 0.001 ± 0.002 and 0.003 ± 0.004 ng/mL until 24 hours postdose. In the 0.6 mL group, the serum trafermin concentration (mean ± SD) was 0.002 ± 0.003 ng/mL at baseline, and ranged between 0.001 ± 0.001 and 0.004 ± 0.004 ng/mL until 24 hours postdose.

Adverse events were reported in 87.5% (7 of 8) of subjects in the 0.2 mL group and 88.2% (15 of 17) of subjects in the 0.6 mL group. Adverse drug reactions were reported in 12.5% (1 of 8) of subjects in the 0.2 mL group and 5.9% (1 of 17) of subjects in the 0.6 mL group.

Table 6 shows adverse events occurring in ≥2 subjects in any treatment group. No adverse drug reaction occurred in ≥2 subjects in any treatment group. No deaths or serious adverse events occurred in this study.

Table 6. Adverse events occurring in ≥2 subjects in any treatment group

	0.2 mL (N = 8)		0.6 mL (N = 17)	
	Incidence (%)	n	Incidence (%)	n
Any adverse event	87.5	7	88.2	15
Albumin urine present	37.5	3	29.4	5
C-reactive protein increased	0.0	0	29.4	5
Beta 2 microglobulin urine increased	0.0	0	11.8	2
Platelet count increased	0.0	0	17.6	3
Blood creatine phosphokinase increased	0.0	0	23.5	4
Beta-N-acetyl-D-glucosaminidase increased	12.5	1	29.4	5
Eosinophil percentage increased	12.5	1	11.8	2

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Events occurring by Week 4 were collected.

6.R Outline of the review conducted by PMDA

The applicant's explanation:

Trafermin, administered to an alveolar bone defect, is unlikely to be transferred into the body, based on the individual changes from baseline in serum trafermin concentrations in Study 1D-04.

PMDA considers that there is no specific problem in the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

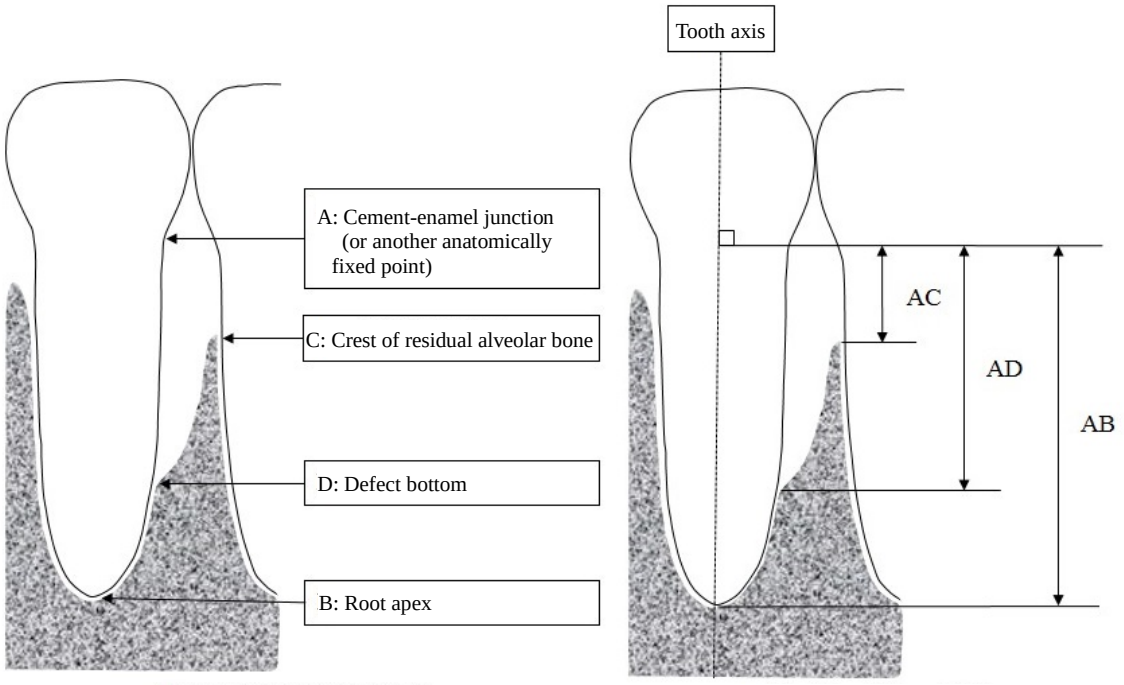
The submitted evaluation data included 2 Japanese phase II studies (Studies 1D-01 and 1D-02) and 2 Japanese phase III studies (Studies 1D-03 and 1D-05) (Table 7).

Table 7. Outline of submitted evaluation data

Study	Study ID	Design	Objective	Group: No. of subjects treated	Observation period	Increase in new alveolar bone at Week 36 (treatment difference)
Phase II	1D-01	Double-blind	Exploratory	Placebo: 20 Trafermin 0.03%: 19 Trafermin 0.1%: 20 Trafermin 0.3%: 20	36 weeks	Difference from placebo in increase rate (%) Trafermin 0.03%: −2.2 Trafermin 0.1%: 6.0 Trafermin 0.3%: 21.3
		Open-label follow-up	Safety	Placebo: 19 Trafermin 0.03%: 15 Trafermin 0.1%: 17 Trafermin 0.3%: 16	Observation was performed at an arbitrary time point after Week 36[c)]	-
	1D-02	Double-blind	Dose-response	Placebo: 63 Trafermin 0.2%: 68 Trafermin 0.3%: 58 Trafermin 0.4%: 64	Efficacy: 36 weeks Safety: 72 weeks	Difference from placebo in increase rate (%) Trafermin 0.2%: 17.6 Trafermin 0.3%: 35.5 Trafermin 0.4%: 30.1
Phase III	1D-03	Double-blind	Confirmatory	Placebo: 108 Trafermin 0.3%: 215	36 weeks	Difference from placebo in increase rate (%) Trafermin 0.3%: 15.6
	1D-05	Blinded evaluator	Confirmatory	FOP[a)]: 43 EMD[b)]: 113 Trafermin 0.3%: 111	36 weeks	Difference from EMD in increase (mm) Trafermin 0.3%: 0.6

a) Flap operation alone
b) Enamel matrix derivative
c) Radiographic examination was performed between Weeks 83 and 132 in subjects enrolled in the follow-up investigation.

Figure 1 shows the methods used to determine and calculate the increase in new alveolar bone and clinical attachment in the Japanese clinical studies.



Reference point of radiogram **Measurement distance of radiogram**

Increase in new alveolar bone	**• Increase in new alveolar bone (mm) = baseline AD − adjusted postdose AD** **• Increase rate of new alveolar bone (%) = increase in new alveolar bone/(baseline AD − baseline AC) × 100** *** Adjustment: Because of errors in the size and angle of radiograms, postdose AD measured by radiography was adjusted for anatomically fixed AB** **Adjusted AD = postdose AD × (baseline AB/postdose AB)** *** Five evaluators independently performed measurement. Median values are shown for the increase and the increase rate of new alveolar bone**
Clinical attachment	**• Clinical attachment gain (mm)** **= Baseline clinical attachment level − postdose clinical attachment level** *** Clinical attachment level:** **Distance to the probe head from cement-enamel junction (or another anatomically fixed point) when a graduated (1 mm) probe is inserted to the bottom of the gingival crevice** [redacted] **In Studies 1D-03 and 1D-05, the measurers confirmed sense of [redacted] g probing pressure, and measurements in the same subject were performed by the same measurer.**

Figure 1. Methods used to calculate increase in new alveolar bone and clinical attachment

7.1 Phase II studies

7.1.1 Japanese phase II study (CTD 5.3.5.1-1; Study 1D-01, [redacted] to February 2004)

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was performed at 12 Japanese sites to evaluate and explore the efficacy, safety, and dose-response of trafermin in patients with periodontitis aged ≥20 and <65 years who required flap operation (Table 8). The planned sample size was 80 subjects (20 in each treatment group).

Table 8. Main inclusion criteria

Patients with periodontitis who require flap operation and meet the following criteria. **1) Diagnosis of 2-wall or 3-wall vertical bone defect (≥3 mm deep from the crest of residual alveolar bone) confirmed by radiography or other examinations** **2) Class 0, 1, or 2, mobility of the test tooth with an attached gingival width eligible for GTR** *** Mobility level is evaluated according to the following criteria using approximately 250 g of force applied with tweezers (this method was used in all subsequent clinical studies.)** **Class 0: Physiological mobility (<0.2 mm and no apparent movement)** **Class 1: Mild mobility (0.2 to 1.0 mm in labiolingual direction)** **Class 2: Moderate mobility (1.0 to 2.0 mm in labiolingual direction + mesiodistal mobility)** **Class 3: Severe mobility (≥2.0 mm in labiolingual direction + vertical mobility)**

A single dose of placebo, trafermin 0.03%, 0.1%, or 0.3% was administered at 0.2 mL to the alveolar bone defect of the test tooth during the flap operation.

Of 80 subjects randomized in the study, 79 (placebo, 20 subjects; 0.03%, 19 subjects; 0.1%, 20 subjects; 0.3%, 20 subjects) were included in the full analysis set (FAS), efficacy analysis set, and safety analysis set. (The remaining 1 subject in the 0.03% group was excluded because the subject discontinued the study before the beginning of study treatment.) One subject receiving study treatment was withdrawn from observation because of withdrawal of consent (the 0.1% group).

Table 9 shows the primary efficacy endpoints (i.e., increase rate of new alveolar bone; clinical attachment gain) at Week 36.

Table 9. Increase rate of new alveolar bone and clinical attachment gain at Week 36 (FAS)

	Increase rate of new alveolar bone	Clinical attachment gain
	Mean ± SD (%)	Mean ± SD (mm)
Placebo (n = 20)	**22.4 ± 27.6**	**2.6 ± 1.5**
0.03% (n = 19)	**20.2 ± 38.1**	**2.0 ± 2.1**
0.1% (n = 20)	**28.4 ± 37.0**	**2.0 ± 2.0**
0.3% (n = 20)	**43.7 ± 69.5**	**1.9 ± 1.6**

Missing values were imputed using the last observation carried forward (LOCF) method.

Adverse events were reported in 90.0% (18 of 20) of subjects in the placebo group, 78.9% (15 of 19) of subjects in the 0.03% group, 95.0% (19 of 20) of subjects in the 0.1% group, and 95.0% (19 of 20) of subjects in the 0.3% group. Adverse drug reactions were reported in 35.0% (7 of 20) of subjects in the placebo group, 42.1% (8 of 19) of subjects in the 0.03% group, 45.0% (9 of 20) of subjects in the 0.1% group, and 60.0% (12 of 20) of subjects in the 0.3% group. Table 10 shows adverse events occurring in ≥2 subjects in any treatment group. Table 11 shows adverse drug reactions occurring in ≥2 subjects in any treatment group.

Table 10. Adverse events occurring in ≥2 subjects in any treatment group

	Placebo (N = 20)		0.03% (N = 19)		0.1% (N = 20)		0.3% (N = 20)	
	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n
Any adverse event	90.0	18	78.9	15	95.0	19	95.0	19
Albumin urine present	10.0	2	31.6	6	10.0	2	35.0	7
C-reactive protein increased	15.0	3	21.1	4	10.0	2	35.0	7
Stomatitis	10.0	2	15.8	3	5.0	1	15.0	3
Device failure[a)]	35.0	7	26.3	5	20.0	4	15.0	3
Beta 2 microglobulin increased	5.0	1	15.8	3	20.0	4	15.0	3
Nasopharyngitis	15.0	3	5.3	1	15.0	3	10.0	2
Blood creatine phosphokinase increased	10.0	2	15.8	3	10.0	2	10.0	2
Gingivitis	0.0	0	5.3	1	5.0	1	10.0	2
Diarrhoea	5.0	1	5.3	1	0.0	0	10.0	2
Pyrexia	0.0	0	0.0	0	20.0	4	5.0	1
Sensitivity of teeth	10.0	2	10.5	2	15.0	3	5.0	1
Blood uric acid increased	0.0	0	5.3	1	15.0	3	5.0	1
Monocyte percentage increased	0.0	0	10.5	2	10.0	2	5.0	1
Periodontitis	0.0	0	5.3	1	10.0	2	5.0	1
Beta-N-acetyl-D-glucosaminidase increased	15.0	3	15.8	3	5.0	1	5.0	1
Blood potassium increased	5.0	1	0.0	0	15.0	3	0.0	0
Gingival swelling	0.0	0	5.3	1	10.0	2	0.0	0
Glucose urine present	5.0	1	0.0	0	10.0	2	0.0	0
Eosinophil percentage increased	5.0	1	5.3	1	10.0	2	0.0	0
Lymphocyte percentage decreased	0.0	0	10.5	2	5.0	1	0.0	0
Gingival pain	10.0	2	10.5	2	0.0	0	0.0	0
Cheilitis	0.0	0	10.5	2	0.0	0	0.0	0
Neutrophil percentage increased	0.0	0	10.5	2	0.0	0	0.0	0
Dental caries	10.0	2	0.0	0	0.0	0	0.0	0

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The following adverse events were collected: systemic adverse events occurring by Week 36, laboratory values measured by Week 4, and intraoral adverse events occuring by Week 36.

a) Damage to medical materials (e.g., detachment of fixation and damage to fillings) due to degradation and abrasion of temporary restoration materials

Table 11. Adverse drug reactions occurring in ≥2 subjects in any treatment group

	Placebo (N = 20)		0.03% (N = 19)		0.1% (N = 20)		0.3% (N = 20)	
	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n
Any adverse drug reaction	35.0	7	42.1	8	45.0	9	60.0	12
Albumin urine present	5.0	1	26.3	5	5.0	1	30.0	6
C-reactive protein increased	5.0	1	5.3	1	5.0	1	20.0	4
Beta 2 microglobulin increased	5.0	1	15.8	3	20.0	4	15.0	3
Blood creatine phosphokinase increased	10.0	2	0.0	0	10.0	2	5.0	1
Beta-N-acetyl-D-glucosaminidase increased	10.0	2	15.8	3	5.0	1	5.0	1

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No deaths occurred. One serious adverse event (colonic polyp) was reported in 1 subject in the 0.03% group, and a causal relationship to the study drug was ruled out.

In total, 67 subjects (placebo, 19 subjects; 0.03%, 15 subjects; 0.1%, 17 subjects; 0.3%, 16 subjects) could be followed up after the completion of the 36-week observation period. The 67 subjects underwent a follow-up investigation (i.e., intraoral symptoms, signs, radiography, and periodontal tissue examination).

Of the 67 subjects who underwent the follow-up investigation, 53 were evaluated for the increase rate of alveolar bone height (placebo, 16 subjects; 0.03%, 11 subjects; 0.1%, 14 subjects; 0.3%, 12 subjects). The remaining 14 subjects were not evaluated, because (a) they had received additional treatment to the test site after administration of the study drug, resulting in the change of the reference point of radiography, or because (b) they had a 1-wall or 4-wall bone defect. Radiography was performed between Week 83 and Week 132 in individual subjects. Although some subjects showed decreases in the alveolar bone height, the alveolar bone mass was maintained in each subject. In the safety assessment, no subject experienced abnormal gingival outgrowth or malignant tumors. No subjects had abnormal increase of alveolar bone beyond the cement-enamel junction or corresponding reference point. No other adverse drug reactions were reported.

7.1.2 Japanese phase II study (CTD 5.3.5.1-2; Study 1D-02, August 2005 to [redacted] 2007)

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was performed at 24 Japanese sites, to evaluate the efficacy, safety, and dose-response of trafermin in patients with periodontitis aged ≥20 years who required flap operation (Table 12). The planned sample size was 240 subjects (60 in each treatment group).

Table 12. Main inclusion criteria

Patients with periodontitis who require flap operation and meet the following criteria.
1) 2-wall or 3-wall vertical bone defect (defect depth ≥3 mm) in the interdental part, confirmed by radiography or other examinations
2) Class 0, 1, or 2 mobility of the test tooth with an attached gingival width eligible for GTR

A single dose of placebo, trafermin 0.2%, 0.3%, or 0.4% was administered at 0.2 mL to the alveolar bone defect of the test tooth during the flap operation.

Of 267 randomized subjects, 253 (placebo, 63 subjects; 0.2%, 68 subjects; 0.3%, 58 subjects; 0.4%, 64 subjects) were included in the safety analysis set. (The remaining 14 subjects [placebo, 4 subjects; 0.2%, 2 subjects; 0.3%, 7 subjects; 0.4%, 1 subject] were excluded because they discontinued the study before the beginning of study treatment.) Of the 253 subjects, 249 subjects (placebo, 61 subjects; 0.2%, 68 subjects; 0.3%, 57 subjects; 0.4%, 63 subjects) were included in the FAS, which was used for the main efficacy analyses. The remaining 4 subjects were excluded, because they had no postdose efficacy data (2 subjects [placebo, 1 subject; 0.4%, 1 subject]), or because radiographic data were unmeasurable at all time points (2 subjects [placebo, 1 subject; 0.3%, 1 subject]). Four subjects receiving study treatment were withdrawn from observation for the following reasons: personal reasons in 2 subjects (0.2%, 1 subject; 0.4%, 1 subject), adverse events in 1 subject (0.4%), and withdrawal of consent in 1 subject (placebo).

Table 13 shows the increase rate of new alveolar bone at Week 36 (the primary efficacy endpoint). The trafermin groups showed statistically significant differences from the placebo group ($P < 0.01$; two-sided significance level, 5%; Dunnett's multiple comparison method).

Table 13. Increase rate of new alveolar bone at Week 36 (FAS)

	Mean ± SD (%)	*P*-value[a)]
Placebo (n = 61)	15.1 ± 21.9	-
0.2% (n = 68)	32.7 ± 33.2	0.005
0.3% (n = 57)	50.6 ± 31.5	<0.001
0.4% (n = 63)	45.2 ± 36.3	<0.001

Missing values were imputed using the LOCF method
a) Dunnett's multiple comparison method, adjusted *P*-value, two-sided significance level of 5%

Adverse events were reported in 82.5% (52 of 63) of subjects in the placebo group, 83.8% (57 of 68) of subjects in the 0.2% group, 75.9% (44 of 58) of subjects in the 0.3% group, and 78.1% (50 of 64) of subjects in the 0.4% group. Adverse drug reactions were reported in 15.9% (10 of 63) of subjects in the placebo group, 19.1% (13 of 68) of subjects in the 0.2% group, 15.5% (9 of 58) of subjects in the 0.3% group, and 20.3% (13 of 64) of subjects in the 0.4% group. Table 14 shows adverse events occurring in ≥5% of subjects in any treatment group. Table 15 shows adverse drug reactions occurring in ≥5% of subjects in any treatment group.

Table 14. Adverse events occurring in ≥5% of subjects in any treatment group

	Placebo (N = 63)		0.2% (N = 68)		0.3% (N = 58)		0.4% (N = 64)	
	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n
Any adverse event	82.5	52	83.8	57	75.9	44	78.1	50
Albumin urine present	23.8	15	22.1	15	29.3	17	18.8	12
Beta-N-acetyl-D-glucosaminidase increased	20.6	13	17.6	12	12.1	7	17.2	11
C-reactive protein increased	7.9	5	11.8	8	3.4	2	14.1	9
Beta 2 microglobulin increased	9.5	6	8.8	6	8.6	5	10.9	7
Nasopharyngitis	9.5	6	5.9	4	10.3	6	7.8	5
Gingival swelling	1.6	1	4.4	3	1.7	1	7.8	5
Periodontitis	0.0	0	1.5	1	0.0	0	6.3	4
Blood creatine phosphokinase increased	11.1	7	10.3	7	10.3	6	4.7	3
Blood bilirubin increased	1.6	1	0.0	0	5.2	3	4.7	3
Eosinophil percentage increased	9.5	6	4.4	3	1.7	1	4.7	3
Lymphocyte percentage decreased	1.6	1	4.4	3	8.6	5	3.1	2
Sensitivity of teeth	3.2	2	2.9	2	5.2	3	3.1	2
Monocyte percentage increased	4.8	3	11.8	8	1.7	1	3.1	2
Neutrophil percentage increased	0.0	0	1.5	1	6.9	4	1.6	1
Neutrophil percentage decreased	6.3	4	4.4	3	0.0	0	1.6	1

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The following adverse events were collected: laboratory values measured by Week 4, systemic adverse events occurring by Week 36, and intraoral adverse events occurring by Week 72.

Table 15. Adverse drug reactions occurring in ≥5% of subjects in any treatment group

	Placebo (N = 63)		0.2% (N = 68)		0.3% (N = 58)		0.4% (N = 64)	
	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n
Any adverse drug reaction	15.9	10	19.1	13	15.5	9	20.3	13
Beta-N-acetyl-D-glucosaminidase increased	6.3	4	4.4	3	0.0	0	6.3	4
Albumin urine present	3.2	2	5.9	4	8.6	5	1.6	1

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No deaths occurred. Serious adverse events were reported in 1 subject (eosinophilic pneumonia chronic) in the placebo group, 1 subject (pneumonia) in the 0.2% group, and 3 subjects (gastric cancer, carcinoid tumor of the gastrointestinal tract, depression in 1 subject each) in the 0.4% group. A causal relationship to the study drug was ruled out for all these serious adverse events.

A follow-up investigation was conducted at Week 72 to evaluate the long-term intraoral safety. The investigation did not reveal abnormal alveolar bone increase, osseous ankyloses, abnormal gingival outgrowth, or malignant tumor.

7.2 Phase III studies

7.2.1 Japanese phase III confirmatory study (CTD 5.3.5.1-3; Study 1D-03, [redacted] 2008 to [redacted] 2010)

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was performed at 23 Japanese sites to evaluate the efficacy and safety of trafermin in patients with periodontitis aged ≥20 years who required flap operation (Table 16). The planned sample size was 300 subjects (placebo, 100 subjects; 0.3%, 200 subjects).

Table 16. Main inclusion criteria

Patients with periodontitis who meet the following criteria: **1) Patients with a probing pocket depth ≥4 mm and Class 0, 1, or 2 mobility who require flap operation** **2) Vertical bone defect (depth ≥3 mm) in the interdental part, confirmed by radiography or other examinations** *** The inclusion criteria were determined based on "Guidelines for diagnosis and treatment of periodontal diseases" (2007 Japanese Society of Periodontology).**

A single dose of placebo or trafermin 0.3% was administered at 0.2 mL to alveolar bone defect of the test tooth during the flap operation.

Of 328 subjects randomized in the study, 323 (placebo, 108 subjects; 0.3%, 215 subjects) were included in the safety analysis set. The remaining 5 subjects (all in the 0.3% group) were excluded because they discontinued the study before the beginning of study treatment. Of the 323 subjects, 320 (placebo, 107 subjects; 0.3%, 213 subjects) were included in the FAS, which was used for the main efficacy analyses. The remaining 3 subjects were excluded, because their postdose efficacy data were missing or unusable (2 subjects in the 0.3% group), or because of a violation of the assignment procedure (1 subject in the placebo group). One subject receiving study treatment was withdrawn from observation (hospital transfer, the 0.3% group).

Trafermin was considered to be effective (i.e., the study was considered successful) if trafermin 0.3% showed a statistically significant difference from placebo in both primary endpoints (the increase rate of new alveolar bone; clinical attachment gain) at Week 36. Table 17 shows the results of the primary endpoints. No statistically significant difference was noted in clinical attachment gain between trafermin 0.3% and placebo.

Table 17. Increase rate of new alveolar bone and clinical attachment gain at Week 36 (FAS)

	Increase rate of new alveolar bone (%)	Clinical attachment gain (mm)
	Mean ± SD	Mean ± SD
Placebo	21.6 ± 26.3 (n = 100)[a)]	2.0 ± 1.5 (n = 106)[b)]
0.3%	37.1 ± 32.0 (n = 208)[a)]	2.1 ± 1.6 (n = 213)
Difference [95% CI]	15.6 [8.3, 22.8]	0.1 [−0.3, 0.5]
P-value	<0.001[c)]	0.541[c)]

Missing values were imputed using the LOCF method
a) Excluding subjects with a radiogram unusable for the calculation of increase rate of new alveolar bone at Week 36
b) Excluding subjects whose clinical attachment level at baseline might not have been appropriately measured
c) t-test, two-sided significance level of 5%

Adverse events were reported in 75.9% (82 of 108) of subjects in the placebo group and 72.6% (156 of 215) of subjects in the 0.3% group. Adverse drug reactions were reported in 10.2% (11 of 108) of subjects in the placebo group and 14.4% (31 of 215) of subjects in the 0.3% group. Table 18 shows adverse events occurring in ≥5% of subjects in any treatment group. Table 19 shows adverse drug reactions occurring in ≥5% of subjects in any treatment group.

Table 18. Adverse events occurring in ≥5% of subjects in any treatment group

	Placebo (N = 108)		0.3% (N = 215)	
	Incidence (%)	n	Incidence (%)	n
Any adverse event	75.9	82	72.6	156
Albumin urine present	21.3	23	32.1	69
Beta-N-acetyl-D-glucosaminidase increased	7.4	8	16.3	35
Beta 2 microglobulin urine increased	12.0	13	12.1	26
C-reactive protein increased	6.5	7	11.2	24
Blood creatine phosphokinase increased	8.3	9	10.2	22
Nasopharyngitis	4.6	5	7.0	15
Eosinophil percentage increased	11.1	12	5.1	11
Monocyte percentage increased	9.3	10	4.7	10

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The following adverse events were collected: systemic adverse events occurring by Week 4, laboratory data measured by Week 4, malignant tumor and abnormal outgrowth in the mouth reported by Week 36 (and other intraoral adverse events occurring by Week 4), and deaths and malignant tumors reported by Week 36.

Table 19. Adverse drug reactions occurring in ≥5% of subjects in any treatment group

	Placebo (N = 108)		0.3% (N = 215)	
	Incidence (%)	n	Incidence (%)	n
Any adverse drug reaction	10.2	11	14.4	31
Albumin urine present	6.5	7	7.0	15
Beta-N-acetyl-D-glucosaminidase increased	2.8	3	6.5	14
Beta 2 microglobulin urine increased	1.9	2	6.0	13

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No deaths occurred. Serious adverse events were reported in 2 subjects (diverticulitis intestinal haemorrhagic and sinusitis in 1 subject each) in the placebo group and 1 subject (breast cancer) in the 0.3% group. A causal relationship to the study drug was ruled out for all these serious adverse events.

7.2.2 Japanese phase III confirmatory study (CTD 5.3.5.1-4; Study 1D-05, October 2012 to [redacted])

A multicenter, randomized, single-blind, parallel-group study[5] was performed at 15 Japanese sites to evaluate the efficacy and safety of trafermin in patients with periodontitis aged ≥20 years who required flap operation (Table 20). The planned sample size was 240 subjects (0.3%, 100 subjects; EMD,[6] 100 subjects; flap operation alone [hereinafter referred to as FOP], 40 subjects).

Table 20. Main inclusion criteria

Patients with periodontitis who meet the following criteria: **1) Patients with a probing pocket depth ≥6 mm and Class 0, 1, or 2 mobility who require flap operation** **2) Radiographically confirmed vertical bone defect (depth ≥4 mm) in the interdental part** *** The criteria for the probing pocket depth and bone defect depth were determined on the basis of data from patients eligible for EMD.**

A single dose of trafermin 0.3% or EMD was administered at an appropriate dose to the alveolar bone defect of the test tooth during the flap operation. No study drug was administered to the FOP group, which was a reference group.

Of 274 randomized subjects, 267 (0.3%, 111 subjects; EMD, 113 subjects; FOP, 43 subjects) received study treatment and were included in the safety analysis set. The remaining 7 subjects (0.3%, 4 subjects; EMD, 3 subjects) were excluded because they discontinued the study before the beginning of study treatment. Of the 267 subjects, 265 (0.3%, 110 subjects; EMD, 112 subjects; FOP, 43 subjects) were included in the FAS. The remaining 2 subjects were excluded because of prohibited concomitant therapy (0.3%, 1 subject) or because of missing efficacy data (EMD, 1 subject). Of the 265 subjects, 260 (0.3%, 108 subjects; EMD, 109 subjects; FOP, 43 subjects) were included in the per protocol set (PPS). The remaining 5 subjects were excluded for the following reasons: efficacy data on new alveolar bone at Week 36 were missing in 4 subjects (0.3%, 1 subject; EMD, 3 subjects); and “radiography at Week 36” was not performed during the protocol-defined period in 1 subject (trafermin 0.3%). The main efficacy analyses were performed in the PPS. Four subjects receiving study treatment were withdrawn from observation.[7]

Table 21 shows increases in new alveolar bone at Week 36, the primary efficacy endpoint, in the PPS. The lower limit of 95% confidence interval (CI) for differences between the 0.3% and EMD groups were larger than the predefined value of −0.30 mm, showing the non-inferiority of trafermin 0.3% to EMD.

[5] Subjects and radiography evaluators were blinded to treatment.
[6] A specially controlled medical device
[7] Three subjects due to adverse events, 2 subjects due to changes in the therapeutic policy, and 1 subject due to withdrawal of consent (all in the EMD group) (with duplication)

Table 21. Increase in new alveolar bone at Week 36 (PPS)

	Mean ± SD	Treatment difference [95% CI]
0.3% (n = 108)	1.93 ± 1.39	0.57 [0.18, 0.96]
EMD (n = 109)	1.36 ± 1.53	
FOP (n = 43)	0.67 ± 1.05	-

Unit, mm

Adverse events were reported in 64.9% (72 of 111) of subjects in the 0.3% group, 74.3% (84 of 113) of subjects in the EMD group, and 69.8% (30 of 43) of subjects in the FOP group. No adverse drug reactions were reported. Table 22 shows adverse events occurring in ≥5% of subjects in any treatment group

Table 22. Adverse events occurring in ≥5% of subjects in any treatment group

	0.3% (N = 111)		EMD (N = 113)		FOP (N = 43)	
	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n
Any adverse event	64.9	72	74.3	84	69.8	30
Albumin urine present	18.0	20	19.5	22	25.6	11
C-reactive protein increased	12.6	14	6.2	7	18.6	8
Beta-N-acetyl-D-glucosaminidase increased	11.7	13	17.7	20	11.6	5
Beta 2 microglobulin urine increased	8.1	9	16.8	19	16.3	7
Blood creatine phosphokinase increased	6.3	7	8.8	10	2.3	1
Monocyte percentage increased	6.3	7	4.4	5	9.3	4
Blood lactate dehydrogenase increased	5.4	6	1.8	2	7.0	3
Stomatitis	2.7	3	6.2	7	9.3	4
Glucose urine present	2.7	3	5.3	6	0.0	0
Blood bilirubin decreased	2.7	3	5.3	6	0.0	0
Eosinophil percentage increased	1.8	2	8.0	9	7.0	3

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The following adverse events were collected: systemic adverse events occurring by Week 4, laboratory data measured by Week 4, malignant tumor and abnormal outgrowth in the mouth reported by Week 36 (and other intraoral adverse events occurring by Week 4), and deaths and malignant tumors reported by Week 36.

No deaths occurred. One serious adverse event was reported in 1 subject (rectal cancer) in the EMD group and a causal relationship to EMD was ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the evaluation and confirmation described in Sections 7.R.1.1 to 7.R.1.3, PMDA considers that administration of trafermin during flap operation can increase alveolar bone mass. PMDA will draw a final conclusion on the efficacy of trafermin based on comments from the Expert Discussion.

7.R.1.1 Design of the Japanese phase III confirmatory studies

The applicant's explanation:

Study 1D-03 was designed as a double-blind study. Study 1D-05 was designed as a single-blind study (only subjects and X-ray evaluators were blinded) because blinding of investigators was unfeasible due to differences in the viscosity of trafermin and EMD, the control agent.

In Study 1D-03, “improvement in alveolar bone level” and “clinical attachment gain” were selected as the primary efficacy endpoints, based on the American Academy of Periodontology “Consensus report. Periodontal regeneration around natural teeth. (*Ann Periodontol.* 1996;1:667-670).” No statistically significant difference was noted in clinical attachment gain between the trafermin and placebo groups [see Section 7.2.1]. In Study 1D-05, however, “increase in new alveolar bone” was selected as a primary endpoint for the following reasons:

(a) After the completion of Study 1D-03, the Ministry of Health, Labour and Welfare issued a notification concerning cell sheets for the treatment of periodontal tissues, entitled “Publication of assessment indices of next generation medical devices (PFSB/ELD/OMDE Notification No. 1207-1, dated December 7, 2011).” The notification recommends “improvement in alveolar bone level” as a primary endpoint in the efficacy assessment of periodontal tissue regeneration, because clinical attachment gain (including epithelial attachment) was observed even in patients undergoing flap operation alone to treat periodontal disease (periodontitis) accompanied by periodontal tissue destruction.

(b) Clinical studies of EMD evaluated efficacy by “increase in new alveolar bone” (FDA review report,[8)] *J Clin Periodontol*. 2001;28:923-929).

According to a 10-year follow-up investigation that evaluated the correlation between depth of vertical bone defect and tooth loss in individuals receiving no treatment, the risk of tooth loss increased with an increase in the depth of vertical bone defect (*J Clin Periodontol.* 1991;18:317-322). This suggests that increased new alveolar bone is related to improved long-term outcomes of teeth with periodontitis.

The efficacy observation period in Studies 1D-03 and 1D-05 was 36 weeks after administration. This duration was selected because it can detect differences in increase in new alveolar bone between the 0.3% and placebo groups (according to the results of Studies 1D-01 and 1D-02), and because of the results of clinical studies of EMD.

In Study 1D-05, EMD was selected as the control group to evaluate the clinical significance of trafermin. Emdogain, the old formulation of EMD, showed a consistent add-on effect to flap operation in terms of the increase in new alveolar bone in 3 studies submitted for the US market approval of a medical device (FDA Review Report[8)]). EMD was demonstrated to be equivalent to Emdogain in the same endpoint (*J Clin Periodontol*. 2001;28:923-929). Therefore, the significance of trafermin can be clarified by demonstrating its non-inferiority to EMD.

The non-inferiority margin in Study 1D-05 was determined as follows: a pooled analysis of 3 clinical studies of Emdogain and 1 equivalence study of EMD calculated that the increase in alveolar bone was 0.81 mm for EMD. The non-inferiority margin in Study 1D-05 was defined as 0.30 mm, approximately a third of 0.81 mm. The allowable limit of error was 0.30 mm, because radiography is not performed in accordance with strict specifications in routine medical examinations, and because radiographic

8) http://www.accessdata.fda.gov/cdrh_docs/pdf/p930021.pdf

measurement of alveolar bone often uses a periodontal probe (1.0 mm or 0.5 mm scale unit). In the 4 studies included in the pooled analysis, the lower limits of 95% confidence interval were 0.43 mm and 0.75 mm in 2 studies that could calculate 95% confidence interval for differences from the control group. On the basis of these results, 0.30 mm was judged to be a statistically acceptable value. Furthermore, the FOP group was used as the reference group in Study 1D-05 so that the appropriateness of the non-inferiority margin could be confirmed in a post-hoc manner.

PMDA considers that there are no particular problems regarding the designs of Studies 1D-03 and 1D-05.

7.R.1.2 Increase in new alveolar bone

In Study 1D-05, increases (mean ± SD) in new alveolar bone at Week 36 in the PPS (the primary endpoint) were 1.93 ± 1.39 mm in the 0.3% group, 1.36 ± 1.53 mm in the EMD group, and the difference [95% CI] between the treatment groups was 0.57 mm [0.18, 0.96]. The lower limit of 95% confidence interval was larger than the predefined value of −0.30 mm, showing the non-inferiority of trafermin 0.3% to EMD.

The increase rates (mean ± SD) of new alveolar bone in the FAS (a primary endpoint of Study 1D-03) were 21.6% ± 26.3% in the placebo group and 37.1% ± 32.0% in the 0.3% group.

On the basis of the above results, PMDA considers that trafermin 0.3% has been shown to increase new alveolar bone after flap operation.

7.R.1.3 Increase rate of new alveolar bone in subgroups

Tables 23 to 26 show the increase rates of new alveolar bone at Week 36 by dental characteristics in the 0.3% and control groups in Studies 1D-03 and 1D-05.

Table 23. Increase rate (%) of new alveolar bone at Week 36 by type of evaluated tooth (FAS)

Study	Tooth type	Placebo	0.3%	EMD	Treatment difference[a)] [95% CI]
1D-03	Front	21.0 ± 32.8 (18)	39.5 ± 33.5 (43)		18.5 [−0.3, 37.2]
	Premolar	23.9 ± 23.8 (46)	40.6 ± 30.4 (96)		16.7 [6.6, 26.8]
	Molar	18.9 ± 26.3 (36)	30.9 ± 32.9 (69)		11.9 [−0.6, 24.5]
1D-05	Front		40.7 ± 21.9 (23)	24.4 ± 24.5 (23)	16.2 [2.5, 30.0]
	Premolar		29.0 ± 21.2 (41)	21.0 ± 22.1 (42)	8.0 [−1.5, 17.5]
	Molar		36.0 ± 27.6 (46)	24.8 ± 28.2 (47)	11.2 [−0.2, 22.7]

Mean ± SD (number of subjects), missing values were imputed using the LOCF method
a) Difference between the 0.3% group and the placebo or EMD group

Table 24. Increase rate (%) of new alveolar bone at Week 36 by vital/non-vital pulp (FAS)

Study	Pulp	Placebo	0.3%	EMD	Treatment difference[a)] [95% CI]
1D-03	Vital	20.1 ± 25.7 (82)	37.8 ± 32.3 (163)		17.7 [9.6, 25.7]
	Non-vital	26.9 ± 28.9 (17)	33.6 ± 31.4 (43)		6.7 [−10.9, 24.3]
1D-05	Vital		35.2 ± 23.8 (93)	22.5 ± 27.3 (87)	12.7 [5.2, 20.2]
	Non-vital		29.8 ± 27.8 (17)	25.9 ± 15.5 (25)	3.8 [−9.7, 17.3]

Mean ± SD (number of subjects), missing values were imputed using the LOCF method
a) Difference between the 0.3% group and the placebo or EMD group

Table 25. Increase rate (%) of new alveolar bone at Week 36 by bone defect depth (FAS)

Study	Bone defect depth	Placebo	0.3%	EMD	Treatment difference[a)] [95% CI]
1D-03	<4 mm	14.9 ± 33.5 (17)	31.8 ± 35.5 (39)		16.9 [−3.4, 37.2]
	≥4 mm and <7 mm	22.0 ± 22.3 (62)	38.1 ± 31.5 (137)		16.1 [7.4, 24.9]
	≥7 mm	25.8 ± 30.1 (21)	39.4 ± 30.3 (32)		13.6 [−3.7, 30.8]
1D-05	<4 mm		- (0)	18.3 ± 30.0 (2)	-
	≥4 mm and <7 mm		32.7 ± 24.1 (84)	22.7 ± 25.9 (77)	10.0 [2.2, 17.8]
	≥7 mm		39.7 ± 25.3 (26)	24.9 ± 23.8 (33)	14.8 [2.0, 27.7]

Mean ± SD (number of subjects), missing values were imputed using the LOCF method
a) Difference between the 0.3% group and the placebo or EMD group

Table 26. Increase rate (%) of new alveolar bone at Week 36 by number of walls in bone defect (FAS)

Study	Number of walls in bone defect	Placebo	0.3%	EMD	Treatment difference[a)] [95% CI]
1D-03	2-wall	17.2 ± 21.1 (40)	35.7 ± 31.8 (86)		18.5 [7.6, 29.4]
	3-wall	28.3 ± 29.9 (35)	36.6 ± 32.3 (64)		8.2 [−4.9, 21.3]
	2- and 3-wall	24.9 ± 27.1 (20)	44.3 ± 32.6 (46)		19.4 [2.8, 36.0]
	Others[b)]	−3.8 ± 15.8 (5)	23.1 ± 27.8 (12)		27.0 [−1.6, 55.6]
1D-05	2-wall		30.2 ± 17.6 (29)	26.6 ± 28.0 (39)	3.6 [−8.2, 15.4]
	3-wall		41.1 ± 29.1 (40)	24.0 ± 26.1 (34)	17.1 [4.1, 30.0]
	2- and 3-wall		30.6 ± 22.1 (38)	17.4 ± 24.1 (22)	13.2 [0.9, 25.4]
	Others[b)]		33.5 ± 34.0 (3)	21.8 ± 16.4 (17)	11.7 [−13.6, 36.9]

Mean ± SD (number of subjects), missing values were imputed using the LOCF method
a) Difference between the 0.3% group and the placebo or EMD group
b) "1-wall bone defect," "4-wall bone defect," and "bone defect with mix of 1-wall or 4-wall bone defect"

PMDA's view:

Although evaluation with a small number of subjects has limitations, the increase rate of new alveolar bone at Week 36 tended to be generally higher in the 0.3% group than in the placebo and EMD groups. The efficacy of trafermin 0.3% did not tend to significantly decrease in any subgroups.

7.R.2 Safety

Based on the evaluation and confirmation described in Sections 7.R.2.1 to 7.R.2.4, PMDA considers that the safety of trafermin is acceptable. PMDA will draw a final conclusion on the safety of trafermin based on comments from the Expert Discussion.

The applicant performed a pooled analysis of 5 Japanese clinical studies: Studies 1D-01, 1D-02, 1D-03, 1D-04, and 1D-05. The pooled safety analysis set consisted of 191 subjects receiving placebo (the placebo group), 600 subjects receiving trafermin (the trafermin group), and 429 subjects receiving trafermin 0.3% (the 0.3% group).

7.R.2.1 Comparison with placebo

The applicant compared the incidence of adverse events in the trafermin 0.3% group with that in the placebo group, and provided the following explanation:

Adverse events were reported in 79.6% (152 of 191) of subjects in the placebo group and 73.0% (313 of 429) of subjects in the 0.3% group. Adverse drug reactions were reported in 14.7% (28 of 191) of

subjects in the placebo group and 12.6% (54 of 429) of subjects in the 0.3% group. The incidences of adverse events and adverse drug reactions in the 0.3% group were similar to those in the placebo group. Table 27 shows adverse events occurring in ≥5% of subjects in any treatment group; most were mild or moderate in severity. The incidences of albumin urine present and C-reactive protein increased tended to be slightly higher in the trafermin group. Albumin urine present was the only adverse drug reaction occurring in ≥5% of subjects in any treatment group: 5.2% (10 of 191) of subjects in the placebo group and 6.3% (27 of 429) of subjects in the 0.3% group (with no significant difference in incidence between the placebo and 0.3% groups).

Table 27. Adverse events occurring in ≥5% of subjects in any treatment group (pooled analysis)

	Placebo (N = 191)		0.3% (N = 429)	
	Incidence (%)	n	Incidence (%)	n
Any adverse event	79.6	152	73.0	313
Albumin urine present	20.9	40	28.2	121
Beta-N-acetyl-D-glucosaminidase increased	12.6	24	14.5	62
C-reactive protein increased	7.9	15	12.1	52
Beta 2 microglobulin urine increased	10.5	20	10.5	45
Blood creatine phosphokinase increased	9.4	18	9.6	41
Nasopharyngitis	7.3	14	5.4	23
Monocyte percentage increased	6.8	13	4.7	20
Eosinophil percentage increased	9.9	19	4.0	17
Device failure	5.8	11	3.0	13

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PMDA's conclusion:

The incidence of albumin urine present and C-reactive protein increased tended to be slightly higher in the 0.3% group than in the placebo group. However, all these adverse events were mild in severity with no tendency to raise clinical concerns. The incidence of adverse drug reactions did not differ between the 0.3% and placebo groups.

7.R.2.2 Serious and significant adverse events

The applicant explained the serious and significant adverse events reported in the trafermin group, including those in the placebo group.

The applicant's explanation:

In Studies 1D-01, 1D-02, 1D-03, 1D-04, and 1D-05 conducted in Japan, no deaths occurred during the observation period. After Week 36 during the follow-up investigation of Study 1D-02, sudden death was reported in 1 subject (the 0.2% group), and a causal relationship to the study drug was ruled out based on the time course.

Serious adverse events were reported in 9 subjects: 1 subject in Study 1D-01 (0.03%, large intestine polyp); 5 subjects in Study 1D-02 (placebo, 1 subject [eosinophilic pneumonia chronic]; 0.2%, 1 subject [pneumonia]; 0.4%, 3 subjects [gastric cancer, carcinoid tumour of the gastrointestinal tract, and depression in 1 subject each]); and 3 subjects in Study 1D-03 (placebo, 2 subjects [diverticulitis

intestinal haemorrhagic and sinusitis in 1 subject each]; 0.3%, 1 subject [breast cancer]). A causal relationship to the study drug was ruled out for all these events.

Malignant tumor and benign tumor were evaluated because they might be significant adverse events. Three subjects experienced malignant tumor or benign tumor that were not serious adverse events: 2 subjects in Study 1D-01 (0.03%, 1 subject [cervical dysplasia]; 0.3%, 1 subject [large intestine polyp]) and 1 subject in Study 1D-03 (0.3%, prostate cancer). A causal relationship to the study drug was ruled out for all these events.

The Contraindications section of the package insert for Fiblast Spray 250 and 500 (the approved trafermin formulation) includes a cautionary statement on the risk of malignant tumor. The package insert for Regroth will also include a cautionary statement on the risk of malignant tumor.

PMDA's view:
According to data available at present, no specific serious adverse events or tumors tended to occur very frequently in subjects receiving trafermin. PMDA accepts the applicant's plan to include a cautionary statement on malignant tumor in the package insert.

7.R.2.3 Intraoral adverse events

The applicant's explanation on the incidence of intraoral adverse events:
Table 28 shows intraoral adverse events occurring in ≥2% of subjects in the placebo or 0.3% group. All intraoral adverse events reported in the 0.3% group were mild or moderate.

Table 28. Intraoral adverse events occurring in ≥2% of subjects in either the placebo group or the 0.3% group

	Placebo (N = 191)		0.3% (N = 429)	
	Incidence (%)	n	Incidence (%)	n
Any adverse event	24.6	47	17.9	77
Device failure	5.8	11	3.0	13
Stomatitis	3.1	6	2.1	9
Sensitivity of teeth	3.1	6	1.4	6
Dental caries	3.7	7	0.7	3
Toothache	2.1	4	0.7	3
Gingival pain	2.1	4	0.5	2

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Adverse events occurring in treated or adjacent teeth were device failure (placebo, 5 of 191 subjects [2.6%]; 0.3%, 10 of 429 subjects [2.3%]) and dental caries (placebo, 4 of 191 subjects [2.1%]; 0.3%, 3 of 429 subjects [0.7%]). There were no intraoral adverse drug reactions or adverse drug reactions in treated or adjacent teeth that occurred in ≥2% of subjects in either the placebo group or the 0.3% group.

No abnormal alveolar bone increase, osseous ankyloses, abnormal gingival outgrowth, or malignant tumor was reported.

PMDA's conclusion:
According to data available at present, no significant difference has been found in the incidence of intraoral adverse events between the 0.3% and placebo groups.

7.R.2.4 Anti-drug antibody

The applicant's explanation on antibodies to trafermin:
In Studies 1D-01, 1D-02, 1D-03, 1D-04, and 1D-05, the presence or absence of serum anti-trafermin antibodies was determined, and if any antibody was identified, the specificity of the antibody was confirmed.

Serum antibody levels exceeded the cut-off value in 3 subjects in Study 1D-01 (placebo, 2 subjects; 0.03%, 1 subject), 13 subjects in Study 1D-02 (placebo, 4 subjects; 0.2%, 4 subjects; 0.3%, 1 subject; 0.4%, 4 subjects), and 1 subject in Study 1D-03 (placebo), but all samples showed a non-specific reaction. No antibody was detected in Study 1D-04 or 1D-05. These results showed that no anti-trafermin antibody was produced in the trafermin concentration range of 0.03% to 0.4%. No anaphylactic reaction was reported in any of the clinical studies.

PMDA confirmed that no specific anti-trafermin antibody production was noted in subjects treated with trafermin.

7.R.3 Indication

The applicant's explanation:
In the Japanese phase III, placebo-controlled, confirmatory study in patients with periodontitis who required flap operation (Study 1D-03), "increase rate of new alveolar bone at Week 36" (the primary endpoint) was greater in the trafermin 0.3% group than in the placebo group. In the Japanese phase III, EMD-controlled, confirmatory study (Study 1D-05) conducted in the same patient population, trafermin was shown to be non-inferior to EMD in "increase in new alveolar bone at Week 36" (the primary endpoint). Since the efficacy of trafermin 0.3% was demonstrated and no safety issues have been observed to date [see Sections 7.R.1 and 7.R.2], the applicant has proposed the indication, "regeneration of periodontal tissues lost as result of periodontitis." The package insert will specify the appropriate depth of periodontal pocket and bone defect for trafermin therapy.

PMDA's view:
The indication should clearly show that Regroth must be used for the treatment of alveolar bone defect due to periodontitis based on the results of Studies 1D-03 and 1D-05.

As the applicant explained, the package insert should specify the appropriate depth of the periodontal pocket and bone defect for trafermin therapy.

PMDA will draw a final conclusion on the indication of Regroth based on comments from the Expert Discussion.

7.R.4 Dosage and administration

The applicant's explanation:

In the Japanese phase II study of trafermin (Study 1D-02), the mean increase rates of alveolar bone at Week 36 were statistically significantly higher in all trafermin groups than in the placebo group: 15.1% in the placebo group, 32.7% in the 0.2% group, 50.6% in the 0.3% group, and 45.2% in the 0.4% group [see Section 7.1.2]. A comparison test of the dose-response trend suggested a dose-response pattern with saturation at ≥0.3%. As a result, the Japanese phase III confirmatory studies (Studies 1D-03 and 1D-05) used trafermin 0.3% and demonstrated its efficacy with no particular safety concerns.

The required dose varies according to the form and depth of a bone defect of individual patients. Therefore, the applicant proposed the following dosage administration based on the dosage evaluated in Study 1D-05: "Administer an appropriate amount of the reconstituted solution that fills the alveolar bone defect."

The applicant's explanation about the maximum dose:

In the clinical pharmacology study (Study 1D-04), trafermin 0.6 mL was administered to 17 subjects. The study revealed no safety concerns, and no subjects had an increased serum trafermin concentration higher than the concentration range of endogenous bFGF. No difference was noted in exposure to serum trafermin between subjects treated with trafermin 0.2 mL and subjects treated with trafermin 0.6 mL [see Section 6.2.1]. In Study 1D-05, trafermin 0.4 mL was administered to 31 subjects and no specific safety concern was reported. Flap operation can be performed simultaneously to multiple teeth. According to the 2014 Statistics of Medical Care Activities in Public Health Insurance (Ministry of Health, Labour and Welfare), approximately 300,000 flap operations were performed (approximately 800,000 teeth treated) per year. The mean number of teeth treated per operation is calculated to be 2.7 teeth. In Study 1D-05, trafermin was administered to ≥2 teeth in 35.5% (39 of 110) of subjects in the trafermin 0.3% group; the study showed no differences that would pose efficacy or safety concerns between subjects treated for 1 tooth and ≥2 teeth. No specific safety concerns have been identified in the estimated clinical dose range to date, and therefore there is no need to specify the maximum dose.

The applicant's explanation about repeated administration:

No anti-trafermin antibody production was observed in 600 subjects treated with trafermin in the clinical studies. Repeated administration of Regroth is unlikely to pose concerns regarding systemic safety for the following reasons: (a) No expression of anti-trafermin antibody was found in the clinical studies of Fiblast Spray 250 and 500. (Fiblast Spray is the approved product containing trafermin, the active ingredient, and is repeatedly administered for the treatment of pressure sores and skin ulcers.) (b) There are no tendency towards an increased incidence of adverse drug reactions after repeated administration of Fiblast Spray 250 and 500.

PMDA's view:

There are no problems with the proposed trafermin concentration (0.3%) or the proposed dosage and administration, which were selected based on the dosage used in the clinical study (Study 1D-05). To

date, no specific safety concerns have been identified in the clinical studies of Regroth or in the safety data of Fiblast Spray 250 and 500. Thus, there is no need to limit the maximum dose or repeated administration. The applicant should prepare materials for healthcare professionals to appropriately provide information on the details of usage of Regroth.

PMDA will draw a final conclusion on the dosage and administration of Regroth based on comments from the Expert Discussion.

7.R.5 Post-marketing investigations

The applicant plans to conduct a drug use-results survey shown in Table 29.

Table 29. Outline of use-results survey (draft)

Objective	**Confirmation of the safety and efficacy in clinical practice**
Survey method	**Central registration method**
Survey period	**4 years**
Planned sample size	**1000 patients (safety analysis set, 600 patients)**
Planned number of institutions	**100 to 200 institutions**
Population	**Patients with periodontitis with vertical bone defect treated with Regroth**
Observation period	**For 36 weeks** **For 52 to 72 weeks, if possible, for the presence or absence of intraoral abnormal findings**
Main survey items	• **Characteristics of patients (e.g., sex, age, complications, medical history, smoking status, flap operation site, condition of evaluated tooth, bone defect depth at the evaluation site, form of bone defect/number of walls in bone defect)** • **Treatment with Regroth (e.g., tooth treated, number of administrations)** • **Concomitant medications and therapies** • **Adverse events (e.g., date of onset, seriousness, action taken, outcome, causality)** • **Key survey items (abnormal findings at the administration site [e.g., malignant tumor, periodontal tissue overgrowth])** • **Alveolar bone height of the evaluated tooth and evaluation site, increase rate of new alveolar bone, clinical attachment level, probing depth, gingival bleeding index, gingivitis index, tooth mobility, plaque index, keratinized gingival width, changes in amount of marginal gingival recession**

PMDA considers that the applicant should collect data on the dose of Regroth as well as on the items shown in Table 29.

In view of comments from the Expert Discussion, PMDA will draw a final conclusion on the risk management plan (draft) and the outline of the post-marketing surveillance plan (draft), both proposed by the applicant.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-2, CTD 5.3.5.1-3, CTD 5.3.5.1-4) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection showed that the clinical studies were conducted generally in compliance with GCP. PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following findings at a clinical trial site and the Sponsor, although the findings had no significant impact on the overall assessment of clinical studies. PMDA notified the head of the site and the Sponsor of the findings, which were classified as "problems to be addressed."

Problems to be addressed

A clinical trial site

- A part of deliberation concerning revision of the protocol and investigator's brochure was performed by expedited review, although the deliberation was out of the scope of expedited review stipulated in the SOP.

Sponsor

- Some information on serious and unexpected adverse drug reactions was not appropriately provided to the investigators and the heads of clinical trial sites.

9. Overall Evaluation during Preparation of the Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of Regroth in the treatment of alveolar bone defect in patients with periodontitis and show acceptable safety in view of the benefits indicated by the data submitted. Regroth is clinically meaningful because it offers a new treatment option for alveolar bone defect in patients with periodontitis. PMDA considers that further evaluation is necessary regarding the efficacy, safety, indication, dosage and administration, and post-marketing investigations.

PMDA has concluded that Regroth may be approved if Regroth is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 15, 2016

Product Submitted for Approval

Brand Name	Regroth Dental Kit 600 μg Regroth Dental Kit 1200 μg
Non-proprietary Name	Trafermin (Genetical Recombination)
Applicant	Kaken Pharmaceutical Co., Ltd.
Date of Application	October 1, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

Of the discussions described in the Review Report (1), the PMDA's conclusions on "7.R.1 Efficacy" and "7.R.2 Safety" were supported by the advisors in the Expert Discussion. The following sections present the expert advisors' comments regarding "7.R.3 Indication," "7.R.4 Dosage and administration," and "7.R.5 Post-marketing investigations."

1.1 Indication

The PMDA's conclusion presented in the Review Report (1) was supported by the expert advisors.

The expert advisors' comments:

- In the non-clinical studies, trafermin was shown to promote regeneration of periodontal tissue. Meanwhile, the clinical studies showed that Regroth was effective only in improving the depth of the alveolar bone defect, and did not directly evaluate the periodontal ligament or cementum. Therefore, the proposed indication of "regeneration of periodontal tissues" is an overstatement.
- No clinical studies have demonstrated the safety or efficacy of Regroth for implant therapy. In the post-marketing settings, however, Regroth may be used for implant therapy, in the hope that the drug would promote bone growth. The applicant should appropriately inform healthcare professionals about the boundaries of efficacy and safety confirmed in the phase III clinical studies.

PMDA's conclusion based on the comments of the expert advisors:

The Precautions for Indication section of the package insert should include the following cautionary statement: The efficacy and safety of Regroth in implant therapy have not been established.

This conclusion was supported by the expert advisors. PMDA instructed the applicant to modify the Indication, and Precautions for Indication sections as follows. The applicant appropriately responded to the request and PMDA accepted the modifications.

Indication
Alveolar bone defect due to periodontitis

Precautions for indication
1) Regroth should be used for the treatment of vertical bone defect with a periodontal pocket depth ≥4 mm and a bone defect depth ≥3 mm.
2) The efficacy and safety of Regroth in implant therapy have not been established.

1.2 Dosage and administration
The PMDA's conclusion presented in the Review Report (1) was supported by the expert advisors.
The expert advisors' comments:
- There is no special need to define the maximum dose or to restrict repeated administration, because no particular safety concerns have been identified from the post-marketing safety data of Fiblast Spray, and because Regroth is expected to be used at lower doses and less frequently than Fiblast Spray. Frequent administration of Regroth is very unlikely, because Regroth is used only during flap operation, and because patients treated with Regroth during a flap operation are very unlikely to undergo another flap operation within 6 month of the initial operation due to the slow speed of bone repair. However, the applicant should disseminate detailed information on how to administer Regroth.

- While there is no need to define the maximum dose or restrict repeated administration, the applicant should suggest an appropriate amount of Regroth to be used.

PMDA's conclusion based on the comments of the expert advisors:
The Dosage and administration section and the Precautions for dosage and administration section should be modified as follows (see below). The Clinical Studies section of the package insert should include detailed information on the amount of trafermin used in the Japanese phase III confirmatory study (Study 1D-05). Information materials for healthcare professionals should contain detailed information on how to administer Regroth.

Dosage and administration
Administer an appropriate amount of the product that fills the alveolar bone defect during a flap operation.

Precautions for dosage and administration
Refer to the Clinical Studies section of the package insert for the appropriate amount of Regroth to be administered.

PMDA requested the applicant to respond to the above requests. The applicant appropriately responded and PMDA accepted the applicant's response.

1.3 Risk management plan (draft)

The PMDA's conclusion shown in [Section 7.R.5 Post-marketing investigations] of the Review Report (1) was supported by the expert advisors.

The expert advisors' comments:

- Information on doses and the form of bone defect should be collected in order to avoid any risk associated with malignant tumor and gingival proliferation. In addition to information on doses, data on leakage level at the time of administration of Regroth should be collected.

Based on the comments of the expert advisors, PMDA instructed the applicant to collect information on doses and leakage level at time of administration in the post-marketing surveillance. The applicant responded appropriately.

In view of the Expert Discussion, PMDA has concluded that the risk management plan (draft) for Regroth should include the safety and efficacy specifications presented in Table 30, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 31 as well as the use-results survey presented in Table 32.

Table 30. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
• **None**	• **Promotion of metastasis and growth of malignant tumor at the administration site** • **Periodontal tissue overgrowth at the administration site**	• **None**
Efficacy specification		
• **Efficacy in clinical practice**		

Table 31. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	**Additional risk minimization activities**
• **Early post-marketing phase vigilance** • **Use-results survey**	• **Disseminate data gathered during early post-marketing phase vigilance** • **Distribution of information materials for healthcare professionals**

Table 32. Outline of use-results survey (draft)

Objective	**Confirmation of the safety and efficacy in clinical practice**
Survey method	**Central registration method**
Survey period	**4 years**
Planned sample size	**1000 patients (safety analysis set, 600 patients)**
Planned number of institutions	**100 to 200 institutions**
Population	**Patients with periodontitis with vertical bone defect treated with Regroth**
Observation period	**For 36 weeks** **For 52 to 72 weeks, if possible, for the presence or absence of intraoral abnormal findings**
Main survey items	• **Characteristics of patients (e.g., sex, age, complications, medical history, smoking status, flap operation site, condition of evaluated tooth, bone defect depth at the evaluation site, form of bone defect/number of walls in bone defect)** • **Treatment with Regroth (e.g., tooth treated, number of administrations, dose, leakage level)** • **Concomitant medications and therapies** • **Adverse events (e.g., date of onset, seriousness, action taken, outcome, causality)** • **Key survey items (abnormal findings at the administration site [e.g., malignant tumor, periodontal tissue overgrowth])** • **Alveolar bone height of the evaluated tooth and evaluation site, increase rate of new alveolar bone, clinical attachment level, probing depth, gingival bleeding index, gingivitis index, tooth mobility, plaque index, keratinized gingival width, changes in amount of marginal gingival recession**

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved under the following condition of approval after modifying the indication, and dosage and administration statements as shown below. The product is a drug with a new route of administration and the re-examination period is 6 years. The product is not classified as a poisonous drug, powerful drug, a biological product, or specified biological product.

Indication

Alveolar bone defect due to periodontitis

Dosage and Administration

Administer an appropriate amount of the product that fills the alveolar bone defect during a flap operation.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.