Clinical trial protocol

Effect of increasing blood flow by botulinum toxin local injection for severe peripheral artery occlusive disease: preliminary report

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CONFIDENTIAL

Contents

1. TITLE

Effect of increasing blood flow by botulinum toxin local injection for severe peripheral artery occlusive disease: preliminary report

2. NAME AND ADDRESS OF CLINICAL TRIAL INSTITUTION

Name	address
Yong in severance hospital	Yongin Severance Hospital 363, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 16995, Republic of Korea

3. CLINICAL TRIAL PERSON IN CHARGE

3.1 Clinical trial person in charge

	Hospital	Major Field	Title	Name
P.I.	Yong in severance hospital	Department of plastic and reconstructive surgery	professor	Hii sun, Jeog

3.2 Clinical trial staff, managing pharmacist, and co-researchers

Hospital	Major Field	Co-researcher	Name
Yong in severance hospital	Nephrology	S.I.	Jung eun, Lee
Yong in severance hospital	Cardiology	S.I.	O hyun, Lee
Yong in severance hospital	Endocrinology	S.I.	Gyung min, Kim
Yong in severance hospital	Plastic and reconstructive surgery	S.I.	Bok ki, Jung
Yong in severance hospital	Plastic and reconstructive surgery	managing pharmacist	Bok ki, Jung

4. INTRODUCTION

4.1 Background

Tissues below the calf are governed by blood flow from the anterior tibial artery, peroneal artery, and posterior tibial artery. When an ulcer occurs due to acute lower extremity ischemia, one of the three blood vessels is blocked by a blood clot, or when the blood vessel is narrowed due to perivascular inflammation, such as Buerger's disease, it occurs in a subacute or chronic form. In particular, in the case of elderly patients with ulcers or diabetic feet due to lower extremity ischemia, the symptoms are often worsened by chronic narrowing of blood vessels due to arteriosclerosis or blockage by blood clots. To treat this, prostaglandin or antithrombotic drugs are taken, and blood flow is resumed through stent surgery, but in the lower extremities, the recurrence rate is relatively high because the blood vessels are smaller than the iliac artery, femoral artery, and popliteal artery.

Botulinum toxin is known to have a positive effect on wound healing and blood flow improvement. Botulinum toxin has been published several times in papers showing its spasmolytic effect by participating in the radiographic hip osteoarthritis Ras homolog A (RhoA)/Rock-assisted protein kinase (ROCK) pathway. In addition, botulinum toxin has a vasodilating effect related to the calcitonin gene-related peptide (CGRP) pathway, and is involved in increasing vascular endothelial growth factor (VEGF) from NO-mediated angiogenesis, inhibiting vasoconstriction, increasing blood flow rate, and promoting angiogenesis.

In this study, in patients with chronic wounds on the feet, whose lower extremity blood vessels circulate mainly through collateral circulation, subcutaneous injection of Botulinum toxin in and around the wound improves blood flow around the wound and confirms the degree of wound healing.

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4.2 Purpose

This is a non-randomly assigned, open-label, prospective comparative clinical study to confirm the effectiveness and safety of the effect of improving blood flow around foot wounds by injecting botulinum toxin into patients with moderate to severe lower extremity ischemia.

5. CLINICAL INVESTIGATIONAL DRUGS

1) Product name: Botulex®
2) Product name: Botulinum toxin A
3) Appearance: It is an injection containing white, freeze-dried powder in a colorless and transparent glass vial. When a solvent (physiological saline solution) is added, it should become a colorless and transparent liquid preparation..
4) Amount of raw drug product: 100 unit/1 vial
5) Storage conditions: Store in refrigerator (2~8℃).
6) Period of use: 36 months from the date of manufacture
7) Manufacturer: Hugel Co., Ltd.

6. TARGET DISEASE

Patients with chronic ulcer on foot among patients with moderate to severe lower extremity ischemia

7. SELECTION OF TEST SUBJECTS

7.1 Inclusion criteria

1. Age ≥ 20 years old
2. Patients who have a lower extremity wound among those who have been diagnosed with moderate or severe lower extremity ischemia
3. Patients who are unable to perform additional procedures (angioplasty, etc.) by performing peripheral vascular examination and CT angiography
4. Wound size ≥ 1x1cm2 to ≤ 3x3cm2
5. Patients who can follow the clinical trial procedure well and abide by the visit schedule
6. Written informed consent to participate in the study after having fully understood the contents of the protocol and restrictions.

7.2 Exclusion criteria

7. Patients with diseases that can affect neuromuscular function, such as myasthenia gravis, Eaton-Lamberton syndrome, amyotrophic lateral sclerosis, and motor neuropathy

8. Within 4 weeks before screening, aminoglycoside antibiotics, curare-like agents, or drugs that inhibit neuromuscular function (muscle relaxants, anticholinergics, benzodiazepines, benzamides, tetracyclines, Rinco Those who have taken mycin antibiotics, etc.)
9. Those taking aspirin, NSAIDs or anticoagulants within 7 days before screening
10. Those who have received botulinum toxin preparations within 3 months before screening
11. Angiography or CT angiography If one or more of the three major blood vessels in the lower extremity are open
12. Cases in which blood flow to the lower extremities can be preserved by performing balloon angioplasty even if all three major blood vessels in the lower extremity are blocked
13. Those who are currently taking steroids or immunosuppressants that affect wounds, or those who have taken them within one month of screening
14. Those who have applied injection drugs or wound coverings that help improve wounds within 1 week of screening
15. Women who are pregnant, lactating, planning to become pregnant during the clinical period, or women of childbearing age who are not using available contraceptive methods (women of childbearing age must be negative in the pregnancy test prior to injection).
16. Those who are allergic or sensitive to botulinum toxin
17. Those who have participated in another clinical trial within 30 days before screening or those who have not passed the half-life of the investigational product of the clinical trial that they participated in, whichever is longer.
18. Those who are not suitable for this clinical trial under the judgment of other investigators

7.3 Number of subjects

10 subjects

7.4 Determination of Sample Size

This study was planned as an investigator-led clinical trial. The purpose is to collect information on the initial safety and effectiveness of drugs, design follow-up confirmatory clinical trials, and provide evidence for evaluation items and evaluation methods, and is scheduled to be conducted on a small number of clinical trial subjects over a relatively short period of time. As this is an exploratory clinical trial using non-random allocation, open label, and clinical case studies, the number of subjects is not calculated statistically.

It is expected that approximately one clinical trial subject will be registered per month. The wound healing treatment period is expected to be more than a month, and the clinical trial period for each

test subject is short, about two weeks, making it difficult for patients to drop out. Therefore, even if dropout is considered, if 10 clinical trial subjects who met the study period complete the clinical trial, the entire study will be terminated, and statistical results will be derived based on this.

8. CLINICAL TRIAL PERIOD

It is expected to take approximately 12 months from the date of IRB approval to completion of administration to the last test subject.

Test subject registration period: approximately 6 months

Clinical trial period for each test subject: approximately 2 weeks

(follow-up for 2 weeks after one administration)

9. CLINICAL TEST METHOD

9.1 Preparation process for clinical investigational drugs

9.1.1 Foreign body inspection

Carefully inspect the presence of foreign substances and discoloration in the vial before and after dilution..

9.1.2 Dilution method

To dissolve the freeze-dried investigational drug, use preservative-free sterile saline solution (0.9% sodium chloride injection). If the investigational drug bubbles or undergoes similar vigorous agitation, it will denature, so gradually add the diluent to the vial. If the diluent does not enter the vial under vacuum, discard the vial. Record the date and time of dissolution on the label and administer within 24 hours after dissolution. During this period, the dissolved investigational drug is stored in the refrigerator (2~8℃). The dissolved clinical trial drug should be colorless and transparent and no unusual substances should be visible. As the formulation and diluent do not contain preservatives, it is not recommended to use one vial for more than one patient. In this clinical trial, 1 vial of Botulex 100 Units is prepared by diluting it in 4 ml of 0.9% physiological saline solution. Before administration, foreign matter inspection, dilution, and syringe filling are performed by a designated dilution manager, and then administration is performed by the researcher in charge of medication administration.

9.2 Dosage and administration method of investigational drugs

1) Botulex® (Main ingredient: Clostridium botulinum toxin type A, Strain: Clostridium Botulinum CBFC26) 100 units(1 vial) is prepared by dissolving in 4 cc normal saline for test subjects who meet the selection criteria as a result of the screening test.

2) Treatment method

① Dissolve 100 units (1 vial) of Botulex in 4 cc of normal saline.

② Prepare 4 syringes by filling 4 cc of Botulex solution into each 1 cc syringe.

③ Attach a 30G, 1/2'' needle to a 1cc syringe filled with 1cc of Botulex solution, and prepare alcohol cotton, gauze, and surgical gloves.

④ Inject the Botulex solution into the subcutaneous fat layer at a dose of 5 units per 1x1 cm2 into and around the wound of a patient with moderate to severe lower extremity ischemia.

⑤ After administration, disinfect the administration site and dress the administration site and wound area.

⑥ The maximum dosage at one time should not exceed 100 units.

9.3 Storage, management and records of investigational drugs

1) Responsibility for the management of investigational drugs used in clinical trials lies with the principal investigator and the investigational drug manager (hereinafter referred to as manager) of the relevant clinical trial institution.

2) The provider of investigational drugs must distribute the investigational drugs used in clinical trials to the manager, and obtain and preserve a receipt of receipt.

3) The manager checks whether the price of the investigational drug used in the clinical trial matches the packaging list, whether it is in good condition, and whether the quantity matches the quantity on the receipt.

4) Managers must store and manage investigational drugs used in clinical trials to ensure that they are not used for purposes other than clinical trials.

5) During the conduct of clinical trials, the manager prepares receipt/disbursement records regarding the receipt/release, inventory, and use status of investigational drugs and the return or disposal of unused investigational drugs. The quantity and storage conditions of investigational drugs used in clinical trials must be confirmed, and measures must be taken to ensure that clinical trials can proceed appropriately. Receipt and payment records include date, quantity, number, etc.

6) The clinical trial director or manager confirms that the quantity of the receipt and payment record of the investigational drug used in the clinical trial matches the contents of the case record. If there is a discrepancy, investigate the cause, record the results, and take necessary action.
7) Drugs for clinical trials are stored in a storage container with a locking device in the drug refrigerator in the plastic surgery outpatient treatment room on the 2nd floor of Yongin Severance Hospital under the supervision of the clinical research director or manager.
8) Once an investigational drug is assigned, it cannot be reassigned to another subject.
9) After injecting the clinical trial drug, the syringe and packaging used must be managed so as not to be reused.
10) The provider of investigational drugs shall recall unused investigational drugs when the clinical trial is suspended or terminated or the clinical trial manager does not conduct the test according to the protocol. At this time, after consultation with the clinical trial director, the manager must return unused clinical trial drugs to the company and keep the return certificate.
11) The provider of investigational drugs must confirm the quality of the investigational drugs by conducting quality control tests by batch number before the start of clinical trials.

9.4 Concomitant drugs and treatment/Contraindicated drugs and treatment

9.4.1 Concomitant drugs

Concomitant drugs and combination therapies that are not defined as treatment contraindications in this clinical trial protocol are permitted. For all drugs taken during the clinical trial period, the drug name, dosage, dosage, and period of use must be recorded. If non-drug treatment such as rehabilitation therapy was received, the treatment method and purpose must be recorded in the case record.

9.4.2 Contraindicated drugs

The following drugs that may affect muscle tone are permitted if taken steadily within 4 weeks prior to participating in the clinical trial. However, there should be no change in dosage during the clinical trial period.

1) Muscle relaxants

classification	drug details
peripheral muscle relaxant	Alcuronium, Tubocurarine, Dimethyltubocurarine, Pancuronium, Gallamine, Vecuronium, Atracurium, Hexafluorenium, Pipecuronium bromide etc.
central muscle relaxant	Phenprobamate, Carisoprodol, Styramate, Baclofen, Tizanidine,

	Pridinol, Tolperisone etc.
muscle relaxant	Dantrolene

2) Benzodiazepines: Diazepam, Chlordiazepoxide, Medazepam, Oxazepam, Potassium clorazepate, Lorazepam etc.

The following drugs are prohibited from co-administration during the clinical trial period.

1) Aminoglycoside antibiotics: Streptomycins, Tobramycin, gentamicin, Kanamycin, Neomycin, Amikacin, Netilmicin, Sisomicin, Dibekacin etc.
2) antibiotics: Spectinomycin, Polymyxin, Tetracycline, lincomycine etc.
3) Anticholinergics: Trihexyphenidyl, Biperiden, Metixene, Procyclidine, Profenamine, Dexetimide, Phenglutarimide, Mazaticol, Benzatrophin etc.
4) Benzamide-based drugs: tiapride hydrochloride, sulpiride etc.

In addition to the administration of clinical trial drugs, concomitant drugs, including general drugs, may be permitted if necessary if they are not contraindicated drugs. During the clinical trial, concomitant medications must be recorded in the case record including drug name, dosage, dosage, and period of use.

In the case of drugs that are used at the discretion of the investigator for reasons such as safety to manage adverse reactions, the reasons may be documented and the clinical trial may be continued.

10. OBSERVATION ITEMS, CLINICAL EXAMINATION ITEMS AND OBSERVATION TEST METHODS

10.1 Observation and clinical examination items by visit period

10.1.1 Visit 1 : Baseline (Day -7~0)

Researchers obtain written consent from test subjects prior to participation in clinical trials. On the day of administration, collect the following data and conduct clinical trials.

The following process occurs at the screening visit (Visit 1).

1) Written consent
2) Demographic information: Check the test subject's information such as initials, gender, and age.

3) Confirmation of prior medications and treatments: Investigate medications and treatments administered or being administered within 4 weeks prior to the baseline visit.
4) Investigate the history of botulinum toxin injections.
5) Check medical history and surgical history: Check medical history and surgical history within 6 months before the baseline visit.
6) Physical examination
   - Wound size, wound depth, condition of the wound bed, degree of discharge of the wound, and whether the wound is inflamed.
7) Vital signs: Measure blood pressure (systolic/diastolic) and pulse.
8) Pregnancy test: Serum β hCG pregnancy test or urine hCG test is performed only on women who have started menarche and are capable of becoming pregnant.
9) Laboratory tests: The following laboratory tests are performed. (However, if results are available within 2 weeks prior to the screening visit, those results can be used instead.)
   - Hematology test: WBC, RBC, Hemoglobin, Hematocrit, Platelet count, WBC differential count (Neutrophil, Lymphocyte, Monocyte, Eosinophil, Basophil)
   - Blood biochemical test: Na, K, Cl, Ca, P, BUN, Glucose, Total bilirubin, Total cholesterol, Uric acid, Total protein, Albumin, Alkaine phosphatase (ALP), SGOT. SGPT, Creatinine
   - Urine test: pH, Specific Gravity, Glucose, Protein, Color
10) Evaluation of selection/exclusion criteria
11) Dressing

10.1.2 Visit 2: Day 0

The following data are collected on the day of administration of the clinical trial drug.

1) Evaluation of exclusion criteria
2) Administration of clinical trial drugs
3) Dressing
4) tcPO2 measurement
5) Thermal imaging camera measurement
6) Photography
7) Concomitant medications
8) Adverse reactions: Check whether the test subject has any signs or symptoms of an infusion reaction within 30 minutes after administration. Anaphylaxis, severe allergic reaction, and severe

infusion reaction are defined as Grade 3 or higher in each of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

10.1.3 Visit 3 : Day 3 ± 2

The following data are collected 3 days after administration of the clinical trial drug.

1) Physical examination

2) Vital signs

3) Dressing

4) Concomitant medications

5) Adverse reactions

10.1.4 Visit 4 : Day 7 ± 2

The following data are collected 7 days after administration of the investigational drug.

1) Physical examination

2) Vital signs

3) Dressing

4) tcPO2 measurement

5) Thermal imaging camera measurement

6) Photography

7) Concomitant medications

8) Adverse reactions

10.1.5 Visit 5 : Day 10 ± 2

The following data are collected 10 days after administration of the investigational drug.

1) Physical examination

2) Vital signs

3) Dressing

4) Concomitant medications

5) Adverse reactions

10.1.6 Visit 6 : Day 14 ± 2

The following data are collected 14 days after administration of the investigational drug.

1) Physical examination

2) Vital signs

3) Pregnancy test

4) Laboratory tests

5) Dressing

6) tcPO2 measurement

7) Thermal imaging camera measurement

8) Photography

9) Concomitant medications

10) Adverse reactions

10.2 Dropout

Subjects who drop out must measure the items at the last visit (Visit 6) of the clinical trial.

10.3 Unscheduled Visits

If the test subject visits on a day other than the scheduled date, vital signs, physical examination, laboratory tests, concomitant drug/non-drug treatment investigation, and confirmation of adverse reactions are performed. Unscheduled visits should not change the schedule of the study plan.

11. CRITERIA FOR PLAN VIOLATION, SUSPENSION AND DISQUALIFICATION

11.1 Criteria for plan violation

If it is known that the protocol has been violated during the clinical trial, the investigator must decide whether the subject should continue or discontinue the clinical trial. If a student drops out due to violation of the plan, the details must be recorded in the case report form.

11.2 Criteria for suspension and disqualification

Subjects who have received the investigational drug but are unable to participate during the entire clinical trial period for any reason are classified as 'withdrawals.' If the test subject requests it or the investigator determines that the test subject should be eliminated, the test subject may be eliminated at any time. The reasons for elimination are as follows.

1) Voluntary termination of test by subject (withdrawal of consent)
2) Subjects who participated in violation of selection/exclusion criteria
3) When the subject does not visit (failure to follow-up)
4) When a concomitant contraindicated drug was administered or when it was deemed necessary to administer a concomitant contraindicated drug
5) When a female test subject is pregnant
6) When it is difficult to perform the test due to adverse reactions
7) If a serious violation of the clinical trial protocol occurs
8) If a systemic disease that was not detected in the pre-procedure examination is discovered
9) During the clinical trial period, if medication or procedures that could affect the test results were administered without the doctor's instructions.
10) In cases where the clinical trial can no longer proceed due to other investigators' judgment

In order to evalute the fact that an adverse reaction has occurred that the tester is not aware of, the test subject who refuses to visit must be contacted directly using all methods such as phone, letter, or in-person visit. The reason for exclusion must be recorded in the case report form. Evaluation at the last visit should also be conducted for subjects who drop out. Subjects who fail are unable to re-participate.

12. EFFECTIVENESS EVALUATION CRITERIA, EVALUATION METHODS AND INTERPRETATION METHODS

12.1 Primary endpoint

1) Change in tissue oxygen tension in tcPO2 (mmHg) in the wound 14 days after administration compared to baseline

12.2 Secondary endpoint

1) Change in the range of colors in the wound areas of both feet on the thermal imaging camera 14 days after administration compared to baseline.
2) Changes in wound area in photography 14 days after administration compared to baseline

12.3 Effectiveness evaluation method

12.3.1 Local transcutaneous Oxygen Pressure Measurement, tcPO ^{2}

Transcutaneous oxygen partial pressure measurement is a technology that attaches a sensor, a measuring device, around the wound, and non-invasively measures the oxygen value diffusing in the subcutaneous blood vessels using an electrical signal. To determine the transcutaneous oxygen partial pressure, the transcutaneous oxygen partial pressure is measured using the PF5040 TcpO2 unit (PeriFlux System5000; Perimed AB, Stockholm, Sweden) and dedicated software (PeriSoft for Windows 2.50; Perimed AB).

The probe of the transdermal oxygen partial pressure meter is attached to the location of the wound or further distal to it with the patient lying horizontally to accurately reflect the amount of oxygen coming from the capillaries. Measurements are taken when the temperature of the skin surface reaches 43.0 C after an equilibrium period of 10 to 15 minutes. The measured room temperature was maintained at 25 to 26 C during the study period. For control comparison, normal areas of the same area are also measured and compared at each measurement.

12.3.2 Thermal imaging camera

After removing the patient's dressing from the wound area, the results of the thermal imaging camera are immediately measured to obtain static thermal imaging camera results.

After applying isopropyl alcohol to the affected area, apply a breeze with a fan for 60 seconds to bring the skin temperature to 23-25 C. Then, use a thermal imaging camera to record the pattern of reheating the skin temperature(dynamic thermal imaging).

They appear as hot spots where perforating blood vessels exist, and they appear as cold spots where there is no subdermal blood vessel layer. Changes in blood flow in the skin near the wound are visually observed using a thermal imaging camera.

12.3.3 Gross photo

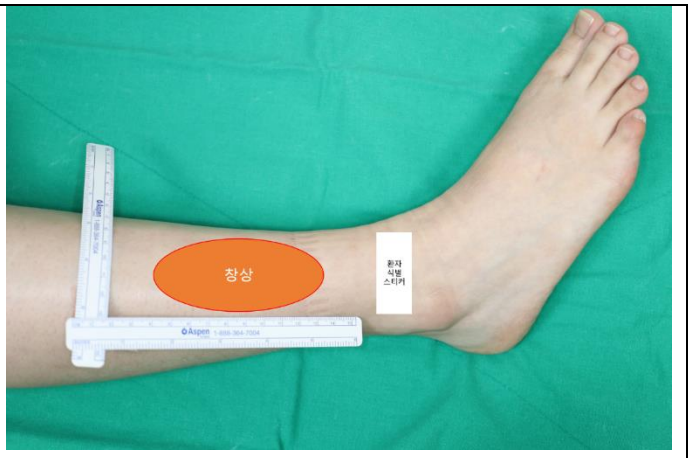
12.3.3.1. photography equipment

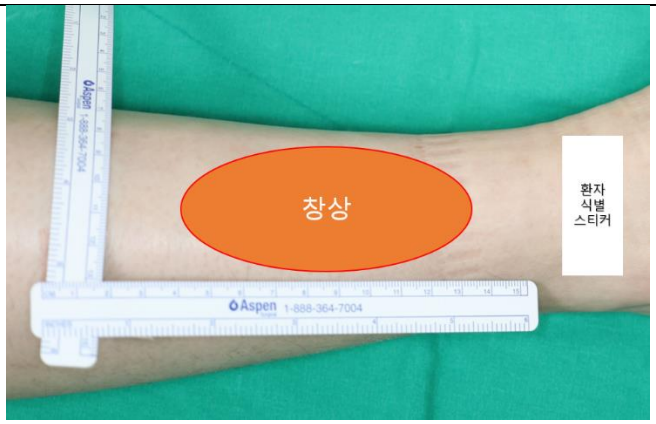
① canon EOS 80D with Macro ring lite MR-14EX II (EF-S 35mm lens)
② Camera tripo with adjustable height
③ Green Background screen in PS OPD clinic
④ Using the lighting installed in the photography room(PS OPD clinic) and the flash (Macro ring lite MR-14EX II) attached to the camera, take pictures under appropriate lighting to best express the wound area.

12.3.3.2. photography

A total of 4 photos are taken: 2 photos each of detailed photos including the wound and the entire lower extremity with the wound.

① Detailed photo: Take a close-up photo centered on the wound so that the 'test subject identification sticker' and 'ruler for measuring the area of the wound area' are visible.
② Full photo: When taking a full photo, use the wound as a reference to include one joint above and below to confirm the location, and shoot to include the entire leg on the left and right. Photograph the entire area, including both the 'test subject identification sticker' and the 'ruler for measuring the area of the wound area.'
(examples)

< Full photo >	

< Detailed photo >	

12.3.3.3. photo conversion

Photos taken with a camera are used to measure the area of the wound using ImageJ 1.45s software (National Institutes of Health, Rockville, MD; http:// https://imagej.nih.gov/ij/).

12.3.3.4. Photo data management

The photographs taken are important data for evaluating the effectiveness of this clinical trial, and the photographic materials can only be accessed by the principal investigator and those authorized by the principal investigator, and can be accessed by regulatory authorities as necessary. Photo data management personnel must pay special attention to the security of collected data.

12.3.3.5. Photo recording and storage

Photos taken for research purposes are prohibited from being used for purposes other than this clinical trial. In addition, stored photos must not be provided to anyone other than the research staff of the conducting institution and the person in charge of the study.

13.STATISTICAL ANALYSIS METHOD

13.1 Definition of analysis group

This clinical trial is a superiority clinical trial, and the efficacy evaluation analysis is primarily conducted on FAS, and the analysis on PPS is performed as a supplement. Additionally, safety evaluation analysis is performed on the safety set.

13.1.1 FAS (Full analysis set)

The subjects are those who received the investigational drug and measured the primary efficacy endpoint at least once.

13.1.2 PPS (Per-Protocol set)

Among the subjects included in FAS, the subjects are those who completed the clinical trial without any serious violation of the clinical trial protocol. The reasons for PPS exclusion are as follows.
1) Violation of selection/exclusion criteria
2) Administration of drugs prohibited from concomitant use
3) Dropout
4) Other serious violations of the plan

13.1.3 Safety set

The subjects are those who have received the clinical trial drug at least once.

13.2 Principles of result analysis

Demographic and baseline information is summarized for FAS. When evaluating effectiveness, FAS is used as the main analysis group, and statistical analysis is additionally performed on PPS. When evaluating safety, the safety set is the target.

For continuous variables, descriptive statistics (mean, standard deviation, median, minimum, maximum, etc.) are calculated and presented, and for categorical variables, frequencies and ratios are presented.

13.3 Demographic and basic information

Regarding basic survey data such as demographic surveys, medical history, and prior medications, the average and standard deviation are calculated for continuous data, and frequencies and ratios are calculated and analyzed for categorical data.

13.4 Analysis of primary efficacy endpoints

1) The change in local transcutaneous oxygen partial pressure measured on the 7th and 14th days after the final administration compared to the baseline value is calculated and compared through the Mann-Whitney test, a non-parametric statistic.

13.5 Analysis of secondary efficacy endpoints

1) The changes in blood flow near the wound using a thermal camera imaging measured 7 and 14 days after the final administration compared to the baseline value.

2) The change in wound area is calculated through photographs taken on the 7th and 14th days of final administration compared to the baseline value, and confirmed and compared using the Mann-Whitney test, a non-parametric statistic.

13.6 Safety evaluation parameters

13.6.1 Adverse reactions

Determine the frequency and proportion of test subjects who experienced adverse reactions (TEAEs) after administration of the investigational drug and adverse reactions related to the investigational drug.

13.6.2 Physical examination

The frequency and ratio of subjects are presented for each physical examination item, and the frequency and percentage of normal/abnormal changes are presented by comparing the subjects' results on the 14th day of final administration compared to the baseline value. .

13.6.3 Laboratory tests

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for laboratory test results performed at each visit are presented. In addition, the results of subjects on the 14th day of final administration compared to the baseline are compared to present the frequency and percentage of normal/abnormal changes.

13.7 Handling of missing values

Analysis is performed using raw data without data correction. If missing values occur for reasons such as a subject dropping out before the end of a clinical trial or missing a test at a specific time, the data are not replaced and analyzed and treated as missing unless specifically specified (Observed Case).

14. TREATMENT STANDARDS FOR SUBJECTS AFTER COMPLETION OF CLINICAL TRIAL

Subsequent treatment for subjects who terminated the clinical trial early and for subjects who completed the clinical trial shall follow standard treatment methods.

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