Clinical Study Protocol

A pilot study to evaluate efficacy and safety of hydrophilic polyurethane foam dressing in patients with pressure ulcer

Pilot Study

Investigational devices : Betafoam®, Medifoam®

No. : BTF16-AP-401

Version : 1.4

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Mundipharma Pte Ltd

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▣ Protocol synopsis

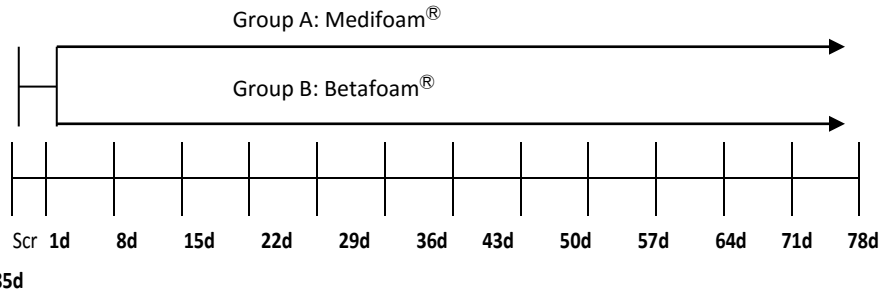
Study title	A Pilot Study to evaluate efficacy and safety of Hydrophilic polyurethane foam dressing in patients with pressure ulcer
Clinical phase and design	Single-center, Randomized, 2-arms, open-label, phase 4 pilot study
Site	Seoul National University Hospital
Sponsor of the study	Mundipharma Pte Ltd
Study objectives	This study aims to exploratively assess the efficacy and safety of the hydrophilic polyurethane foam in pressure ulcer patients. As the primary objective, the percentage of completely healed patients and the time to complete healing will be assessed after applying the study device, Medifoam® or Betafoam®, for 12 weeks to pressure ulcer patients. In addition, the pressure ulcer size reduction rate over 12 weeks will be evaluated. # The definition of complete healing Epithelial tissue covering 100% of the study ulcer, no abrasion or ulceration, intact dermis and epidermis
Study indication	Pressure ulcer of the NPUAP Stage III
Inclusion and exclusion criteria	**<Inclusion criteria>** 1) Adults aged at least 19 years old as of the consent date 2) Pressure ulcer of the NPUAP(National Pressure Ulcer Advisory Panel) Stage III at screening 3) Pressure ulcer size of 3-100 cm^2 at screening 4) Written consent provided by the subject or representative (In case a subject has more than one pressure ulcers that meet all inclusion criteria, the largest one is selected as a target lesion.) **<Exclusion criteria>** 1) Any study ulcer of the NPUAP Stage I, II or IV 2) Diabetic ulcer or Venous ulcer (or stasis ulcer) 3) Past history of surgical treatment within 1 year or irradiation at the target pressure ulcer within 1 year 4) Hypersensitivity reaction to this product or povidone-iodine 5) Hyperthyroidism or thyroid disorder requiring drug treatment 6) Signs of a current underlying systemic infection (sepsis/bacterial infection/tuberculosis) or cellulitis or osteomyelitis 7) Type 1 diabetes 8) Current malnutrition 9) Heavy smoker: Current smoking level of ≥1 pack (20 cigarettes)/day of

<table>
<tr><td></td><td>tobacco
10) Drug or alcohol addiction
11) Requirement of immunosuppressants during the study or current chemotherapy or radiotherapy
12) Application of other investigational product/medical device within 1 month prior to the investigational device application (1d)
13) Pregnant or breastfeeding women
14) Other renal, hepatic, neurological, immunological disorder that may interfere with the wound healing process, at the discretion of the investigator</td></tr>
<tr><td>Target number of subjects</td><td>The target number of subject enrollment is 20 subjects, with 10 subjects per group.
This study has a purely exploratory goal so that no formal sample size calculation was conducted but it was planned to enroll 10 subjects per group as the minimum sample size to achieve study objectives from a scientific perspective.

✓ Medifoam group: 10 subjects
✓ Betafoam group: 10 subjects

Even if a subject is withdrawn from the study, the subject will not be replaced.</td></tr>
<tr><td>Study method</td><td><Overall study flow>
Subjects who consent to the study will be assessed for eligibility with screening tests. Subjects can have a 2-week screening period.
After screening, subjects who meet the inclusion/exclusion criteria will apply Medifoam® or Betafoam® for 12 weeks, after randomization. Targeted subjects are outpatient clinic or hospitalized patients. Subjects will make once weekly site visits.

<table>
<tr><td></td><td>Group A</td><td>Group B</td></tr>
<tr><td>Study device</td><td>Medifoam®</td><td>Betafoam®</td></tr>
</table>

<Dressing>
During the 12-week treatment period, dressing is performed twice weekly, and the End-of-Study visit is conducted 12 weeks after the investigational device application. However, an additional dressing change is allowed, depending on the</td></tr>
</table>

	condition of the pressure ulcer, such as excessive exudates at the study ulcer. Nevertheless, the frequency of additional dressing is limited to twice per day. In case of further exceeding the limited additional dressing (twice per day), the change frequency should be recorded in the Case Report Form. On weekly site visit days, the investigator(or clinical research coordinator) will change the dressing; on other occasions, the subject or guardian will perform self-dressing. The investigator(or clinical research coordinator) trains the subject or guardian on the dressing method at every visit. **<Early completion>** Subjects who achieve complete healing of the target pressure ulcer within 12 weeks will have early completion. At the early completion visit, all tests scheduled for the Week 12 (End-of-Study) visit should be conducted. **<Efficacy assessment>** Efficacy assessment is conducted for a total of 12 times at a 1-week interval, after the investigational device application (8d, 15d, 22d, 29d, 36d, 43d, 50d, 57d, 64d, 71d, 78d, 85d). At each efficacy assessment, the investigator(or clinical research coordinator) should take a digital photograph of the target pressure ulcer and retain it as a source document.
Investigational devices and application methods	**[Investigational devices]** Medifoam® (Mundipharma) Betafoam® (Mundipharma) **[Investigational device application methods]** ① Carefully wash the target pressure ulcer with normal saline. ② After washing, wipe the study ulcer for drying with sterilized gauze, if necessary. During this process, take care not to irritate the study ulcer with the gauze. ③ Select a study device larger than the wound, open the product packaging, take out the device using tweezers, and remove the release film. Directly cover the wound with the foam side without the release film, paying attention to completely cover the wound. ④ If necessary, fix around the edge of this product with surgical tape or Band-Aid, taking care not to attach too tight to avoid skin irritation. ⑤ If there is a lot of exudate and a leak is likely to occur at the study ulcer, exchange the dressing more frequently than planned (twice weekly). **[Standard treatment]** ✓ Position change: The investigator(or clinical research coordinator) instructs the subject or guardian on the daily position changes. A subject who stays sitting or lying only should be instructed to change the position once every 2 hours. **[Prohibited concomitant medication]**

	✓ Any external use for pressure ulcer treatment (however, povidone-iodine may be allowed, if necessary.) ✓ Local antibiotics applied to the target pressure ulcer: However, in case of inevitable treatment, it can be applied. Other than local antibiotics, systemic antibiotics including injectable or oral preparations are allowed. ✓ Immunosuppressants ✓ Glucocorticoids. However, they may be administered when necessary, at the discretion of the investigator.
Assessment methods	**1. Efficacy assessment** 1) Endpoints of main interest ① Number of patients with complete healing# of ulcer within 12 weeks ② Time to complete healing of ulcer within 12 weeks ③ Pressure ulcer size reduction rate based on using a scale at each time point # The definition of complete healing Epithelial tissue covering 100% of the study ulcer, no abrasion or ulceration, intact dermis and epidermis 2) Other endpoints ① The PUSH(Pressure Ulcer Scores for Healing) reduction rate from baseline to each time point ② Dressing change frequency during the entire period ③ Number of subjects with Early completion due to complete healing during the study ④ Incidence of **new** infections at the pressure ulcer until Week 12 based on the CSSC **2. Safety assessment** ◆ Vital signs, laboratory tests ◆ Local adverse events at the target pressure ulcer: Erythema, edema, itching, flare, rash, other ◆ Other adverse events
Statistical analysis methods	Efficacy is assessed in the FAS while safety is evaluated in the SS. - SS(Safety set): Subjects who had at least 1 application of the investigational device and had at least 1 safety assessment - FAS(Full analysis set): Subjects who had at least 1 application of the investigational device and then had at least 1 available endpoints of main interest review 1. Efficacy assessment 1) Endpoints of main interest Of Endpoints of main interest, for subjects achieving complete healing within 12 weeks, present frequency and percentage. For the time to 100% complete healing, analyze using the Kaplan-Meier method. Subjects not achieving 100% complete healing within 12 weeks will not be

	considered for evaluation for end point of main interest. For the pressure ulcer size reduction rate by group, present mean and standard deviation. 2) Other endpoints For other endpoints, present mean and standard deviation for continuous variables ①, and frequency and percentage for categorical variables ②, ③, ④. 2. Safety assessment 1) Adverse events List all adverse events that occurred by group. Record the frequency of adverse events related or unrelated with the investigational device by group. For the number of adverse events and the percentage of subjects who had at least 1 adverse event, present the 95% confidence interval in each treatment group. Analyze adverse events separately for local adverse events at the target pressure ulcer and other adverse events. 2) Laboratory test findings For continuous data, present descriptive statistics (mean, standard deviation, median, minimum, maximum) by group and time point. In addition, tabulate the proportion of normal/abnormal results by time point in each group. 3) Vital signs For continuous variables, present descriptive statistics (mean, standard deviation, median, minimum, maximum) for the baseline and end-of-study test findings by group and time point.

▣ Schedule of study activities

Item \ Schedule	Screening	Treatment period																								Closing
	1*	2*		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**		**12**		**13**		**14****
	-14d~0d	**1d**	5d¥ (±1d)	**8d (±1d)**	12d¥ (±1d)	**15d (±1d)**	19d¥ (±1d)	**22d (±1d)**	26d¥ (±1d)	**29d (±1d)**	33d¥ (±1d)	**36d (±1d)**	40d¥ (±1d)	**43d (±1d)**	47d¥ (±1d)	**50d (±1d)**	54d¥ (±1d)	**57d (±1d)**	61d¥ (±1d	**64d (±1d)**	68d¥ (±1d	**71d (±1d)**	75d¥ (±1d	**78d (±1d)**	82d¥ (±2d)	**85d (±2d)**
Informed Consent Form	V																									
Demographic/medical history review	V																									
Physical examination	V	V		V		V		V		V		V		V		V		V		V		V		V		V
Vital signs[1]	V			V		V		V		V		V		V		V		V		V		V		V		V
Laboratory tests[2]	V																									V
Height	V																									
Body weight	V									V																V
Pregnancy test[3]	V							V																		
Inclusion/exclusion criteria review	V	V																								
Randomization		V																								
Investigational device application[4]		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	
Investigational device prescription[5]		V		V		V		V		V		V		V		V		V		V		V		V		
Pressure ulcer assessment[6] (digital photograph taking, investigator's photo evaluation) - Ulcer size (Using a scale) - Complete healing status	V [7]	V		V		V		V		V		V		V		V		V		V		V		V		V

Item \ Schedule	Screening	Treatment period																								Closing
	1*	2*		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**		**12**		**13**		**14****
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PUSH		V				V				V				V				V				V				V
Self-dressing training		V		V		V		V		V		V		V		V		V		V		V		V		
Dressing change frequency review				V		V		V		V		V		V		V		V		V		V		V		V
Infection sign checklist [8] (CSSC)		V		V		V		V		V		V		V		V		V		V		V		V		V
Subject diary distribution [9]		V		V		V		V		V		V		V		V		V		V		V		V		
Subject diary return				V		V		V		V		V		V		V		V		V		V		V		V
Concomitant medication/treatment review	V	V		V		V		V		V		V		V		V		V		V		V		V		V
Adverse event review		V		V		V		V		V		V		V		V		V		V		V		V		V

* Visit 1 and Visit 2 can take place on the same day.

** Subjects who have complete healing during the study or are withdrawn from the study will have all tests scheduled for V14.

¥ Subject do not make a site visit but perform self-dressing.

† Except for Randomization visit, Home Health Care system through study coordinator will be used for those subjects who aren't able to make a visit during the treatment period. Physical examination and measuring weight may be exempt in case of replacing visit with Home Health Care.

1. Blood pressure, pulse, body temperature measurement

2. Laboratory tests: If test findings within 2 weeks prior to the consent date are available, they may be used instead of screening findings.

   - Hematology: WBC, RBC, platelet, WBC count, Hb, Hct

   - Blood chemistry: AST, ALT, ALP, creatinine, BUN, total bilirubin, glucose, protein, albumin, gamma GTP, TSH (TSH is conducted at screening only)

3. Urine hCG pregnancy test is conducted only in women of child-bearing potential.

4. The investigational device is changed twice weekly; additional changes are allowed depending on the pressure ulcer condition, without any limitation to frequency.

5. Investigational devices for self-dressing are prescribed. Remaining investigational devices after use are returned at the next visit.

6. Pressure ulcer is evaluated comprehensively based on the investigator's photo evaluation. Photograph is taken using the same camera settings and environmental conditions for all subjects. For pressure ulcer assessment, record the following 2 results in the Case Report Form.
   - Ulcer size: Record the size of the residual pressure ulcer not achieving re-epithelization. The size is evaluated by a scale, using photographs that have been taken.
   - Complete healing status: Determine whether complete healing was achieved based on the ulcer size and the investigator's photo evaluation.
   (Re-epithelization: New epithelial tissue covering the pressure ulcer, with no exudate, transudate, or avascular tissue)
7. At screening, measure the ulcer size with a scale to confirm whether the size meets the inclusion criteria.
8. Infection signs are evaluated by the investigator using the CSSC (Clinical Signs and Symptoms Checklist). An infection is defined as a baseline condition of presence of 'Purulent exudates' or '2 or more symptoms of the CSSC'.
9. Record the number of body posture changes per day and the additional dressing change frequency.

▣ Abbreviations

ADE	: Adverse Device Effect
AE	: Adverse Event
ALT	: ALanine Transaminase
ALP	: ALkaline Phosphatase
AST	: ASpartate Transaminase
BUN	: Blood Urea Nitrogen
CRF	: Case Report Form
CSSC	: Clinical Signs and Symptoms Checklist
FAS	: Full Analysis Set
Hb	: Hemoglobin
Hct	: Hematocrit
ITT	: Intent to Treat
IRB	: Institute Review Board
MedDRA	: Medical Dictionary for Regulatory Activities
NPUAP	: National Pressure Ulcer Advisory Panel
PUSH	: Pressure Ulcer Scores for Healing
RBC	: Red Blood Cell
WBC	: White Blood Cell
γ-GT	: Gamma Glutamyl Transferase

1. Title and clinical phase of the study

A Pilot Study to evaluate efficacy and safety of Hydrophilic polyurethane foam dressing in patients with pressure ulcer

2. Name and address of the site

APPENDIX 3. Name and address of the site, names and titles of the principal investigator and sub-investigators

3. Names and titles of the principal investigator and sub-investigators

3.1 Principal investigator

APPENDIX 3. Name and address of the site, names and titles of the principal investigator and sub-investigators

3.2 Sub-investigator and investigational device manager

APPENDIX 3. Name and address of the site, names and titles of the principal investigator and sub-investigators

4. Name and address of the sponsor

Sponsor: Mundipharma Pte Ltd
Address: 12 Marina View, #22-01 Asia Square Tower 2, Singapore 018961

5. Background and objectives of the study

5.1 Background of the study

<Current context of pressure ulcers>

Pressure ulcer is a state that is caused by application of persistent and repeated pressure on any part of body, but mostly upon the protruding part of the bone, resulting in poor blood circulation and tissue death. As a common cause of such symptoms is pressure, it is more appropriately termed as a pressure ulcer. This has been a persistent issue not only domestically but overseas, and more and more attention is being paid to prevention and treatment of pressure ulcers, in particular in aging societies, due to rising social and medical expenses caused by pressure ulcers.

Development of pressure ulcer causes physical and mental suffering to a patient as well as financial losses due to increased treatment and hospitalization duration, so that appropriate treatment is necessary. Pressure ulcer is healed through 1-4 steps; during Step 1, non blanching erythema disappears; during Step 2, re-epithelization takes places and the wound is covered with epithelial cells; and during Steps 3-4, the lesion is filled with a new connective tissue and covered with new epithelial cells.

<Medifoam® and Betafoam®>

Medifoam® is a dressing that can be used for burn, pressure ulcer, or serious wounds by providing a wet environment to the wound and thereby protecting the wound and promoting recovery. Medifoam® consists of 3 polyurethane layers and each plays a role of a protective layer, absorption layer, and wound-contacting layer. The protective layer protects the polyurethane layer from external infection and prevents infiltration of infectious microorganism, and maintains the optimal moisture vapor transmission rate(MVTR) to provide a wet environment to the wound (MVTR mean 811 g/m^2/day). The absorption layer provides a wet environment to the wound, and immediately absorbs exudates from the wound. The product has the absorption capacity of ≥13.5-fold of the pre-absorption weight, and the moisture retention capacity of ≥6-fold. The wound-contacting layer has a mean 25-75 ㎛ pore size (similar to fibroblasts and keratinocytes), and prevents newly formed epidermis from penetrating into the wound-contacting layer of the product or being removed while changing the dressing. As a result, damage to the recovering wound during the dressing change can be minimized, enhancing prompt wound recovery. Furthermore, as the layer is not adhesive to the wound, exudates can be absorbed effectively and the dressing can be changed while causing less physical and mental suffering.

Currently, Medifoam® is available as various formulations, including a foam type for a wound with oozing, a hydrocolloid type for relatively little oozing or exposed wound, and a liquid type for a wound requiring waterproof protection, so that they can be customized by wound type and lesion.

Meanwhile, Genewel Co., Ltd., the manufacturer of Medifoam®, newly developed povidone-iodine

containing polyurethane foam named Betafoam®. Povidone iodine(PVP-I) is known as a very effective local antibacterial agent and has been widely used as an effective disinfectant for various wounds. PVP-I has a broad antibacterial therapeutic window against bacteria, acid fast bacilli, fungus, protozoa, and viruses, and can be used to treat both acute and chronic wounds. Betafoam® is essentially a polyurethane foam dressing recognized for its effectiveness in various wounds. Based on characteristics of PVP-I and a foam dressing, Betafoam® is expected to support a routine wound healing process while also reducing the risk of wound infection.

<Summary of clinical study results>

(1) Medifoam N

Among 80 burn patients who received a split-thickness skin graft, half of the grafted donor sites were covered with Medifoam N and the other half were covered with Vaseline gauze dressings. Two days after the procedure, dressings were removed, and it was monitored everyday whether epithelization occurred or any complication developed. Results indicated that it took an average of 10.1 days in the Medifoam N group and 13.0 days in the control group, and 80 subjects recovered with no serious complications.

(2) Medifoam Silver

Medifoam Silver was investigated for the effectiveness in re-epithelization in 31 patients with 2- or 3-degree burns with a wound area of 12.6% and 24 patients with a skin graft donor site and a wound area of less than 1.000 cm^2. In 27 burn patients, re-epithelization was achieved in mean 18.6 days (5-29 days). In 4 patients, it took mean 14.3 days (12-18 days) until an eschar fell off. In 24 patients with a skin graft donor site, successful re-epithelization was achieved after mean 9.5 days (7-15 days) following skin graft. During this period, no complication or side effect occurred and exudates were absorbed well.

This medical device is registered product and currently in use for burn, skin graft, lacerated skin, surgical wound as well as pressure ulcer in clinical field. Clinical trials in burn, skin graft, wound, surgical wound have been done and confirmed the efficacy among those indications. However, clinical trial data on pressure ulcer is not adequate (refer to 8. BETAplast™ PRODUCT MONIGRAPH on protocol reference 24). Therefore, this pilot study is designed to figure out the efficacy of this device on pressure ulcer and additional clinical trial will be conducted upon using the result of this study.

(3) Medifoam H

Medifoam H and DuoDERM were used for 7 days on 66 various wounds including laceration, abrasion, mild burn, and surgical wounds. In some patients, Medifoam H caused mild pruritus when compared to DuoDERM. In terms of exudate improvement, both groups achieved improvement, and the extent of improvement from baseline (pre-dressing) was 82% for Medifoam H and 67% for DuoDERM.

Based on these results, it was planned to apply each of Medifoam® and Betafoam® to subjects with pressure ulcer, and exploratively observe efficacy of two study devices at the pressure ulcer.

5.2 Study objectives

This aim of this study is to exploratively assess the efficacy and safety of hydrophilic polyurethane foam in pressure ulcer patients.

For this purpose, the percentage of completely healed patients and the time to complete healing will be assessed after applying a study device, Medifoam® or Betafoam®, for 12 weeks to pressure ulcer patients. In addition, the pressure ulcer size reduction rate over 12 weeks will be evaluated.

6. Investigational devices

6.1 Study device 1

- Brand name: Betafoam® (Mundipharma)
- Generic name: Polyurethane, povidone iodine
- Indications of use: This product is an absorbent foam dressing, used for secondary care of pressure ulcers, venous ulcers, diabetic ulcers, burns, donor sites, bacterial/malignant infection wounds, chronic/acute full/partial thickness losses such as surgical wounds, and wounds with exudates on a thin and rough surface.
- Storage conditions: Store in a sealed container at ambient temperatures (1~30℃), by avoiding direct sunlight and hot and humid conditions.

6.2 Study device 2

- Brand name: Medifoam® (Mundipharma)
- Generic name: Polyurethane
- Indications of use: Contamination prevention and protection of wounds
- Storage conditions: Store in a sealed container at ambient temperatures (1~30℃), by avoiding direct sunlight and hot and humid conditions.

6.3 Management of investigational devices

The principal investigator and the investigational device manager (hereafter 'manager') are responsible for receipt · retention · management and return of the medical devices used in a clinical study.

The manager should confirm receipt and the received quantity of investigational devices in writing which should be signed and appropriately managed. Investigational devices should be stored in a locked cabinet with access limited to study site staff, and investigational devices should be applied to subjects only according to the protocol, and the quantity and management of investigational devices provided to each subject should be documented accurately. The monitor should periodically check the inventory retained by the investigator or manager to confirm accountability of used investigational devices. Unused investigational devices will be retained until the sponsor makes a decision on their return or destruction, and upon study completion, all used device packaging, unused investigational devices, labels, and a copy of medical device management records will be submitted to the responsible monitor.

6.4 Packaging and labeling of investigational devices

Investigational devices will be labeled according to the Enforcement Regulations of the Medical Device Act (enforcement date 2015.07.29), Article 43, Attachment, and the label should include the following contents.

<Contents of the label>

1. “For a clinical study”
2. Brand name and model number
3. Lot No. and manufacturing date (can be substituted with an expiry date)
4. Storage conditions
5. Company name of the manufacturer or importer (including names of a manufacturer and a country, in case of commissioned manufacturing or import)
6. “Cannot be used for purposes other than a clinical study”
7. Subject number (if necessary)

7. Study subject

Pressure ulcer patients of the NPUAP Stage III

8. Subject Inclusion and exclusion criteria

This study will involve subjects who meet all of the following inclusion criteria and none of the exclusion criteria.

8.1 Inclusion criteria

1) Adults aged at least 19 years old as of the consent date
2) Pressure ulcer of the NPUAP (National Pressure Ulcer Advisory Panel) Stage III at screening
3) Pressure ulcer size of 3-100 cm^2 at screening
4) Written consent provided by the subject or representative
   (In case a subject has more than one pressure ulcers that meet all inclusion criteria, the largest one is selected as a target lesion.)

8.2 Exclusion criteria

1) Any study ulcer of the NPUAP Stage I, II or IV
2) Diabetic ulcer or Venous ulcer (or stasis ulcer)
3) Past history of surgical treatment within 1 year or irradiation at the target pressure ulcer within 1 year
4) Hypersensitivity reaction to this product or povidone-iodine
5) Hyperthyroidism or thyroid disorder requiring drug treatment
6) Signs of a current underlying systemic infection (sepsis/bacterial infection/tuberculosis) or cellulitis or osteomyelitis
7) Type 1 diabetes
8) Current malnutrition
9) Heavy smoker: Current smoking level of ≥1 pack (20 cigarettes)/day of tobacco
10) Drug or alcohol addiction
11) Requirement of immunosuppressants during the study or current chemotherapy or radiotherapy
12) Application of other investigational product/medical device within 1 month prior to the

investigational device application (1d)

13) Pregnant or breastfeeding women
14) Other renal, hepatic, neurological, immunological disorder that may interfere with the wound healing process, at the discretion of the investigator

9. Target number of subjects and the rationale

The target number of subject enrollment is 20 subjects, with 10 subjects per group.

This study has a purely explorative goal so that no formal sample size calculation will be conducted but it was planned to enroll 10 subjects per group as the minimum sample size to achieve study objectives from a scientific perspective.

- ✓ Medifoam group: 10 subjects
- ✓ Betafoam group: 10 subjects

Even if a subject is withdrawn from the study, the subject will not be replaced.

10. Study method

10.1 Study design

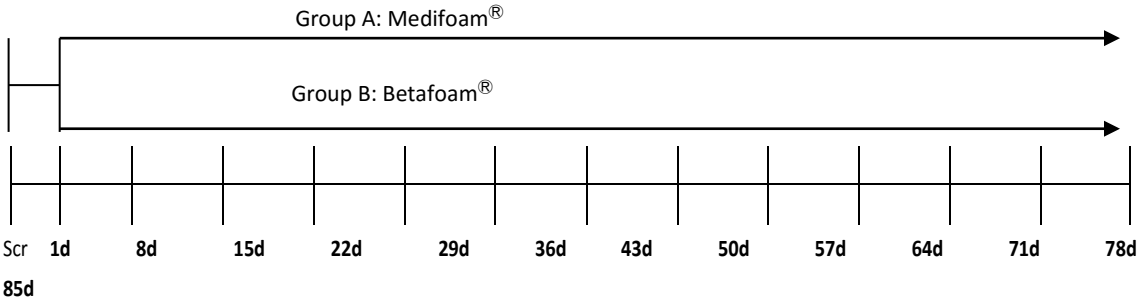
This is a single-center, randomized, 2-arms, open-label pilot study.

Subjects who consent to the study will be assessed for eligibility with screening tests. Subjects can have a 2-week screening period.

After screening, subjects who meet the inclusion/exclusion criteria will apply Medifoam® or Betafoam® for 12 weeks, after randomization. Targeted subjects are outpatient clinic or hospitalized patients. Subjects will make once weekly site visits.

During the treatment period, dressing is performed twice weekly, but additional dressing changes are allowed, depending on the condition of the pressure ulcer, such as excessive exudates at the study ulcer. Nevertheless, the frequency of additional dressing is limited to twice per day. On the weekly site visit days, the investigator (or clinical research coordinator) will change the dressing; on other occasions, the subject or guardian will perform self-dressing. Subjects who achieve complete healing of the target pressure ulcer within 12 weeks will have early completion.

Efficacy assessment is conducted for a total of 12 times at a 1-week interval, after the investigational device application (8d, 15d, 22d, 29d, 36d, 43d, 50d, 57d, 64d, 71d, 78d, 85d). At each efficacy assessment, the investigator (or clinical research coordinator) should take a digital photograph of the target pressure ulcer and retain it as a source document.



10.2 Investigational device application methods

[Investigational devices]

Medifoam® (Mundipharma)

Betafoam® (Mundipharma)

[General investigational device application method]

An appropriate type of the investigational device should be selected for the study ulcer size and it should be able to completely cover the target pressure ulcer. At every dressing change, record the selected investigational device size in the source document.

[Investigational device application sequence]

① Carefully wash the target pressure ulcer with normal saline.

② After washing, wipe the study ulcer for drying with sterilized gauze, if necessary. At this time, pay attention not to irritate the study ulcer.

③ Select a study device that is larger than the pressure ulcer, open the product packaging, take out the device using tweezers, and remove the release film. Directly cover the wound with the foam side without the release film, paying attention to completely cover the wound.

④ If necessary, fix around the edge of this product with surgical tape or Band-Aid while paying attention not to attach too tight to avoid skin irritation.

⑤ If there is a lot of exudate and a leak is likely to occur at the study ulcer, exchange the dressing more frequently than planned (twice weekly).

[Application frequency]

- Twice weekly

During the 12-week treatment period, dressing is performed twice weekly, but additional dressing changes are allowed, depending on the condition of the pressure ulcer, such as excessive exudates at the lesion. Nevertheless, the frequency of additional dressing is limited to twice per day. In case of additional dressing changes beyond twice weekly changes, the change frequency should be recorded in the Case Report Form.

On the weekly site visit days, the investigator (or clinical research coordinator) will change the dressing; on other occasions, the subject or guardian will perform self-dressing. The investigator (or clinical research coordinator) will train the subject or guardian on the dressing method at every visit.

10.3 Subject enrollment method

As this study will enroll 10 subjects per group without using a control group through randomization. Note that it was planned to enroll 10 subjects per group as follows, as the minimal sample size to achieve study objectives from a scientific perspective.

	Group A	Group B
Study device	Medifoam®	Betafoam®

Subjects will be enrolled to a Medifoam group and a Betafoam group by randomization to reduce the possible bias which may caused by the investigator, and once 10 subjects are enrolled in each group, no further enrollment will take place. In addition, even though a subject is withdrawn during the study, the subject will not be replaced.

Clinical Research team of this trial will request to create Randomization List to independent st atistician (person in charge of randomization) who is not involving in this study. Randomizatio n list contains the information of subjects assigned upon randomization code. A person in cha rge for randomization will create and operate Randomization list independently.

Randomization will be generated by randomization program of SAS system. And the permutati on of random numbers (random number of A and B) will start from number 1 in consecutive order (i.e. A: Group A, B: Group B). Block size won't be stated in this protocol.

The site will assign the following number to subjects in the order of signing the Informed Consent Form.

Screening Number SXYY (X: Site number/A, YY: Serial Number in two digits / 01, 02, 03~)
(i.e. : SA01, SA02, SA03, SA04,…)

Investigator will grant assigned number to the appropriate subject who is eligible for inclusion /exclusion criteria in consecutive order, and the subject will go through randomization. And pr oper investigation device will be applied to the subject upon assigned group.

Assigned Number RXYY (X: Site number/A ; YY: Serial Number in two digits / 01, 02, 03~)
(i.e. : RA01, RA02, RA03, RA04,…)

10.4 Concomitant therapy and standard treatment

During the study, the following drugs are prohibited from concurrent use. In addition, in case a drug/medical device used for treatment without being determined by the principal investigator is expected to possibly affect the efficacy assessment of this study, the relevant subject may be excluded from efficacy analysis during result analysis. The final efficacy set will be determined in a blinded

meeting.

<Prohibited concomitant medication>

- ✓ Any external use preparation for pressure ulcer treatment (however, povidone-iodine may be allowed, if necessary.)
- ✓ Local antibiotics applied to the target pressure ulcer: However, in case of inevitable treatment, it can be applied. Other than local antibiotics, systemic antibiotics including injectable or oral preparations are allowed.
- ✓ Immunosuppressants
- ✓ Glucocorticoids. However, they may be administered when necessary, at the discretion of the investigator.

<Standardization of pressure ulcer care>

- ✓ Position change: The investigator (or coordinator) will instruct the subject or guardian on the daily position changes. A subject who stays sitting or lying only should be instructed to change the position once every 2 hours.

11. Study period

24 months from the protocol approval date by the Institutional Review Board

12. Observation and test items

12.1 Schedule of study activities

12.1.1 Visit 1 (screening, -14d~0d)

Written Informed Consent Form should be first obtained from subjects prior to any test. Tests to be conducted at screening are as follows, and in case all tests are completed and test findings can be confirmed on the day of screening, Visit 1 and Visit 2 can be take place together. If Visit 1 and Visit 2 are taken place on the same day, duplicated tests (Physical Examination, Inclusion/Exclusion criteria, , Concomitant medication/treatment review) are only done once.

① Before involving a subject in the study, the subject will be informed of the study process and then the subject (or representative) will provide informed consent.
② Subject numbers will be assigned in the order of completing the Informed Consent Form.
③ Collect demographic information and medical history.
④ Conduct the physical examination.
⑤ As vital signs, measure blood pressure, pulse, and body temperature.
⑥ Conduct laboratory tests (hematology, blood chemistry). If test findings within 2 weeks prior to the consent date are available, they can be used instead.
⑦ Measure height and body weight of the subject.
⑧ Conduct a urine pregnancy test in women of child-bearing potential. Do not conduct the test in case the subject had menopause, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
⑨ Take a photograph of the target pressure ulcer.
⑩ Check the NPUAP Stage and size (using a scale) based on the pressure ulcer assessment and confirm whether the subject meets the inclusion criteria.
⑪ Review concomitant medication/treatment.

12.1.2 Visit 2 (enrollment, 1d)

Subject enrollment will take place at the second visit, and the following assessment will be conducted.

① Conduct the physical examination.
② Review the inclusion/exclusion criteria, and subjects who are finally determined eligible will go through the process of randomization.

③ Before applying the investigational device, check the infection signs using the CSSC(Clinical Signs and Symptoms Checklist).
④ Before applying the investigational device, take a photograph of the study ulcer, investigator will conduct a photo evaluation, and record the pressure ulcer size by a Scale.
⑤ After conducting standard dressing, apply the investigational device.
⑥ Record the baseline PUSH score.
⑦ Review concomitant medication and treatment-emergent adverse events.
⑧ Prescribe the investigational devices and train the subject or guardian on the self-dressing method.
⑨ Dispense the subject diary to record the frequency of position changes per day (if applicable) and the frequency of additional self-dressing.

12.1.3 Visit 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 (interim visit, 8d, 15d, 22d, 29d, 36d, 43d, 50d, 57d, 64d, 71d, 78d)

The following tests will be conducted at the interim visit. It can be replaced by home health care through coordinator's visit if the subject is not able to visit the institution.

① Conduct the physical examination.
② As vital signs, measure blood pressure, pulse, and body temperature.
③ Measure body weight (only 29d).
④ After removing the investigational device, take a photograph of the study ulcer, conduct the investigator's photo evaluation, and record the pressure ulcer size by a Scale and complete healing status.
⑤ Check the infection signs using the CSSC (Clinical Signs and Symptoms Checklist).
⑥ After conducting standard dressing, apply the investigational device.

⑦ After conducting the pressure ulcer assessment, record the PUSH score (15d, 29d, 43d, 57d, 71d).
⑧ Review concomitant medication and adverse events (all adverse events, local adverse events at the study ulcer).
⑨ Prescribe the investigational devices and train the subject or guardian on the self-dressing method.
⑩ At the last visit, investigational devices that have been prescribed but not used are to be returned.
⑪ Based on the subject diary, record the frequency of self-dressing beyond once-weekly in the Case Report Form.
⑫ Dispense the subject diary to record the frequency of position changes per day (if applicable) and the frequency of additional self-dressing.

12.1.4 Visit 14 (End-of-Study visit/85d or early completion)

The following tests will be conducted at the End-of-Study visit or early completion (only in subjects with complete healing).

① Conduct the physical examination.
② As vital signs, measure blood pressure, pulse, and body temperature.
③ Measure body weight.
④ Conduct laboratory tests (hematology, blood chemistry).
⑤ After removing the investigational device, take a photograph of the study ulcer, conduct the investigator's photo evaluation, and record the pressure ulcer size by a Scale and complete healing status.
⑥ Check the infection signs using the CSSC (Clinical Signs and Symptoms Checklist).
⑦ Conduct standard dressing.
⑧ After conducting the pressure ulcer assessment, record the PUSH score.
⑨ Review concomitant medication and adverse events (all adverse events, local adverse events at the study ulcer).
⑩ At the last visit, investigational devices that have been prescribed but not used are to be returned.
⑪ Based on the subject diary, record the frequency of self-dressing beyond once-weekly in the Case Report Form.

12.1.5 Unscheduled visit

In case it is necessary to conduct an unexpected and unscheduled visit due to reasons such as an adverse event, identify the purpose of the visit, review vital signs, adverse events and concomitant medication, and conduct laboratory tests, if necessary. There is no formal limitation in tests to be conducted during an unscheduled visit.

12.2 Methods for each study item

12.2.1 Demographic, medical history review

Before a subject enters into the study, the following subject background (demographic survey) and medical history information will be investigated with an interview, chart review, and questioning, and recorded in the Case Report Form.

① Demographic survey: Subject's initial, age, sex, etc.

② Medical history review: Pressure ulcer size/stage, pressure ulcer onset date and illness duration, current illnesses other than the study indication, hypersensitivity to drugs including similar prior medications, smoking status, smoking level, etc.

③ Concomitant medication/treatment survey: Current medication or concurrent treatment

④ Other disease history review: Prior surgical history of the target pressure ulcer, prior irradiation history of the target pressure ulcer over the past year, life expectancy, malnutrition status, alcohol or drug addiction status, etc.

⑤ Mobility: Mobility and condition of the subject, such as whether the subject is ambulatory/stays sitting only/stays lying only/is capable of sitting or lying, etc.

12.2.2 Laboratory tests, urine hCG test

Laboratory test and urine hCF test will be conducted once at screening and at study completion/early completion.

- Sample collection and documentation: Blood samples are collected from subjects according to the test schedule using an aseptic technique, and collected blood samples are analyzed in a QC-certified clinical pathology lab using commercialized hematology, blood chemistry test methods. Test findings are recorded in the Case Report Form and assessed for normal/abnormal status or clinical significance, and for clinically significant abnormal findings, the investigator's opinion will be recorded.
- Test parameters:
    ① Hematology: WBC, RBC, WBC Differential count, hemoglobin, hematocrit, platelets
    ② Blood chemistry: AST, ALT, ALP, creatinine, BUN, total bilirubin, glucose, protein, albumin, gamma GTP, TSH (TSH is conducted at screening only.)
    ③ Urine hCG test (to be conducted in all women, except for those who have been menopausal for at least 1 year or had hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)

12.2.3 Physical examination

Noticeable findings prior to the investigational device application are recorded in the Medical History section of the Case Report Form, and clinically remarkable physical examination findings after the investigational device application are recorded in the Adverse Event section.

12.2.4 Pressure ulcer assessment

Pressure ulcer assessment during the study based on a scale and the investigator's photo evaluation **is to be conducted by the same investigator for the same subject.**

(1) Pressure ulcer stage (National Pressure Ulcer Advisory Panel's classification)

Stage	Definition	Description
I	Non-blanchable erythema of intact skin	Intact skin with non-blanchable erythema of a localized area usually over a bony prominence. Discoloration of the skin, warmth, edema, hardness or pain may also be present. Darkly pigmented skin may not have visible blanching
II	Partial thickness skin loss or blister	Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum or sero-sanguinous-filled blister
III	Full thickness skin loss	Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present. May include undermining and tunneling
IV	Full thickness tissue loss	Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often includes undermining and tunneling.

(2) Pressure ulcer assessment time points

At each scheduled visit (once weekly until the End-of-Study visit) from screening to the end of treatment, photograph will be taken to evaluate ulcer size(using a scale) and complete healing status. At baseline, conduct the assessment prior to the investigational device application and subsequently, conduct assessment after completely removing the applied study device and before applying a new dressing.

(3) Measurement of the pressure ulcer size

After removing all dressings applied on the study ulcer, the investigator takes a photograph with a scale measuring the study ulcer size, and records the study ulcer size (surface area of the pressure ulcer) using a scale. At this time, MediRule® will be used as Scale. Width and length are measured using the longest diameter on the pressure ulcer surface area. When taking the photograph, the same illumination, camera model and camera settings should be used for all subjects and a horizontal angle should be maintained between the study ulcer and the camera lens. In addition, manual camera settings should be used to maintain the same settings (such as a shutter speed, aperture, sensitivity, light metering, etc.), and the distance between the study ulcer and the camera focal length should be controlled for each study ulcer, but the same distance should be maintained throughout the study for the same subject. The same scale will be used for assessment of photographs from all subjects. Photographs used for size assessment should be maintained as source documents with subject identification numbers.

(4) Investigator's photo evaluation

The investigator conducts a photo evaluation of the target pressure ulcer, and makes an assessment of the study ulcer size (pressure ulcer surface area) and complete healing status.

(5) Pressure ulcer size and complete healing status documentation

Screening documentation

Record the pressure ulcer development site, size, the target lesion in case there are multiple pressure ulcer sites, and the NPUAP Stage.

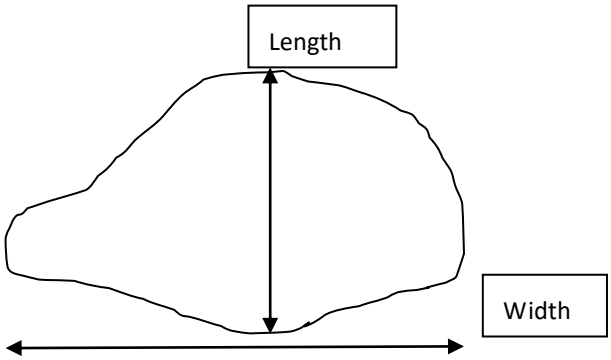
* Pressure ulcer size: At screening, record width and length in cm using a scale, to 1 decimal place. Width and length are measured using the longest diameter on the pressure ulcer surface area.

** Target lesion: If there are one or more pressure ulcers, select the largest ulcer of 3 ~ 100 cm^2 as a target.

(Example of pressure ulcer size measurement recording)

Site of the lesion	Pressure ulcer size		NPUAP Stage	Target lesion (check only 1 among those sized 3~10 cm^2)
	Width	Length		
Coccyx	1.8cm	1.0cm	□ 1 □ 2 □ 3 □ 4	
Low back	4.7cm	1.0cm	□ 1 □ 2 □ 3 □ 4	ㅅ
Left heel	2.0cm	1.5cm	□ 1 □ 2 □ 3 □ 4	

(Example of pressure ulcer size measurement for screening)



Documentation at baseline and each visit

In the Case Report Form, the pressure ulcer surface area size based on a scale and the complete healing* status based on the investigator's photo evaluation will be recorded. As the pressure ulcer surface area size, record **the size of the residual pressure ulcer that has not achieved re-epithelization**** in cm^2 to 1 decimal place.

Pressure ulcer size: From Visit 2 onwards, the investigator takes a photograph with a scale measuring the study ulcer size and records area (multiplying width and length) in cm using a scale, to 1 decimal place. Width and length are measured using the longest diameter on the pressure ulcer surface area.

(* Complete healing: Defined as the condition with the epithelial tissue covering 100% of the study ulcer, no abrasion or ulceration, intact dermis and epidermis.)

(**Re-epithelization: New epithelial tissue covering the pressure ulcer, with no exudate, transudate, or avascular tissue)

[Example of target pressure ulcer size recording]

	1d (Prior to the study device application, baseline)	8d (Size of a burn lesion with no re-epithelization)	…… (Size of a burn lesion with no re-epithelization)	29d (Size of a burn lesion with no re-epithelization)
Using a scale	5 cm^2	3.5 cm^2	2.2 cm^2	0 cm^2
Investigator's final photo evaluation	Complete healing □ Y ☑ N	Complete healing □ Y ☑ N	Complete healing □ Y ☑ N	Complete healing □ Y ☑ N

(6) Photograph taking and prior meeting

Hold a prior meeting of investigators before study initiation to ensure consistent application during the study period by discussing matters related with the investigator's photo evaluation and photograph taking, such as the camera settings and model, study ulcer and camera focal length, and a scale, etc.

12.2.5 Vital signs

As vital signs, measure blood pressure (sitting), pulse rate, and body temperature.

12.2.6 CSSC(Clinical Signs and Symptoms Checklist)

Infection signs are checked using the CSSC by the investigator at each visit. In case infection signs are suspected, laboratory tests and wound culture may be additionally conducted for confirmation. In case additional tests are performed, the result should be recorded in the Case Report Form.
According to [Baranoski, Elizabeth A. Ayello, Wound Care Essentials: Practice Principles], define an infection as the development of 'Purulent exudates' or '2 or more symptoms of the CSSC'.

At every visit after the study device application, evaluate the previous infection signs as well as any newly developing infection signs.

Clinical Signs and Symptoms Checklist	
Signs and symptoms	**Check (+) if present**
Increasing pain in the ulcer area The patient reports increased level of peri-ulcer pain since the ulcer developed. Ask him to select the most appropriate statement for current level of ulcer pain from the following choices: 1. I can't detect pain in ulcer area. 2. I have less ulcer pain now than I had in the past. 3. The intensity of the ulcer pain has remained the same since the ulcer developed. 4. I have more ulcer pain now than I had in the past. If the patient selects number 4, his pain is increasing. Write n/a if the patient can't respond to the question.	□
Erythema The presence of bright or dark red skin or darkening of normal ethic skin color immediately adjacent to the ulcer opening indicates erythema.	□
Edema The presence of shiny, taut skin or pitting impressions in the skin adjacent to the ulcer	□

Clinical Signs and Symptoms Checklist	
Signs and symptoms	**Check (+) if present**
but within 4cm from the ulcer margin indicates edema. Assess pitting edema by firmly pressing the skin within 4cm of ulcer margin with a finger, release and waiting 5 seconds to observe indentation.	
Heat A detectable increase in temperature of the skin adjacent to the ulcer but within 4cm of the ulcer margin as compared to the skin 10cm proximal to the wound indicates heat. Assess differences in skin temperature using the back of your hand or your wrist.	□
Purulent exudates Tan, creamy, yellow, or green, thick fluid that's present on a dry gauze dressing removed from the ulcer 1 hour after the wound was cleaned and dressed indicates purulent exudate.	□
Sanguinous exudates Bloody fluid that's present on a dry gauze dressing removed from the ulcer 1 hour after the wound was cleaned and dressed indicates sanguinous exudate.	□
Serous exudates Thin, watery fluid that's present on a dry gauze dressing removed from the ulcer 1 hour after the wound was cleaned and dressed indicates serous exudate.	□
Delayed healing of the ulcer The patient reporting no change, or increase in the volume or surface area of the ulcer, over the preceding 4 weeks indicates delayed healing. Ask the patient if the ulcer has filled with tissue or is smaller around than it was 4 week ago.	□
Discoloration of granulation tissue Granulation tissue that is pale, dusky, or dull in color compared to surrounding, health tissue. Note variations of normal, beefy-red appearance of granulation tissue.	□
Friable granulation tissue Bleeding of granulation tissue when gently manipulated with a sterile cotton-tipped applicator indicates friable tissue.	□
Pocketing at base of wound The presence of smooth, nongranulating pockets of ulcer tissue surrounded by beefy red granulation tissue indicates pocketing.	□
Foul odor The ulcer may have a putrid or distinctively unpleasant smell	□
Wound breakdown Small open areas in newly formed epithelia tissue not caused by reinjury or trauma indicate wound breakdown.	□

[Reference: Sharon Baranoski, Elizabeth A. Ayello, Wound Care Essentials: Practice Principles]

12.2.7 Adverse events

Treatment-emergent adverse events will be identified during the study by the investigator's medical care, such as an interview and medical examination by interview, and the onset and resolution dates, intensity and outcome of the adverse event, action taken for the study device and causal relationship with the study device, suspected drug/medical device other than the study device, and treatment of the adverse event and details will be recorded.

In addition, the following local adverse events at the target pressure ulcer will be separately recorded with a visual evaluation and medical examination by interview.
Local adverse events: Erythema, edema, itching, flare, rash, and others

12.2.8 Concomitant medication review

For drugs/treatment administered during the study, survey the dosing period, administered dose, administration frequency and reason for administration via a medical examination by interview, and record in the Case Report Form.

12.2.9 Self-dressing training and frequency review

As a subject is to perform dressing twice weekly by himself/herself or a guardian, the investigator (or clinical research coordinator) will train the subject or guardian on standard dressing for self-dressing at every visit. Depending on the condition of the pressure ulcer such as excessive exudates, a subject may conduct self-dressing more frequently than twice weekly. In case of conducting self-dressing beyond twice weekly, the subject should inform the investigator of the additional dressing frequency during the site visit, and the investigator will record the frequency of self-dressing beyond twice weekly in the Case Report Form.

Standard dressing method will be trained as follows.

① Carefully wash the target pressure ulcer with normal saline.
② After washing, wipe the study ulcer for drying with sterilized gauze, if necessary. In this process, pay attention not to irritate the study ulcer with the gauze.
③ Open packaging of the study device, take out the device using tweezers, and remove the release film. Directly cover the wound with the foam side without the release film, paying attention to completely cover the wound.
④ If necessary, fix around the edge of this product with surgical tape or Band-Aid while paying attention not to attach too tight to avoid skin irritation.
⑤ If there is a lot of exudate and a leak is likely to occur at the study ulcer, exchange the dressing more frequently than planned for self-dressing (once weekly).

12.2.10 Prescription of the study device

For a subject's self-dressing, the study devices will be prescribed at every visit from Visit 2 (1d), and unused medical devices are to be brought to the site at the next visit.

12.2.11 PUSH(Pressure Ulcer Scale for Healing)

From Visit 2 (1d), the PUSH score will be checked at a 2-week interval (15d, 29d, 43d, 57d, 71d, 85d). Using a Version 3.0 PUSH tool, the score will be calculated according to the following criteria, and each sub-score and the total score will be recorded in the Case Report Form.

DIRECTIONS:

Observe and measure the pressure ulcer. Categorize the ulcer with respect to surface area, exudate, and type of wound tissue. Record a sub-score for each of these ulcer characteristics. Add the sub-scores to obtain the total score. A comparison of

Length	0 0 cm^2	1 <0.3 cm^2	2 0.3–0.6 cm^2	3 0.7–1.0 cm^2	4 1.1–2.0 cm^2	5 2.1–3.0 cm^2	
× Width	-	6 3.1–4.0 cm^2	7 4.1–8.0 cm^2	8 8.1–12.0 cm^2	9 12.1–24.0 cm^2	10 >24.0 cm^2	Sub-score
Exudate Amount	0 None	1 Light	2 Moderate	3 Heavy	-	-	Sub-score
Tissue Type	0 Closed	1 Epithelial Tissue	2 Granulation Tissue	3 Slough	4 Necrotic Tissue	-	Sub-score
-	-	-	-	-	-	-	Total Score

total scores measured over time provides an indication of the improvement or deterioration in pressure ulcer healing.

Length × Width: Measure the greatest length (head to toe) and the greatest width (side to side) using a centimeter ruler. Multiply these two measurements (length x width) to obtain an estimate of surface area in square centimeters (cm^2). Caveat: Do not guess! Always use a centimeter ruler and always use the same method each time the ulcer is measured.

Exudate Amount: Estimate the amount of exudate (drainage) present after removal of the dressing and before applying any topical agent to the ulcer. Estimate the exudate (drainage) as none, light, moderate, or heavy.

Tissue Type: This refers to the types of tissue that are present in the wound (ulcer) bed. Score as a "4" if there is any necrotic tissue present. Score as a "3" if there is any amount of slough present and necrotic tissue is absent. Score as a "2" if the wound is clean and contains granulation tissue. A superficial wound that is reepithelializing is scored as a "1." When the wound is closed, score as a "0."

4 - Necrotic Tissue (Eschar): black, brown, or tan tissue that adheres firmly to the wound bed or ulcer edges and may be either firmer or softer than surrounding skin.
3 - Slough: yellow or white tissue that adheres to the ulcer bed in strings or thick clumps, or is mucinous.
2 - Granulation Tissue: pink or beefy red tissue with a shiny, moist, granular appearance.
1 - Epithelial Tissue: for superficial ulcers, new pink or shiny tissue (skin) that grows in from the edges or as islands on the ulcer surface.
0 - Closed/Resurfaced: the wound is completely covered with epithelium (new skin).

[Reference: 1. PUSH Tool @ national Pressure Ulcer Advisory Panel
2. A Prospective Study of the Pressure Ulcer Scale for Healing (PUSH), Journal of Gerontology: MEDICAL SCIENCES 2005, Vol. 60A, No. 1, 93–97]

12.2.12 Subject diary

At every visit from Visit 2 (1d), a subject diary will be dispensed to record the frequency of self-dressing and the frequency of position changes per day.

13. Predicted precautions for use

13.1 Betafoam®

A. Contraindications

(1) Hypersensitivity to povidone iodine included in this product

(2) In case of rash, pyrexia, allergic reactions or infection symptoms developing while using this product, use of this product is prohibited and appropriate treatment should be instituted as instructed by the physician or pharmacist.

(3) Thyroid dysfunction (in particular, nodular goiter, endemic goiter, Hashimotos thyroiditis), renal failure, newborns and infants less than 6 months old, herpeticum dermatitis, and before and after radioactive iodine treatment

B. Side effects

Dyspnea, flushing, hives, itching, rash, burning sensation, electrolyte and serum osmotic disorder, temporary renal failure, transient increase in serum protein-bound iodine, pulmonary edema

C. Warning or precautions

(1) As this product is sterilized, it should be used immediately after opening the package, taking care to avoid contamination of the wound-contacting side.

(2) This product should be used after consulting a physician or pharmacist.

(3) In case of development of pruritus (flushing, inflammation), burning sensation, rash, or allergic reactions, consult a specialist.

(4) Do not use the product if the sterilized pack is already opened or broken.

(5) In case of severe bleeding, use the product after hemostasis.

(6) On an infected wound (wound with symptoms such as flare, swelling, pain, feeling hot, strong malodor and pus discharge), use this product after eliminating the cause of bacterial proliferation such as a foreign substance, pus, or necrotized tissue.

(7) As this product is for single-use only, re-use is prohibited.

(8) In case of using this product immediately before delivery, wash the eyes of a newborn and bathe him/her as soon as possible after birth.

(9) In case of using the product in broad burn patients, sufficient hydration should be implemented.

(10) As this product may influence scintigraphy-based thyroid diagnosis, use of this product and scintigraphy should be separated by 1~2 weeks.

(11) In case of long-term, continuous use of this product, attention should be paid to thyroid dysfunction.

(12) Due to a possibility of a shock (anaphylaxis) in rare cases, in case of sudden development of itching, edema, heartburn, concurrently with severe facial pallor, cold extremities, cold sweat, or shortness of breath after using this product, immediately seek medical attention.

(13) Routine, long-term or broad use of this product is prohibited in pregnant women or women of childbearing potential or breastfeeding women.

(14) Concurrent use of this product with lithium, chlorhexidine, silver sulfadiazine compound, alkali, or mercury-containing agents may result in decreased antiseptic effects and discoloration. In addition, this product should not be used in combination with hydrogen peroxide.

13.2 Medifoam®

A. Contraindications

In case of rash, pyrexia, allergic reactions or infection symptoms while using this product, use of this product is prohibited and appropriate treatment should be instituted as instructed by a physician.

B. Precautions and warnings

(1) As the status of exudate absorption can be observed from the back side of this product, exchange a dressing when the exudate has been absorbed or expanded to about 90% of the margin.

(2) In case of severe bleeding, use the product after hemostasis.

(3) On an infected wound (wound with symptoms such as flare, swelling, pain, feeling hot, strong malodor and pus discharge), use this product after eliminating the cause of bacterial proliferation such as a foreign substance, pus, or necrotized tissue.

(4) As this product is for single-use only, re-use is prohibited.

14. Discontinuation/withdrawal criteria and early completion criteria

14.1 Discontinuation and withdrawal criteria

In case of meeting the following criteria for study device discontinuation, application of the study device and the study should be discontinued, and the reason for discontinuation and findings should be recorded in the Case Report Form.

- Criteria for discontinuation of the study device application

1) Acute reactions (allergy, hypersensitivity reactions, etc.) to the study device

2) It is determined that continuation of the study is difficult due to an accidental intercurrent condition.
3) It is determined that continuation of the study is impossible due to worsening of the pressure ulcer (Stage 4 or higher).
4) Debridement was performed during the study, after the study device application.
5) Pregnant during the study period
6) It is otherwise determined by the investigator that continued application of the study device is not appropriate due to reasons such as serious malnutrition, etc.
7) It is determined by the investigator that study participation is not appropriate due to a "serious adverse event".

   "Serious adverse event" is an event, irrespective of a causal relationship with the study device, that is as follows:

   ① Results in death or is life-threatening
   ② Requires inpatient hospitalization or prolongation of existing hospitalization
   ③ Results in persistent or significant disability or dysfunction
   ④ Results in congenital anomaly or birth defect
   ⑤ Other medically important events as identified by the Investigator

In case of discontinuation due to worsening of a pressure ulcer, the treating physician will ensure safety of the patient with appropriate tests and treatment, equivalent to the case of an adverse event.

14.2 Early completion criteria

Subjects who achieve complete healing* of the target pressure ulcer will terminate the study early. Subjects who can terminate the study early will conduct all tests scheduled for the End-of-Study (85d) visit and then complete the study.

(* Complete healing: Defined as the condition with the epithelial tissue covering 100% of the study ulcer, no abrasion or ulceration, intact dermis and epidermis.)

15. Statistical analysis methods

15.1 General principles of result analysis

Data obtained from subjects in this study will be analyzed as the SS(Safety Set) and the FAS(Full Analysis set).

1) In the SS(Safety set), data obtained from subjects who were enrolled in the study, had at least

1 application of the study device, and had at least 1 safety assessment will be analyzed.

2) In the FAS(Full analysis set), data obtained from subjects who were enrolled in the study, had at least 1 application of the study device and then had at least 1 available endpoints of main interest review will be included in analysis.

Efficacy and demographics will be analyzed using the FAS and safety data will be analyzed using the SS.

For subjects with a missing value during the study or who are withdrawn from the study prior to study completion, efficacy analysis will be conducted by applying the LOCF (Last Observation Carried Forward), only in case such subjects have available endpoints of main interest assessment results after the investigational device application. However, in case of missing values for Other endpoints and safety endpoints, raw data will be used for analysis, without applying LOCF.

15.2 Baseline demographics

For each study group and the entire group, the mean, standard deviation, minimum & maximum will be presented for continuous data, and absolute and relative frequency will be provided for categorical data. For baseline demographics, only descriptive statistics will be presented.

15.3 Analysis of efficacy endpoints

(1) Analysis of endpoints of main interest

① Number of patients with complete healing# of ulcer within 12 weeks
: Subjects who achieved complete healing and had early completion will be included.

② Time to complete healing# of ulcer within 12 weeks
: Time to complete healing is calculated as the number of days from baseline (1d).
(# The definition of complete healing: Epithelial tissue covering 100% of the study ulcer, no abrasion or ulceration, intact dermis and epidermis)

③ Pressure ulcer size reduction rate based on a scale at each time point

$$\text{Reduction rate} = \frac{\text{Pressure ulcer size on 1d*} - \text{Pressure ulcer size at each time point from 8d to End-of-Study**}}{\text{Pressure ulcer size on 1d}} \times 100\%$$

* Using a scale-based pressure ulcer area (cm^2) measured prior to the study device application

** Using a scale-based pressure ulcer area (cm^2) without re-epithelization*** measured at each time point after the study device application

(***Re-epithelization: New epithelial tissue covering the pressure ulcer, with no exudate, transudate, or avascular tissue)

① For subjects achieving complete healing within 12 weeks, present frequency and percentage.
② For the time to 100% complete healing, analyze using the Kaplan-Meier method. Subjects not achieving 100% complete healing within 12 weeks will not be considered for evaluation for end point of main interest.
③ For the pressure ulcer size reduction rate, present the mean and standard deviation.
For the analysis for efficacy, conduct sub-analyses by use of local antibiotics and glucocorticoids for the pressure ulcer during the study.

(2) Analysis of other endpoints

① PUSH reduction rate at each time point

$$\text{Reduction rate} = \frac{\text{PUSH score on 1d} - \text{PUSH score at each time point}}{\text{PUSH score on 1d}} \times 100\%$$

② Dressing change frequency during the entire study period
: Calculated as the additional dressing frequency beyond twice weekly
③ Number of subjects with early completion due to complete healing during the study
④ Incidence of new infections at the pressure ulcer until Week 12 based on the CSSC

$$\text{Infection incidence} = \frac{\text{Number of subjects with at least 1 new infection** until Week 12, after the study device application}}{\text{Total number of subjects}} \times 100\%$$

(** Infection: Presence of 'Purulent exudates' or 2 or more symptoms of the CSSC. However, for subjects with an infection at baseline, it is defined as development of an additional symptom other than those confirmed at baseline or recurrence of baseline-identified symptoms after being completely healed.)

For other endpoints, present the mean and standard deviation for continuous variables ①, and frequency and percentage in case of categorical variables ②, ③, and ④.

15.4 Analysis of safety endpoints

(1) Adverse events

List all adverse events that occurred by group. Record the frequency of adverse events related or unrelated with the investigational device by group. For the number of adverse events and the percentage of subjects who had at least 1 adverse event, present the 95% confidence interval in each

treatment group. Analyze adverse events separately for local adverse events at the target pressure ulcer and other adverse events.

(2) Laboratory test findings

For continuous data, present descriptive statistics (mean, standard deviation, median, minimum, maximum) by group and time point. In addition, tabulate the proportion of normal/abnormal results by time point in each group.

(3) Vital signs

For continuous variables, present descriptive statistics (mean, standard deviation, median, minimum, maximum) for the baseline and end-of-study test findings by group and visit time point.

16. Efficacy assessment methods and criteria, and interpretation methods

16.1 Endpoints

(1) Endpoints of main interest

① Number of patients with complete healing# of ulcer within 12 weeks

② Time to complete healing# of ulcer within 12 weeks

(# The definition of complete healing: Epithelial tissue covering 100% of the study ulcer, no abrasion or ulceration, intact dermis and epidermis)

③ Pressure ulcer size reduction rate based on a scale at each time point

(2) Other endpoints

① PUSH reduction rate at each time point compared to the baseline level

② Dressing change frequency during the entire study period

③ Number of subjects with early completion due to complete healing# during the study

④ Incidence of new infections** at the pressure ulcer until Week 12 based on the CSSC

(** Infection: Presence of 'Purulent exudates' or 2 or more symptoms of the CSSC. However, for subjects with an infection at baseline, it is defined as development of an additional symptom other than those confirmed at baseline or recurrence of baseline-identified symptoms after being completely healed.)

16.2 Assessment criteria and methods

This study is a pilot study with no comparator, so that no formal statistical test will be conducted.

17. Safety assessment methods and criteria, and interpretation methods, including adverse events

17.1 Assessment method

An adverse event (AE) is any unintended sign (including abnormal laboratory finding), symptom, or disease occurring in a subject during the study, and does not necessarily have a causal relationship with the relevant investigational device.

An adverse device effect(ADE) is any untoward and unintended reaction caused by an investigational

device for which a causal relationship with the investigational device cannot be ruled out.

It is the responsibility of the principal investigator and sub-investigators to record all adverse events occurring during the study. Adverse events are to be recorded according to the MedDRA(Medical Dictionary for Regulatory Activities) and in case it is not possible, terms on signs and symptoms observed by the principal investigator or sub-investigators or spontaneously reported by a subject are to be recorded using medical terms.

In the Case Report Form, signs and symptoms of the adverse event, duration (onset and resolution dates), severity, causal relationship with the study device, action taken for the adverse event, and outcome should be recorded without omission.

The followings will be evaluated for safety assessment.

1) Adverse event
At every visit, review both local adverse events at the target pressure ulcer and other adverse events.
(Local adverse events at the target pressure ulcer: Erythema, edema, itching, flare, rash, others)

2) Vital signs
Vital signs are analyzed by measuring at every visit until study completion. Measured vital signs are blood pressure (in sitting), pulse, and body temperature. In addition, body weight is measured at screening, Week 4, and at the End-of-Study visit.

3) Laboratory tests and physical examination
Laboratory tests are conducted at screening and study completion. For physical examination, normal/abnormal status of findings at screening is confirmed, and it is assessed whether the subject is eligible for study participation.

17.2 Assessment criteria

(1) Severity of the adverse event

Severity (intensity) of an adverse event is assessed using the following criteria.

① Mild: While signs or symptoms can be perceived, they can be easily tolerated.
② Moderate: May interfere with daily activities.

③ Severe: It is not possible to engage in daily activities.

(2) Causal relationship with the investigational device

In case of an adverse event, the relationship with the investigational device is classified by a treating physician as follows, and the sub-investigator's opinion is specified.

- **Definitely related**
  - There is the evidence that the study device was used, and there is a reasonable temporal relationship with the adverse event occurrence.
  - The adverse event is most plausibly explained by application of the study device than any other reasons.
  - The adverse event disappears upon discontinuation of the study device application.
  - Outcome of re-application (only when possible) of the study device is positive.
  - The event shows a consistent profile with already known information for the study device or medical devices in the same class.

- **Probably related**
  - There is the evidence that the study device was used, and there is a reasonable temporal relationship with the adverse event occurrence.
  - The event is most plausibly explained by application of the study device than any other reasons.
  - The event disappears upon discontinuation of the study device application.

- **Possibly related**
  - There is the evidence that the study device was used, and there is a reasonable temporal relationship with the adverse event occurrence.
  - The event is determined to be equally attributable to application of the study device as to other possible causes.
  - The event disappears upon discontinuation of the study device application.

- **Possibly not related**
  - There is the evidence that the study device was applied.
  - There is more likely cause of the event.
  - Outcome of discontinuation of the study device application is negative or ambiguous.
  - Outcome of re-application of the study device is negative or ambiguous.

- **Definitely not related**
  - The subject has not applied the study device.
  - There is no reasonable temporal relationship between the study device application and the adverse event occurrence.
  - There is other clear cause of the event.

- **Unknown**
  - There is insufficient evidence to determine the relationship.
  - Source data has poor quality or data are not consistent.

17.3 Adverse event reporting method

The principal investigator or sub-investigators will inform the subject or guardian of all possible adverse events after the investigational device application, and instruct them to report all events occurring after the study device application.

For all local, systemic, and clinical pathological findings after using the investigational device, the type, onset time, intensity, treatment, drug, course, causal relationship with the investigational device will be recorded and retained in the subject's Case Report Form, according to the Korea Good Clinical Practice for a Medical Device (enforcement date 2016.01.29).

A serious adverse event(SAE) is an adverse event occurring after the investigational device application that corresponds to any of the followings:

① Results in death or is life-threatening
② Requires inpatient hospitalization or prolongation of existing hospitalization
③ Results in persistent or significant disability or dysfunction
④ Results in congenital anomaly or birth defect
⑤ Other medically important events as identified by the Investigator

In the event that is not included in the above-listed conditions but is thought to likely have a serious influence on the subject's well-being and health in medical aspects, it will be determined whether the event should be considered a serious adverse event at the medical discretion of the investigator and relevant experts, and an appropriate measure will be taken accordingly.

The principal investigator should also review Serious Adverse Event Reports from other sites as notified by the sponsor, and report them according to the SOP of the site IRB.

Unexpected adverse device effect is an event that has a different profile of the adverse device effect or extent of the risk in light of available information on the medical device, such as the Investigator's Brochure or package insert.

All serious and unexpected adverse device effects should be reported within the timeline classified as follows.

<Reporting timeline to the Ministry of Food and Drug Safety>

(1) In case of a subject's death or seriously life-threatening event during the study, within 7 days after being informed of the event. However, in this case, further information should be additionally reported within 8 days after the initial reporting date.
(2) For all other serious and unexpected adverse device effects, within 15 days after the sponsor is informed or learned of the event.

The principal investigator will implement every aspect of the study conduct according to ICH GCP, the Declaration of Helsinki and local regulations.

In case of a "serious adverse event" during the study, responsibilities of each party are as follows.

1) Responsibilities of the investigator

In case of a serious adverse event during the study, the principal investigator should report to the Institutional Review Board and the sponsor within required timelines, and ensure that an appropriate medical action is taken for the relevant subject.

The Investigator must complete and send the SAE report form to Mundipharma Korea Ltd Product Safety Center via email within 24 hours of knowledge of the serious adverse event.
E-mail: Safety@mundipharma.co.kr

2) Responsibilities of the Institutional Review Board

In case of a serious adverse event, the Institutional Review Board should conduct an expedited review and inform the principal investigator of relevant actions to be taken, such as instruction of discontinuation of all or part of the study or continuation of the study.

3) Responsibilities of the sponsor

In case of being informed of an unexpected serious adverse device effect by the principal investigator or sub-investigators, the sponsor should attach a copy of the report submitted from the principal investigator or sub-investigators to an Adverse Event Report, and immediately submit to the Minister of Food and Drug Safety, and in case of a multicenter study, immediately inform the relevant site.

17.4 Follow-up of an adverse event

The investigator should follow up on subjects until all adverse events are determined to have resolved or become stable. In case of a serious adverse event, the change of a subject's condition should be investigated and submitted to the responsible personnel of the sponsor, by recording the change of a subject's status such as being discharged from hospital and/or the outcome once the subject's condition is recovered or has become stable.

17.5 Pregnancies

In case a pregnancy occurring during study, the principal investigator should promptly report to Mundipharma Korea Ltd Product Safety Center within 24 hours of Investigator's knowledge of the pregnancy. If a subject becomes pregnant during clinical trial period, it is not considered Serious AE/AE but the subject should be discontinued. And the pregnancy, fetus and birth should be followed up and reported.

18. Indemnification Provisions

[APPENDIX 1] Subject Indemnification Provisions

19. Informed Consent Form and Subject Information Sheet

[APPENDIX 2] Informed Consent Form and Subject Information Sheet

20. Medical care and treatment criteria for subjects after the study

Subjects withdrawn from the study will be instructed to receive other appropriate treatment, and subjects who complete the study will be able to receive medical care as instructed by a treating physician, in case of a delayed, unexpected adverse event.

21. Measures for safety protection of subjects

21.1 Site

The site director should be implement thorough preparation for the appropriate study conduct by arranging a clinical laboratory, facilities, and professional personnel required for the relevant study, according to each clinical phase.

21.2 Approval and amendment of the protocol

To get approval of the clinical study or implement an amendment of the previously approved clinical study, obtain approval of the IRB for the protocol or protocol amendment for each clinical phase. Subjects cannot be involved in a study before obtaining approval.

21.3 Full knowledge of the protocol

This protocol was developed by prioritizing rights and well-being of subjects based on ICH GCP, the Declaration of Helsinki and local regulations, and the principal investigator and sub-investigators will accurately analyze and remain fully aware of the protocol, and actively address problems of subjects.

21.4 Consent to the study

Before entering into the study, a subject or subject's representative will be informed of details of the study, effects, adverse events and safety of the study device, and then the subject will take part in the study, after the subject or representative provides the Informed Consent Form on voluntary participation in this study. Informed Consent will be obtained by the principal investigator or sub-investigator after informing subject in details.

21.5 Selection of appropriate subjects

Prior to this study, a subject's eligibility will be thoroughly assessed with a sufficient interview with the subject and the guardian and tests.

21.6 Confidentiality of subjects

Records that may identify a subject will be kept as confidential, and even if results from the study are published, confidentiality of the subject's identity will be maintained. Details are as follows.

The sponsor, monitor, and auditor involved in this study may have access to records of subjects for purposes of monitoring of this study, audit, and management of the study progress. By signing this protocol, the investigator recognizes that monitors and auditors from the sponsor or Contract Research Organization may review or copy records on subject charts and Case Report Forms for validation according to local laws and regulations and from an ethical perspective. Such information should be maintained as confidential and a facility and relevant management standards should be in place to ensure confidentiality. Meanwhile, on all study-related documents including the Case Report Form, a subject will be documented and identified using an identification code (in general, a subject's initial) instead of the subject's name.

21.7 Site monitoring

Monitoring is conducted to ensure protection of rights and well-being of subjects; to verify whether reported study-related data are accurate, complete, and verifiable in comparison to source documents; and to confirm whether the study is conducted according to the approved protocol and regulations such as the Korea Good Clinical Practice for a Medical Device.
Monitoring of the study will be conducted by periodic site visits and phone calls by monitors of the sponsor or the sponsor's delegated CRO (Person in charge of monitoring: ADM Korea CRA, 02-730-1457). Seven times of regular monitoring is being planned during the study period, but it may be altered upon enrollment status. During a visit, a monitor should essentially verify the original subject records, medical device management records, and data retention (study files).

In addition, the monitor should carefully examine the study progress status, and discuss with the investigator if there is any problem. And it may be reported to IRB when needed. In such case, monitoring report will be submitted to the sponsor.

The appropriate schedule of such visits should be distributed in discussion between the investigator and the monitor. The investigator should also allow monitors to have access to source data of subjects (source documents: hospital or personal charts, laboratory reports, appointment records, etc.) for verification of entries in the Case Report Forms as defined in the Korea Good Clinical Practice for a Medical Device.

21.8 Audit of the study progress

The sponsor may check the study progress status with periodic monitoring, and conduct an audit, as necessary.

21.9 Management of investigational devices

- The investigational devices are stored according to the storage conditions of each medical device and cannot be used without an instruction (prescription) by the principal investigator or sub-investigators.
- The sponsor should distribute investigational devices directly to the manager, receive a receipt certificate and retain it. The investigational devices should be marked as “For a clinical study”.
- The manager should retain and manage investigational devices not to be used for purposes other than a clinical study.
- The sponsor should check the quantity and storage conditions of investigational devices during the course of the study, and take actions to ensure appropriate study conduct.
- In case the study is discontinued or completed or the responsible personnel does not conduct the study according to the protocol, the sponsor will collect and dispose of used device packaging and unused investigational devices. In this case, the manager should return unused investigational devices to the sponsor after discussing with the principal investigator, and retain the return certificate.

21.10 Actions to be taken in case of an adverse event

In case of an adverse event, necessary tests and treatment will be immediately conducted by the treating physician, and a prompt and appropriate action will be taken according to Sections 17.3 and 17.4, Actions to be taken in case of an adverse event.

For a subject with an adverse event, the subject’s safety should be confirmed by continuously monitoring the event with the investigator‘s phone calls or the subject’s outpatient visits until the event

is resolved or determined to be persistent in a semi-permanent condition, and the continuation date should be recorded in the Case Report Form.

21.11 Data retention

The principal investigator has the responsibility to maintain and provide essential documents. Essential document is a document that enables individual or overall assessment of the study conduct and quality of data obtained from the study. Essential documents include all worksheets, source documents, monitoring records and appointment schedules, correspondences between the sponsor and the investigator, and regulatory documents (example: protocol and the amendment signed by the investigator, Institutional Review Board-related letters, approval-related documents, approved/signed Informed Consent Form, investigational device receipt certificate, accountability records, laboratory test findings, etc.) Source documents include all observation records and records on clinical activities, as well as all reports and records required for assessment and reconstruction of the study. Therefore, source documents include both records on all treatment conducted based on the protocol, and similar records. For observation records, the original document should be retained as a source document, if possible.

Source documents and other study-related documents should be retained at the site at all times, and the investigator should keep all study-related records until the Clinical Study Report is written (or until completion of an inspection in case an inspection by the Minister of Food and Drug Safety is required), and subsequently, transfer then to the retention personnel at the site. The site director and the sponsor will retain the protocol, documents, approval letters and all other data related to the study for 3 years after study completion. After 3 years, related data will be discarded upon the sponsor’s SOP.

21.12 Compensation for subjects

If a subject consents to take part in this study, study-related tests, investigational devices, and medical care will be provided at no charge, while expenses for hospitalization, tests, and medical care unrelated to the study should be covered by the subject.

In case of damage due to this study, the sponsor will take legal responsibilities and compensate for the damage according to the Subject Indemnification Provisions.

21.13 Rationale for recruitment of vulnerable subjects and measures to protect them

Why vulnerable subjects should be included in the study

Given the characteristics of the study indication, pressure ulcer, this study is expected to include individuals who have limited motor ability or communication ability because of physical impairment or who have limited cognitive ability because of dementia.

Expected risks and benefits

The medical devices to be used in this study have been approved and are available in the market; they are clinically applied to patients with burn, skin graft, skin tear, surgical wound, as well as with the study indication, pressure ulcer.

Description of procedures designed to minimize risks to subjects

The subjects and/or their guardians will be thoroughly interviewed and tested to confirm their willingness and eligibility to participate in the study. All study procedures will be conducted after obtaining informed consent.

To minimize risks to vulnerable subjects, the study will continuously be monitored for scientific and ethical conduct.

Plans to assess the subject's ability to provide informed consent

The followings will be assessed to confirm that the subject has the ability to provide informed consent:

1. The subject understands the study related information.
2. The subject is capable of handling the study related information in a logical manner.
3. The subject explicitly expresses his/her choice regarding whether or not he/she wants to participate in the study.

If there is a change in the subject's ability to provide informed consent as a result of a change in his/her conditions during the course of the study, the subject's understanding of and willingness for study participation may be re-assessed.

Plans for informed consent if appropriate

Unless the subject severely lacks the ability to make a judgment, including the ability to understand and express opinions, the study should be fully explained to the subject to the extent it can be understood, and voluntarily written informed consent should be obtained from the subject as well as from his/her guardian.

If there is a change in the subject's conditions, his/her understanding of and willingness for study participation will be re-confirmed at each visit. In addition, if the subject becomes capable of providing informed consent during the course of the study, the investigator will obtain informed consent from the subject.

Plans to include informed consent from legally acceptable representatives

If it is not possible to obtained informed consent from the subject due to lack of his/her abilities to understand and express opinions, informed consent will be obtained from the subject's legally acceptable representative (person with parental rights, spouse, or guardian). In this case, the investigator should confirm that this individual is a legally acceptable representative of the subject through a document proving this fact and should record in the subject information sheet and the source document the reason the informed consent was obtained from the legally acceptable representative.

The investigator should also confirm that vulnerable subjects were given sufficient information about the study and voluntarily provided informed consent.

22. Compliance with the study and handling of protocol deviations

The principal investigator and sub-investigators of this study should remain fully aware of and thoroughly implement the protocol to prevent any protocol deviation. In this study, training will be given for application of the investigational devices to subjects as scheduled, and the investigator should take appropriate measures so that subjects would not miss but make outpatient visits on scheduled dates to ensure compliance with the study schedule.

Meanwhile, unavoidable protocol deviations will be handled as follows:

- In case of a serious deviation, the subject may be excluded from the efficacy set during the efficacy assessment of the study.
- For minor deviations, the extent of the deviation or delay and the reason will be accurately recorded, and it will be considered whether they influenced the study results during result analysis. The final efficacy set will be determined in a data review meeting.

23. Publication policy

23.1 Ownership

Mundipharma Pte Ltd has the right to all data generated from this study and all data that is provided to Mundipharma Pte Ltd.

23.2 Confidentiality

All Investigators should comply with the confidentiality of information provided by Mundipharma Pte Ltd. This information includes, but is not limited to, all data and records generated from the conduct of the study. Investigators should not use the information, data, and records for reasons other than the conduct of the study. All data collected from subjects in this study will be kept anonymously and any identifiable information of subjects will not be included.

23.3 Publication

Mundipharma Pte Ltd is owner of the data. No Investigator may publish the results of this study without prior approval from Mundipharma Pte Ltd.

24. Reference

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