STUDY PROTOCOL

A Phase I/II Study to Evaluate the Safety and Efficacy of TWB-103 in Adult Patients with Split-Thickness Skin Graft Donor Site Wounds (DSW)

Project Number: 16-FDF-C001

Investigational Product: TWB-103

Sponsor: TRANSWELL BIOTECH CO., LTD.
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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH guidelines.

Principal Investigator:

_____ _____

Name Date

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate transaminase
bFGF	Basic fibroblast growth factors
BUN	Blood urea nitrogen
CI	Confidence intervals
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse events
DSMB	Data and Safety Monitoring Board
DSW	Donor site wounds
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICH	International Conference on Harmonisation
IND	Investigative New Drug
IP	Investigational Product
IQR	Inter-quartile range

IRB	Institutional review board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PDGF	platelet-derived growth factor
PI	Principal investigator
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Per-protocol
PRA	Panel reactive antibodies
RBC	Red blood cell
SAE	Serious adverse event
SOC	System/Organ/Class
SOP	Standard Operating Procedure
TFDA	Taiwanese Food and Drug Administration
TWBIO	Transwell Biotech Co., Ltd.
ULN	Upper limit normal
WBC	White blood cell

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PROTOCOL SUMMARY

Full Title	A Phase I/II Study to Evaluate the Safety and Efficacy of TWB-103 in Adult Patients with Split-Thickness Skin Graft Donor Site Wounds (DSW)
Short Title	TWB-103 for Adult Patients with Split-Thickness Skin Graft Donor Site Wounds
Project No	16-FDF-C001
Study Phase	Phase I/II
Sponsor	TRANSWELL BIOTECH CO., LTD.
Objectives	Primary objective: 1. To evaluate the safety of TWB-103 in split-thickness skin graft donor site wounds (DSW) for Phase I in terms of incidence of treatment-related AEs and SAEs (including infections and bleeding) 2. To evaluate the efficacy for Phase I+II of TWB-103 in split-thickness skin graft donor site wounds (DSW) in terms of the healing time from DSW creation to 100% re-epithelialization Secondary objective: 1. To evaluate the efficacy of TWB-103 in split-thickness skin graft donor site wounds (DSW) in secondary efficacy endpoints 2. To evaluate the safety of TWB-103 in split-thickness skin graft donor site wounds (DSW) in secondary safety endpoints
Study Design	This study will be designed in a Phase I/II randomized, double-blind, additional evaluator-blind, placebo-controlled, multi-center, multi-nation (Taiwan and Japan), parallel manner. In Phase I proportion, eligible patients will be recruited sequentially with one week staggering in the initiation of study treatment. Eligible patients will also be randomized into Treatment (TWB-103+Tegaderm™) and Control (placebo+Tegaderm™) groups in 1:1 ratio. Phase I plan to recruit 3 evaluable TWB-103+Tegaderm™

treated and 3 evaluable placebo+Tegaderm™ treated patients. Patients in phase I are considered as evaluable when (1) he/she receives at least one dose and has follow-up evaluation at least 14 days after first dose or (2) he/she receives at least one dose and has early withdrawn due to safety reasons before Day 28. When all of those 6 evaluable patients complete the planned treatment period (14 days or till first 100% re-epithelialization, which comes first), the recruitment of patients will be temporarily stopped for 14 days for safety observation. The safety data of TWB-103 before and on Day 28 Visit will be reviewed by the sponsor and the principal investigator. If no safety issue of TWB-103 is decided, the study will enter Phase II portion and eligible patients will be randomized into Treatment and Control groups in 1:1 ratio.

All subjects are scheduled to attend a follow-up visit at Day 28 to evaluate the status of the target wound and then enter a 360-day follow-up phase. If the complete wound closure occurs by Day 14, the re-confirmation of wound closure should be performed on Day 28 follow-up. In the case that complete wound closure occurs at some point between Day14 and Day 28, an additional follow-up visit will be scheduled on Day 42 for the re-confirmation before subject enters the 360-day follow-up phase. If the complete wound closure is not observed on Day 28, patients will have other appropriate treatment at the investigator's discretion. The DSWs will be followed till 100% re-epithelialization.

During the 360 days of follow-up, four follow-up visits will be scheduled on 90±14 days, 180±14 days, 270±14 days and 360±14 days following the subject's Day 28 visit (if no Day 42 visit) or Day 42 visit. In total, 5~6 follow-up visits will be scheduled in this study for all randomized subjects.

The study will be stopped when > 1/3 of patients in the phase I have developed study drug related grade 2 or above SAEs defined as in Section 8. The investigator will determine if SAEs are study drug

related without breaking the blind. If the cause of SAE is inconclusive, the investigator can request to break the blind following the procedure stated in Section 4.2.

Patients who experience > Grade 2 skin allergic reaction or > Grade 2 systemic allergic reaction related to the product or placebo must not receive any further TWB-103 or placebo treatment. If a patient should develop infection at the DSW site before Day 10, he/she will stop the TWB-103 or placebo application at the investigator's discretion. Patients with the aforementioned conditions, before or at Visit 8, should finish the scheduled assessments (except that application of TWB-103/placebo is stopped; that the application and dispensation of Tegaderm™ will be at the investigator's discretion; and that the return of Tegaderm™ will be asked if applicable). Patients with allergic reaction or infection may receive appropriate treatments at the PI's discretion, will be monitored throughout the healing process (including the recovery from allergic reaction or infection, and the complete closure of DSW) and will continue the remaining visits (application of TWB-103 or placebo will be stopped if planned originally). In these cases of TWB-103/placebo discontinuation, wound assessments performed after onset of allergic reaction or infection will be excluded from statistical analysis.

Unscheduled visits can be requested when patients require the investigator's medical attention, e.g. the reopen of DSW but self-care is insufficient, infection, or allergic reaction. Patients should finish the assessments of Day 14 (except that the completion of hemogram and serum biochemistry as well as the application and dispensation of Tegaderm™ will be at the investigator's discretion; and that the return of Tegaderm™ is not required) during the unscheduled visit. Patients will resume the original planned visits and/or come in additional unscheduled visits at the investigator's discretion. The option to choose Vaseline Gauze or Non-Stick Gauze

	such as silastic foam dressings only can be selected on or after Day 14.
Study Population	Patient aged at 20-65 years old presenting a split-thickness skin graft donor site wound
Number of Patients	The sample size is determined to be 15 versus 15 evaluable (= per-protocol for Phase I+II) patients (1:1 ratio) for Treatment versus Control groups, 30 evaluable patients in total. To ensure the completion of 30 evaluable patients, around 36 patients will be recruited.
Study Product, Dose, Route, Regimen	TWB-103, allogeneic human fibroblasts + gelatin-based hydrogel, applied 2 to 3 times till 100% re-epithelialization or up to 10 days (around once every 3 days); a matching placebo, freezing solution with gelatin-based hydrogel, is used as the control and applied to patients in the same duration and dosing frequency as TWB-103.
Duration of Treatment	During the planned treatment period (14 days), each patient will receive TWB-103+Tegaderm™ or placebo+Tegaderm™ for up to 10 days or to the day of 100% re-epithelialization, whichever comes first, followed by Tegaderm™ alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10.
Study Visits	Patients will be scheduled to attend the following visits: 1. Screening (within 2 weeks prior to DSW creation) 2. Day 0 (treatment begins) 3. Day 3 (± 1 day) 4. Day 7 (± 1 day) 5. Day 10 (± 1 day) 6. Day 14 (± 2 days, end of treatment) 7. Day 28 (± 3 days, Follow-up) 8. Day 42 (± 3 days, Follow-up)

	9. 90 ± 14 days after Visit 7 or Visit 8 (Follow-up) 10. 180 ± 14 days after Visit 7 or Visit 8 (Follow-up) 11. 270 ± 14 days after Visit 7 or Visit 8 (Follow-up) 12. 360 ± 14 days after Visit 7 or Visit 8 (Follow-up) Note: (1) For patients with complete wound closure by Day 14, the confirmation of wound closure will be assessed on Day 28. (2) Day 42 follow-up is only scheduled when the wound closure is not completed by Day 14 but is observed on Day 28. The wound closure will be re-confirmed on Day 42. (3) If no Visit 8, Visit 9~12 should be scheduled following Visit 7. (4) In case patients achieve 100% re-epithelialization before or at Day 10, patients will finish up the assessments on the day with 100% re-epithelialization. This day of 100% re-epithelialization will be the end of treatment and the remaining scheduled treatment visits, if applicable, will be dismissed.
Patient Assignment	Patients who meet all eligibility requirements for entry into the study will be randomized into one of the treatment group or control group in 1:1 ratio as shown below: Treatment Group: TWB-103 add-on Tegaderm™ till 100% re-epithelialization or up to 10 days, whichever comes first, followed by Tegaderm™ alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10. If 100% re-epithelialization is not observed on Day 14 (the end of treatment), patients will have application of Tegaderm™ up to Day 28. Control Group: Placebo+Tegaderm™ till 100% re-epithelialization or up to 10 days, whichever comes first, followed by Tegaderm™ alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10. If 100% re-epithelialization is not

	observed on Day 14 (the end of treatment), patients will have application of Tegaderm™ up to Day 28. Note: 1. Tegaderm™ will be renewed at each visit between Visit 3 (Day 3) to Visit 7 (Day 28) if 100% re-epithelialization is not observed. Whenever Tegaderm™ falls off from DSW site, new Tegaderm™ should be applied immediately. If necessary, drainage is allowed, but re-application of TWB-103 or placebo is not necessary in this case. 2. If the first 100% re-epithelialization is observed on Day 28, patients will be scheduled Day 42 follow-up and dispensed with Tegaderm™. 3. If the first 100% re-epithelialization is not observed on Day 28, patients will receive the application of Tegaderm™ on site for protection of wound site and/or have other appropriate treatment at the investigator's discretion. The DSWs will be followed till 100% re-epithelialization. 4. To prevent the itchiness and skin reaction caused by the long-term usage of Tegaderm™, Vaseline Gauze or Non-Stick Gauze such as silastic foam dressings can be used on and after Day 14 at the investigator's discretion.
Patients Inclusion Criteria	A patient is eligible for the study if all of the following apply: 1. Female/male patients, aged 20-65 years old 2. Presenting a split-thickness skin graft donor site wound with a minimum size of 15 cm^2 but no more than 100 cm^2, with a minimum width of 3 cm and with an approximate thickness of 0.010~0.012 inches. The graft cannot be harvested from a site from which a skin graft was previously obtained. 3. If the primary wound is a result of a thermal or chemical burn, the total body surface area of the said wound must be less than 15%. Note: The burn area is estimated based on the method used at the local site. The Rule of Nines Chart (1% body surface area equals one patient's palm size) or Lund and Browder Chart are acceptable. 4. Females of childbearing potential must have a documented negative serum pregnancy test done at the screening visit, which is within 2 weeks prior the DSW creation and the treatment

	5. Both male and female patients must agree to use highly effective contraceptives from signing informed consent to 30 days after the last dose administration. Acceptable contraceptive forms include: a. Established use of oral, injected or implanted hormonal methods of contraception b. Placement of an intrauterine device (IUD) or intrauterine system (IUS) c. Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps) 6. Willing to comply with the study protocol and has signed the Informed Consent Form Note: The rationale for the inclusion criteria is described in section 3.2.
Patients Exclusion Criteria	Any patient meeting any of the exclusion criteria will be excluded from study participation. 1. Female patients who are pregnant or lactating or planning a pregnancy and any male patient whose partner (wife) planning a pregnancy from signing informed consent to 30 days after the last dose administration. 2. Clinically significant disease or condition that may compromise graft taken and/or donor site healing (e.g. the presence of a bleeding disorder, capillary fragility, venous or arterial disorder directly affecting the donor site to be treated, known or suspected systemic malignancies, human immunodeficiency virus infection, renal or liver disease, uncontrolled diabetes mellitus, thrombocytopenia, vasculitis, poor nutritional status). 3. Patients who are currently receiving or have received the following treatments within 4 weeks prior to Screening Visit are excluded from the study: a) systemic, or inhaled corticosteroids or immunosuppressant agents; or

b) therapeutic doses of anticoagulants (e.g. Coumadin, Heparin, low molecular weight Heparin) for pre-existing medical conditions, for whom a dose interruption from Screening through the end of the study period is contraindicated.

4. Autoimmune disease, e.g. lupus erythematosus, multiple sclerosis.
5. Hematologic disease, malignancy or hypo-immunity.
6. History of HIV infection or congenital immunodeficiency.

Note: HIV = human immunodeficiency virus

7. History of alcoholism or drug abuse.
8. Have used any tobacco product within 1 week prior to Day 0.
9. Patients previously treated with any cell-based product, including autologous tissue at the treatment site.
10. Received an investigational drug, device or biological/bioactive treatment within 30 days prior to Screening Visit.
11. Any clinical condition or significant concurrent disease judged by the investigator to complicate the evaluation of the trial treatment.
12. History of sensitivity to bovine or porcine origin of materials, or human serum albumin.
13. DSWs located in the face, over joints, lower legs or the buttocks
14. Any of the following hematologic abnormalities:
    a. Hemoglobin < 10.0 g/dL
    b. ANC < 1,500/μL,
    c. Platelets < 75,000 /μL
15. Any of the following serum chemistry abnormalities:
    a. Total bilirubin > 1.5 × ULN,
    b. AST or ALT > 3 × ULN,

c. γ-GT > 2.5 x ULN,

d. Alk-P > 2.5 x ULN,

e. Serum albumin < 2.7 g/dL,

f. Creatinine >1.5 x ULN

g. Any other ≥ Grade 2 laboratory abnormality (based on CTCAE) at baseline (other than those listed above)

16. DSWs in area with active skin infection or with skin condition that is considered highly susceptible to infection judged by the investigator

Note: The rationale for the exclusion criteria is described in section 3.3.

Primary Endpoint

Phase I

Safety:

Incidence of treatment-related AEs and SAEs (including infections and bleeding)

Note: AE = adverse event; SAE = Serious adverse event

Phase I+II

Efficacy:

The healing time from DSW creation to the first 100% re-epithelialization with confirmation for at least 10 days apart assessed by the investigator

Secondary Endpoints

Phase I+II

Efficacy:

1. The healing time from DSW creation to the first 100% re-epithelialization with confirmation for at least 10 days apart, assessed by the first additional evaluator
2. The healing rates (complete wound closure) of patients at Day 7, 10 and 14 after DSW creation

   Note: Complete wound closure is defined as skin 100% re-

	epithelialization without drainage or dressing requirements. 3. The healing percentage of wounds (ratio of healing area and original area) at Days 7, 10 and 14 after DSW creation 4. The pain change from baseline to post-wound creation visits based on short-form McGill pain questionnaire score Safety: 1. Incidence of treatment-related AEs and SAEs (including infections and bleeding) 2. Incidence of AEs and SAEs 3. Changes in post-treatment physical examination, vital signs, and general laboratory assessment compared to baseline Note: The investigator will determine the end of treatment based on the healing progress. Wound healing will be assessed based on the wound observation by the investigator and an additional evaluator. An additional evaluator who is not aware of the treatment given will evaluate based on photos of the wound. The additional evaluator will receive photos of the wound from CRO and will return the assessment to CRO. A second additional evaluator, who is also blinded, will be requested when the discrepancy occurs between the investigator and the first additional evaluator in the determination of 100% re-epithelialization.
Statistical Analysis	For this study, the sample size is 30 evaluable patients in total. This sample size is based on clinical judgment and not based on power calculation. Two populations will be introduced for statistical analysis: Intent-to-treat (ITT) population: • Patients randomized • Patients ever treated by at least one dose of trial medication • Patients with any post-treatment evaluation Per-protocol (PP) population: • Dosed with planned dosing regimen of investigational

product

- With efficacy endpoint measurement at wound assessment (with first 100% re-epithelialization or complete Day 14 visit evaluation)
- Fulfilling all inclusion and exclusion criteria
- Without taking prohibited medication

Since the dosing regimen designed in Phase I are exactly those designed for Phase II, and the procedures/schedules of assessment that patients receive are identical in both phases, the data collected in Phase I portion will be combined with those in the Phase II portion for statistical analysis.

Primary endpoints and secondary efficacy endpoints in Phase I/II will be analyzed on ITT and PP population. Non-primary safety endpoints, demographics and baseline characteristics will be analyzed on ITT population. Conclusion of primary endpoint in Phase I will be made based on ITT population analysis results and that in Phase II will be made according to the result of ITT population analysis. For all assessments, the baseline will be defined as the most recently available data before the administration of 1st dose treatment.

Descriptive statistics will be provided by treatment group/country and by all for all of the endpoints, including primary and secondary ones. Frequency table will be provided for categorical data, while mean, standard deviation, maximum, minimum, median, inter-quartile range (IQR), and 95% two-sided confidence interval will be calculated for continuous measurements.

AEs and SAEs will be reported by treatment group/country and physiological systems as appropriate. The incidence of treatment-related AEs and SAEs between treatments will be analyzed by Cochran-Mantel-Haenszel test (CMH) test.

Incidence of AEs and SAEs will be analyzed by CMH test. Changes in physical examinations will be displayed for each individual system. Net changes from pre-treatment laboratory test results and vital signs will be analyzed by descriptive statistics.

Healing time from DSW creation to 100% re-epithelialization will be estimated by using Kaplan-Meier methods and compared between groups by using log-rank test. The healing time is defined as from DSW creation to the first 100% re-epithelialization with confirmation for at least 10 days apart, observed by the investigator and the first additional evaluator.

If the first 100% re-epithelialization is observed at any visit by Day 28 with confirmation for at least 10 days apart, the healing time is noted as the duration from the day of DSW creation to the day of the first 100% re-epithelialization. The fulfilling of the visits and/or follow-ups after the 100% re-epithelialization day will not be taken into account to determine the healing time. If the 100% re-epithelialization is not observed by Day 28 visit, the healing time will be censored on day of the last visit up to Day 28 visit. If the 100% re-epithelialization is observed by Day 28 visit but no confirmation is made, the healing time will be censored on day of the last visit up to Day 28 visit. The censoring rules will be applied immediately once patients leave the study regardless the participation and/or completion of the long-term (360 days) follow-ups.

If patient develops grade 2 or above SAEs and should exit the study prematurely before Day 14, he/she should be excluded from the primary efficacy analysis, because early censor will result in under estimation of the healing time while treatment group (TWB-103+Tegaderm™) is prone to have higher risk of developing treatment related SAE.

In the cases of TWB-103/placebo discontinuation due to allergic reaction or infection, wound assessments performed after onset of

allergic reaction or infection will be excluded from statistical analysis.

Healing rates (complete wound closure) of patients at Days 7, 10 and 14 after DSW creation will be analyzed by CMH test. Healing percentage of wounds (ratio of healing and original areas) at Days 7, 10 and 14 after DSW creation will be analyzed by Analysis of variance (ANOVA) model with treatment group and country as factor. Score on short-form McGill pain questionnaire will be analyzed by using Analysis of covariance (ANCOVA) model with treatment group and country as factor and baseline characteristics as covariate. Vancouver Scar Scale will be analyzed by Wilcoxon ranked sum test. The score in each category (pigmentation, vascularity, pliability and height) and the sum score of all category in Vancouver Scar Scale will be analyzed.

All treatment group comparisons will be conducted with significance level of 0.05, using 2-tailed tests.

Demographics and baseline characteristics will be summarized for each group/country by using descriptive statistics.

SCHEDULE OF ASSESSMENTS

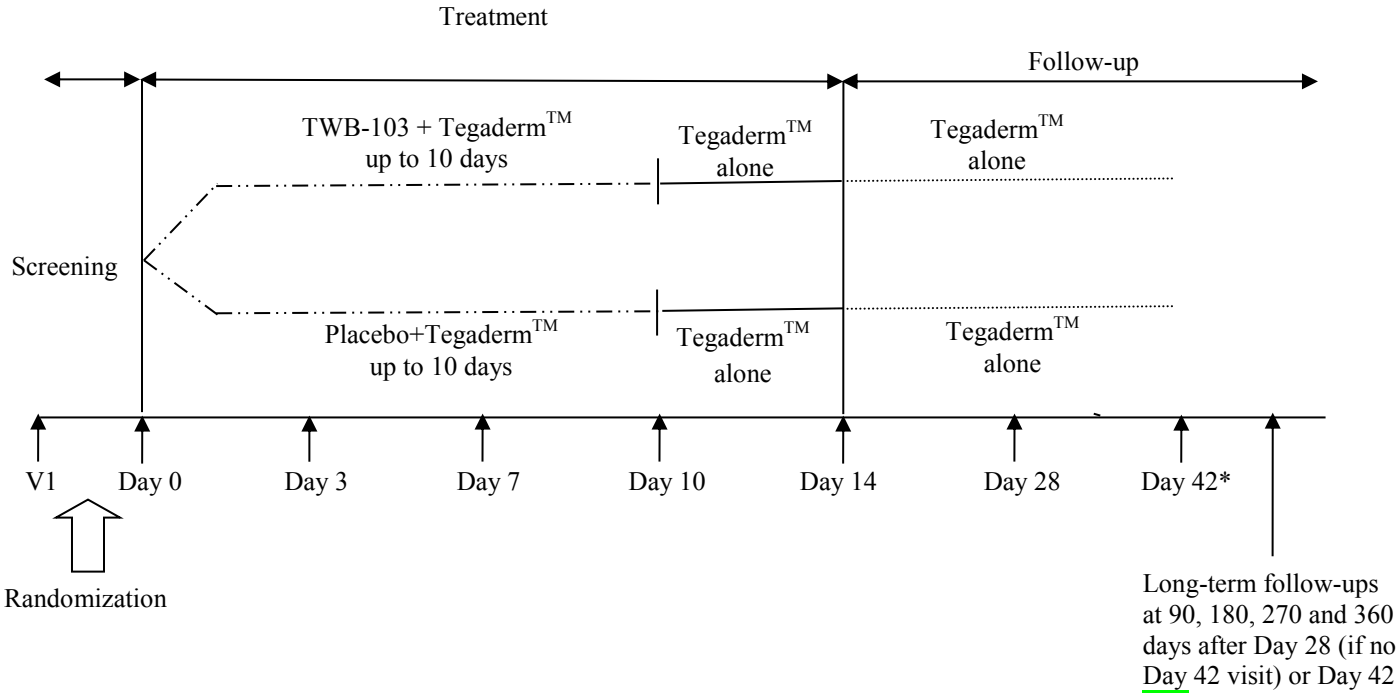
	Screening[1]	Treatment[12, 13]					Follow-up		
Procedure	Within 2 weeks prior to DSW creation	Day 0[1]	Day 3 (± 1 day)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 2 days)[14]	Day 28 (± 3 days)[2,11]	Day 42 (± 3 days)[3,11]	90, 180, 270, 360 days (± 14 days) from visit 7 or 8[4,11]
Visit	1	2	3	4	5	6	7	8	9, 10, 11, 12
Informed consent	X								
Screening no. assign	X								
Inclusion / Exclusion	X								
Randomization[19]	X								
Demographics	X								
Medical History	X								
Physical Examination	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Pregnancy Test (Serum)	X								
PRA test: Class I HLA.		X[20]					X		
Hemogram	X	X[20]	X	X	X	X	X	X	
Serum Biochemistry	X	X[20]	X	X	X	X	X	X	
TWB-103+Tegaderm™ or placebo+Tegaderm™ [5,6]		X	X	X					
Tegaderm™ applying at site[6]					X[7]	X[7, 22]	X[7, 10, 22]		
Tegaderm™ dispensing[6, 8]		X	X	X	X	X[22]	X[22, 23]		
Tegaderm™ return[9]			X	X	X	X[22]	X[22]	X[22, 23]	
Wound assessment[15]		X	X	X	X	X	X[2]	X	X[16]
Pain questionnaire[21]	X		X	X	X	X	X	X	X
AE assessment	X[17]	X	X	X	X	X	X	X	X[18]
Prior/Concomitant treatment	X	X	X	X	X	X	X	X	

1. Visit 1 (screening) and Visit 2 (Day 0) can be performed on the same day.
2. When DSW reaches 100% re-epithelialization by Day 14, a re-confirmation of wound closure will be performed on Day 28.

3. Day 42 visit is only for patients whose DSWs do not reach to 100% re-epithelialization on Day 14 but heal on Day 28 as a re-confirmation.
4. For patients whose visit 8 (Day 42) is scheduled, these visits will be arranged at 90, 180, 270 and 360 days after visit 8 (Day 42); otherwise, these follow-ups will be planned at 90, 180, 270 and 360 days after visit 7 (Day28). These long-term follow-ups should be scheduled even if 100% re-epithelialization is not observed on Day 28 or Day 42.
5. For treatment group: TWB-103+Tegaderm™. For the control group: placebo+Tegaderm™. The application will be discontinued when the 100% re-epithelialization of DSW is observed by the investigator.
6. The size of Tegaderm™ to be used for each patient will be determined by the investigator based on the size of DSW. Whenever Tegaderm™ falls off from DSW site, new Tegaderm™ should be applied immediately. If necessary, drainage is allowed, but re-application of TWB-103 or placebo is not necessary in this case.
7. Tegaderm™ is applied to the wound site after the investigator has finished the wound assessment if the DSW has not reached 100% re-epithelialization, regardless the original group assignment.
8. Tegaderm™ is dispensed to the patient regardless of the condition of DSWs. Patients are advised to apply Tegaderm™ to DSW site if the wound open remains or reappears, and to re-apply new Tegaderm™ every 2~3 days till next visit or wound closure. The amount of Tegaderm™ dispensed should be adequate for patient's use till next visit.
9. Unused Tegaderm™ is returned to the study site if Tegaderm™ is dispensed to the patient at the previous visit. Re-dispensing of unused Tegaderm™ to the same patient is allowed when the primary package of Tegaderm™ remains intact.
10. The patient will receive the application of Tegaderm™ on site for protection of wound site and/or start with other treatment recommended by the investigator if DSW does not reached 100% re-epithelialization by Day 28.
11. When patients are withdrawn from the study by Day 28, they are required to finish all assessments of Day 28, except the application and dispensation of Tegaderm™. The unused Tegaderm™ should be returned if received from the previous visit. For patients who have initially scheduled Day 42 visit but make the decision between Day 28 to Day 42 to withdraw from the study, he/she should be encouraged to complete assessments planned for Day 42 visit at the earliest date convenient for the patients. If patients have entered the long-term follow-up period (i.e. after Day 28 or Day 42 if scheduled) and the decision of withdrawal is confirmed, effort must be made to understand and record the reason of withdrawal
12. In case patients achieve 100% re-epithelialization before or at Day 10, patients will finish up the assessments on the day with 100% re-epithelialization. This day of 100% re-epithelialization will be the end of treatment and the remaining scheduled treatment visits, if applicable, will be dismissed.
13. When patients experience > Grade 2 skin allergic reaction or > Grade 2 systemic allergic reaction related to the product/placebo or develop infection that the continuation of TWB-103/placebo is considered inappropriate at the investigator's discretion, patients should finish the scheduled assessments (except that application of TWB-103/placebo is stopped; that the application and dispensation of Tegaderm™ will be at the investigator's discretion; and that the return of Tegaderm™ will be asked if applicable) and will continue the remaining visits (application of TWB-103 or placebo will be stopped if planned originally).
14. When unscheduled visits are requested, patients should finish the assessments of Day 14 (except that the completion of hemogram and serum biochemistry as well as the application and dispensation of Tegaderm™ will be at the investigator's discretion; and that the return of Tegaderm™ is not required) during the unscheduled visit. The option to choose Vaseline Gauze or Non-Stick Gauze such as silastic foam dressings only can be selected on or after Day 14.
15. When the first 100% re-epithelialization is not observe by Day 28, the DSWs will be followed till 100% re-epithelialization.
16. At Visit 9~12, recording of 100% re-epithelialization and the area of target wound are not required. Instead, wound assessment will include scar assessment (Vancouver Scar Scale and if necessary, additional comments on scar elasticity, scar color and pigmentation), skin texture (relationship to surrounding skin, texture, margins, size and multiplicity) and any altered sensations.
17. Adverse events will start recording after signing informed consent.
18. At Visit 9~12, only TWB-103/placebo-relative and DSWs-relative adverse events will be recorded.

19. Randomization will be done before DSW creation but after all baseline procedures are completed and the subject has been deemed eligible for the study.
20. For Visit 2, the hematologic, biochemical and PRA tests conducted within 7 days prior to Day 0 are acceptable.
21. Patients should evaluate pain level at the (future) DSW site.
22. To prevent the itchiness and skin reaction caused by the long-term usage of Tegaderm™, Vaseline Gauze or Non-Stick Gauze such as silastic foam dressings can be used on and after Day 14 at the investigator's discretion.
23. Tegaderm™ is dispensed only when Day 42 is scheduled. Unused Tegaderm™ should be returned on Day 42.

STUDY SCHEMA



*Note:
Day 42 visit is only for patients whose DSWs do not reach to 100% re-epithelialization on Day 14 but heal on Day 28 as a re-confirmation.

1. BACKGROUND AND RATIONALE

1.1 General Introduction

The skin is a vital organ with several major functions: protection, sensation, thermoregulation, excretion, absorption, and metabolism. Any breach in skin integrity may lead to the disruption of one or more functions as well as pain, discomfort and possible infection. Some wounds may be sutured (primary intention healing) whereas open wounds may heal by secondary intention, which is a slower process. The longer a wound exists, the greater the potential for infection as it will require regular dressing changes over a period of time; a procedure that will always carry a risk of potential infection.

Depending on the healing time of a wound, it can be classified as acute or chronic:

- Those classified as acute wounds heal with little or no complications in the predicted amount of time, such as surgical, thermal and chemical or any traumatic type of wounds.
- Those classified as chronic wounds take a longer time to heal and often have different degree of complications, such as infectious, ischemic, diseases (Epidermolysis Bullosa), radiation-poisoning (therapeutic or accidental) or any ulceration type of wounds (pressure ulcer, venous leg ulcer, diabetic foot ulcer).

When wounds are extensive, unsuitable for closure by suturing, or are likely to cause physical or psychological problems through scarring, skin grafts should be considered in order to accelerate healing and minimize scarring of wounds[1].

Split-thickness skin grafting is the most frequently used reconstructive technique to repair damaged or missing skin (e.g. burns, chronic, and traumatic wounds), including

those that cannot be covered by a skin flap, which consists of skin and subcutaneous tissue that survives based on its own blood supply, or are not likely to be ameliorated by secondary intention. The wound created after harvesting the skin is called the donor site wound (DSW). Treatment of the split-thickness graft donor sites has been studied over the years, but no standard treatment for managing these sites is confirmed. Depending on the thickness of the split skin grafting, the DSW should spontaneously re-epithelialize completely in 7 to 21 days. Optimum local care for these DSWs should facilitate the wound healing process and be cost-effective, while it should prevent associated complications, such as pain, discomfort, infection, and scarring and consider the patients' physical and mental well-being during the treatment process. Particularly pain and discomfort are reported to occur with more frequency from DSWs than on the recipient site[2,3].

TWB-103 is supplied as a two-component therapeutics consisting of one vial of living allogeneic fibroblasts (TWB-102 cells) and one vial of gelatin-based hydrogel (TWB-103 hydrogel). While the mechanism of healing is multi-modal, TWB-103 does not function as a barrier dressing, but rather than a "stimulus" or "aid" to wound healing. TWB-102 cells do not persist as occurs in a graft. It is believed that, upon application to the wound, the production of cytokines and growth factors by the living cells are the key factors responsible for the ability of TWB-103 to enhance healing by secondary intention.

Nonclinical studies have shown that the fibroblasts present within TWB-103 produce many of the signaling molecules, such as basic fibroblast growth factors (bFGF), platelet-derived growth factor (PDGF), and other growth factors and cytokines that are known to be beneficial to the various phases of wound healing (i.e. hemostasis, inflammation, proliferation, and remodeling). Additionally, TWB-103 can also

provide wound site a number of matrix proteins that play key structural roles in skin and in healing.

1.2 Rationale and Justification for the Study

1.2.1 Rationale for the Study Purpose

Transwell Biotech Co., Ltd. (TWBIO) seeks approval of an Investigative New Drug (IND) for TWB-103. Specifically, TWBIO is seeking regulatory permission to apply the product for first-time-in-human for managing surgical and donor site wounds in adults due to autografting procedure. The purpose of the present phase I/II study is to explore the safety and efficacy profiles of TWB-103 in split-thickness skin graft DSW. This study will be conducted via a randomized, double-blind, additional evaluator-blind, placebo-controlled, multi-center, multi-nation (Taiwan and Japan), parallel fashion.

1.2.2 Rationale for Doses Selected

TWB-103 has not yet been previously approved by any regulatory authorities in the world. However, the overall safety of TWB-103 has been characterized in the animal models of cutaneous wounds. Nonclinical studies of TWB-103 in the burn indication have not been performed as the general acute cutaneous wounds have more similarities than differences to the wounds of the donor site. The nonclinical set of data on TWB-103 includes product characterization, cell migration, tumorigenicity and immune-toxicity. The results of these studies do not suggest a potential for immunological, toxicological, or oncogenic risks. Moreover, efficacy is further supported by more than 15 years of human use safety experience in Switzerland of FE002-SK2, the same cell line making TWB-103.

1.2.3 Rationale for Study Population

The study population designed to be enrolled are patients aged at 20-65 years old presenting a split-thickness skin graft DSW with a minimum size of 15 cm^2 but no more than 100 cm^2, with a minimum width of 3 cm, and with an approximate thickness of 0.010~0.012 inches. Since TWB-103 is believed to have the ability to regenerate functional skin tissue by modulating and improving secondary intention wound healing, the study population is therefore selected.

1.2.4 Rationale for Study Design

This is a phase I/II study intending to explore the safety and efficacy of TWB-103 in split-thickness skin graft DSW by adding on TWB-103 to Tegaderm™, the standard of wound care to compare with placebo+Tegaderm™. In this study, TWB-103 will be applied as an adjuvant therapy besides Tegaderm ™ for safety concern since this is a first-time-in-human study for TWB-103 even though TWB-103 is believed to be relatively safe and also for ethical concern. The ethical issue is also concerned with employing placebo+Tegaderm ™ as a control. To avoid systematic bias, the study is designed as a double-blind, additional evaluator-blind, randomized study.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

1. To evaluate the safety for Phase I of TWB-103 in split-thickness skin graft donor site wounds (DSW) for Phase I in terms of incidence of treatment-related AEs and SAEs (including infections and bleeding)

2. To evaluate the efficacy for Phase I+II of TWB-103 in split-thickness skin graft donor site wounds (DSW) in terms of the healing time from DSW creation to 100% re-epithelialization

2.1.2 Secondary Objectives

1. To evaluate the efficacy of TWB-103 in split-thickness skin graft donor site wounds (DSW) in secondary efficacy endpoints

2. To evaluate the safety of TWB-103 in split-thickness skin graft donor site wounds (DSW) in secondary safety endpoints

2.2 Endpoints

2.2.1. Primary endpoints

The primary endpoint for this study is:

Phase I

Safety:

Incidence of treatment-related AEs and SAEs (including infections and bleeding)

Phase I+II

Efficacy:

The healing time from DSW creation to the first 100% re-epithelialization with confirmation for at least 10 days apart, assessed by the investigator

2.2.2. Secondary endpoints

The endpoints used to achieve the secondary objectives of this study are listed below:

Phase I+II

Efficacy:

1. The healing time from DSW creation to the first 100% re-epithelialization with confirmation for at least 10 days apart, assessed by the first additional evaluator
2. The healing rates (complete wound closure) of patients at Days 7, 10 and 14 after DSW creation

   Note: Complete wound closure is defined as skin 100% re-epithelialization without drainage or dressing requirements.
3. The healing percentage of wounds (ratio of healing area and original area) at Days 7, 10 and 14 after DSW creation
4. The pain change from baseline to post-wound creation visits based on short-form McGill pain questionnaire score

Safety:

1. Incidence of treatment-related AEs and SAEs (including infections and bleeding)

2. Incidence of AEs and SAEs

3. Changes in post-treatment physical examination, vital signs, and general laboratory assessment compared to baseline

Note: The investigator will determine the end of treatment based on the healing progress. Wound healing will be assessed based on the wound observation by the investigator and an additional evaluator. An additional evaluator who is not aware of the treatment given will evaluate based on photos of the wound. The additional evaluator will receive photos of the wound from CRO and will return the assessment to CRO. A second additional evaluator, who is also blinded, will be requested when the discrepancy occurs between the investigator and the first additional evaluator in the determination of 100% re-epithelialization.

3. STUDY POPULATION

3.1 The Number of Patients to Be Enrolled

The sample size is determined to be 15 versus 15 evaluable (per-protocol for Phase I+II) patients (1:1 ratio) for Treatment versus Control groups, 30 evaluable patients in total. To ensure the completion of 30 evaluable patients, around 36 patients will be recruited.

3.2 Inclusion Criteria

A patient is eligible for the study if all of the following apply:

1. Female/male patients, aged 20-65 years old
2. Presenting a split-thickness skin graft donor site wound with a minimum size of 15 cm^2 but no more than 100 cm^2, with a minimum width of 3 cm and with an approximate thickness of 0.010~0.012 inches. The graft cannot be harvested from a site from which a skin graft was previously obtained.
3. If the primary wound is a result of a thermal or chemical burn, the total body surface area of the said wound must be less than 15%.

   Note: The burn area is estimated based on the method used at the local site. The Rule of Nines Chart (1% body surface area equals one patient's palm size) or Lund and Browder Chart are acceptable.
4. Females of childbearing potential must have a documented negative serum pregnancy test done at the screening visit, which is within 2 weeks prior the DSW creation and the treatment
5. Both male and female patients must agree to use highly effective contraceptives from signing informed consent to 30 days after the last dose administration. Acceptable contraceptive forms include:

a. Established use of oral, injected or implanted hormonal methods of contraception

b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

c. Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps)

6. Willing to comply with the study protocol and has signed the Informed Consent Form

Note: The rationale for the inclusion criteria is described as below.

1. The lower limit of age, 20 years old is set as the age to participate in clinical trial by self-responsibility (the legal age of consent is 20 years old in Taiwan and Japan). Upper limit 65 years old is set because elderly patients tend to be poor in compliance and have poor skin quality.

2. Maximum size of DSW, 100 cm^2, is set by the standard of the investigational product, and a minimum size of 15 cm^2 is set considering that smaller DSW can heal easily and the existing standard treatment is sufficient. Minimum width of 3 cm is defined based on commonly medical appliance used for DSW creation. The thickness (0.010 - 0.012 inches) of the split skin grafting is defined based on clinical practice. And then, to minimize the complexity of safety and efficacy evaluation, the skin graft should be obtained from the area that has no previous use for skin graft.

3. To ensure the safety of patients, only mild burn patient (total burn surface area less than 15%) can be considered for recruitment

4-5. The criteria are to ensure the safety of patients, patient's partners, fetuses and infants.

6. It is to confirm that the patient complies with this study protocol.

3.3 Exclusion Criteria

Any patient meeting any of the exclusion criteria will be excluded from study participation.

1. Female patients who are pregnant or lactating or planning a pregnancy and any male patient whose partner (wife) planning a pregnancy from signing informed consent to 30 days after the last dose administration.
2. Clinically significant disease or condition that may compromise graft taken and/or donor site healing (e.g. the presence of a bleeding disorder, capillary fragility, venous or arterial disorder directly affecting the donor site to be treated, known or suspected systemic malignancies, human immunodeficiency virus infection, renal or liver disease, uncontrolled diabetes mellitus, thrombocytopenia, vasculitis, poor nutritional status).
3. Patients who are currently receiving or have received the following treatments within 4 weeks prior to Screening Visit are excluded from the study:
   a) systemic, or inhaled corticosteroids or immunosuppressant agents; or
   b) therapeutic doses of anticoagulants (e.g. Coumadin, Heparin, low molecular weight Heparin) for pre-existing medical conditions, for whom a dose interruption from Screening through the end of the study period is contraindicated.
4. Autoimmune disease, e.g. lupus erythematosus, multiple sclerosis.
5. Hematologic disease, malignancy or hypo-immunity.
6. History of HIV or congenital immunodeficiency.

Note: HIV = human immunodeficiency virus

7. History of alcoholism or drug abuse.
8. Have used any tobacco product within 1 week prior to Day 0.
9. Patients previously treated with any cell-based product, including autologous tissue at the treatment site.

10. Received an investigational drug, device or biological/bioactive treatment within 30 days prior to Screening Visit.
11. Any clinical condition or significant concurrent disease judged by the investigator to complicate the evaluation of the trial treatment.
12. History of sensitivity to bovine or porcine origin of materials, or human serum albumin.
13. DSWs located in the face, over joints, lower legs or the buttocks
14. Any of the following hematologic abnormalities:
    a. Hemoglobin < 10.0 g/dL
    b. ANC < 1,500/μL,
    c. Platelets < 75,000 /μL
15. Any of the following serum chemistry abnormalities:
    a. Total bilirubin > 1.5 × ULN,
    b. AST or ALT > 3 × ULN,
    c. γ-GT > 2.5 x ULN,
    d. Alk-P > 2.5 x ULN,
    e. Serum albumin < 2.7 g/dL,
    f. Creatinine >1.5 x ULN
    g. Any other ≥ Grade 2 laboratory abnormality (based on CTCAE) at baseline (other than those listed above)
16. DSWs in area with active skin infection or with skin condition that is considered highly susceptible to infection judged by the investigator

Note: The rationale for the exclusion criteria is described as below.

1. It is to ensure the safety of patients, patient's partners, fetuses and infants.

2-7., 12., 14-15. Criteria are set to ensure the safety of patients due to the potential increased chance of infection, prolonged wound closure, immunological over-reaction, or other complications resulted from these conditions.

3., 5-8. These conditions and habits may affect the efficacy evaluation of investigational product.

9-11., 16. Those are to minimize the complexity of safety and efficacy evaluation.

13. DSW located on face is excluded with ethical consideration. Other locations are excluded to minimize the complexity of safety and efficacy evaluation.

3.4 Withdrawal Criteria

Patients may be withdrawn from the trial due to any of the following conditions:

1. The patient decides to withdraw her/his informed consent form.
2. Investigator considers that the patient is no longer physically and/or psychologically feasible to remain in the study.
3. The patient refuses to proceed with critical measures for the study endpoints, defined as all variables required for primary endpoint evaluation.
4. The patient has lost to follow-up

The reasons for discontinuation must be recorded in the Case Report Form (CRF) and in the patient's medical records for all early terminated cases. All study participants withdrawn from the study before Day 28 will finish assessments of Visit 7 (Day 28), except the application and dispensation of Tegaderm™. If the patient has received Tegaderm™ from the visit before withdrawal, the return of Tegaderm™ should be made. For patients who have initially scheduled Day 42 visit but make the decision between Day 28 to Day 42 to withdraw from the study, he/she should be encouraged to complete assessments planned for Day 42 visit at the earliest date convenient for the

patients. If patients have entered the long-term follow-up period (i.e. after Day 28 or Day 42 if scheduled) and the decision of withdrawal is confirmed, effort must be made to understand and record the reason of withdrawal. If a patient is discontinued due to an AE, every effort will be made to follow the event until resolution.

3.5 Patient Replacement

All patients who drop out of the study will not be replaced. New patients will be screened with a newly assigned patient number until the target evaluable patients are reached in this study.

3.6 Concomitant Treatments

All medications and supplements taken by the study participant beginning four weeks prior to Screening Visit till Visit 8 will be recorded on the appropriate page of the Case Report Form (CRF). This record will include the name of the medication, frequency, unit dose, dates of the drug was started and stopped, and the indication for the use of the drug.

Patients are allowed to receive routinely used medications or treatments for other indications which is judged by the investigator as not affecting the efficacy and safety assessments of this study.

- Prohibited Medications/Treatment

a) systemic, or inhaled corticosteroids or immunosuppressant, chemotherapeutic agents

b) therapeutic doses of anticoagulants (e.g. Coumadin, Heparin, low molecular weight Heparin)

c) Any treatment/therapy applied to wound area that may affect the efficacy evaluation of study medication at the investigator's discretion

d) Any treatments containing povidone-iodine, chlorhexidine, polymyxin and mycostatin, for DSW.

4. STUDY DESIGN

This study will be designed in a Phase I/II randomized, double-blind, additional evaluator-blind, placebo-controlled, multi-center, multi-nation (Taiwan and Japan), parallel manner. This study is to evaluate the safety and efficacy of the TWB-103 in adult patients with split-thickness skin graft donor site wounds (DSW). The study will recruit 30 evaluable patients, approximately up to 36 patients to be recruited to complete a total of 30 evaluable patients. Eligible patients will be randomly assigned in 1:1 ratio to one of the following groups:

Treatment Group:

TWB-103 add-on Tegaderm™ till 100% re-epithelialization or up to 10 days, whichever comes first, followed by Tegaderm™ alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10. If 100% re-epithelialization is not observed on Day 14 (the end of treatment), patients will have application of Tegaderm™ up to Day 28.

Control Group:

Placebo+Tegaderm™ till 100% re-epithelialization or up to 10 days, whichever comes first, followed by Tegaderm™ alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10. If 100% re-epithelialization is not observed on Day 14 (the end of treatment), patients will have application of Tegaderm™ up to Day 28.

Note:

1. Tegaderm™ will be renewed at each visit between Visit 3 (Day 3) to Visit 7 (Day 28) if 100% re-epithelialization is not observed. Whenever Tegaderm™ falls off from DSW site, new Tegaderm™ should be applied immediately. If necessary, drainage is allowed, but re-application of TWB-103 or placebo is not necessary in this case.

2. If the first 100% re-epithelialization is observed on Day 28, patients will be scheduled Day 42 follow-up and dispensed with Tegaderm™.

3. If the first 100% re-epithelialization is not observed on Day 28, patients will receive the application of Tegaderm™ on site for protection of wound site and/or have other appropriate treatment at the investigator's discretion. The DSWs will be followed till 100% re-epithelialization.

4. To prevent the itchiness and skin reaction caused by the long-term usage of Tegaderm™, Vaseline Gauze or Non-Stick Gauze such as silastic foam dressings can be used on and after Day 14 at the investigator's discretion.

In Phase I proportion, eligible patients will be recruited sequentially with one week staggering in the initiation of study treatment. Eligible patients will also be randomized into 1:1 ratio into one of Treatment (TWB-103+Tegaderm™) and Control (placebo+Tegaderm™) groups. Phase I plan to recruit 3 evaluable TWB-103+Tegaderm™ treated and 3 evaluable placebo+Tegaderm™ treated patients. Patients in phase I are considered as evaluable when (1) he/she receives at least one dose and has follow-up evaluation at least 14 days after first dose or (2) he/she receives at least one dose and has early withdrawn due to safety reasons before Day 28. When all of those 6 evaluable patients complete the planned treatment period (14 days or till first 100% re-epithelialization, which comes first), the recruitment of patients will be temporarily stopped for 14 days for safety observation. The safety data of TWB-103 before and on Day 28 Visit will be reviewed by the sponsor and the principal investigator. If no safety issue of TWB-103 is decided, the study will enter Phase II portion and eligible patients will be randomized into 1:1 ratio into one of Treatment and Control groups.

Each patient will have treatment for up to 14 days or to the day of 100% re-epithelialization, whichever comes first. Patients assigned to the Treatment Group will receive TWB-103 add-on Tegaderm™ till 100% re-epithelialization or up to 10 days,

whichever comes first and will receive Tegaderm™ alone from Day 10 to Day 14 if re-epithelialization can not be attained by Day 10. Patients assigned to the Control Group will receive placebo+Tegaderm™ till 100% re-epithelialization or up to 10 days, whichever comes first and will receive Tegaderm™ alone from Day 10 to Day 14 if re-epithelialization can not be attained by Day 10. Patients from either group (treatment or control) will have application of Tegaderm™ alone up to Day 28 if 100% re-epithelialization of DSWs is not observed on Day 14 (end of treatment).

Patients will be required to attend scheduled visits at Screening, Day 0 (treatment start day), Day 3, Day 7, Day 10, Day 14 (end of treatment). In case patients achieve 100% re-epithelialization before or at Day 10, patients will finish up the assessments on the day with 100% re-epithelialization. This day of 100% re-epithelialization will be the end of treatment and the remaining scheduled treatment visits, if applicable, will be dismissed.

All subjects are scheduled to attend a follow-up visit on Day 28 to evaluate the status of the target wound and then enter a 360-day follow-up phase. If the complete wound closure occurs by Day 14, the re-confirmation of wound closure should be performed on Day 28 follow-up. In the case that complete wound closure occurs at some point between Day14 and Day 28, an additional follow-up visit will be scheduled on Day 42 for the re-confirmation before subject enters the 360-day follow-up phase. If the complete wound closure is not observed on Day 28, patients will have other appropriate treatment at the investigator's discretion. The DSWs will be followed till 100% re-epithelialization.

During the 360-day follow-up, four follow-up visits will be scheduled at 90±14 days, 180±14 days, 270±14 days and 360±14 days following the subject's Day 28 visit (if no

Day 42 visit) or Day 42 visit. In total, 5~6 follow-up visits will be scheduled in this study for all randomized subjects.

4.1 Treatment Assignment

Eligible patients will be assigned a randomization number in sequential order and each of the randomization will determine the allocation of one of the two groups in 1:1 ratio as shown below:

Treatment Group:

TWB-103 add-on Tegaderm™ till 100% re-epithelialization or up to 10 days, whichever comes first, followed by Tegaderm™ alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10. If 100% re-epithelialization is not observed on Day 14 (the end of treatment), patients will have application of Tegaderm™ up to Day 28.

Control Group:

Placebo+Tegaderm™ till 100% re-epithelialization or up to 10 days, whichever comes first, followed by Tegaderm™ alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10. If 100% re-epithelialization is not observed on Day 14 (the end of treatment), patients will have application of Tegaderm™ up to Day 28.

Note:

1.Tegaderm™ will be renewed at each visit between Visit 3 (Day 3) to Visit 7 (Day 28) if 100% re-epithelialization is not observed. Whenever Tegaderm™ falls off from DSW site, new Tegaderm™ should be applied immediately. If necessary, drainage is allowed, but re-application of TWB-103 or placebo is not necessary in this case.

2. If the first 100% re-epithelialization is observed on Day 28, patients will be scheduled Day 42 follow-up and dispensed with Tegaderm™.

3. If the first 100% re-epithelialization is not observed on Day 28, patients will receive the application of Tegaderm™ on site for protection of wound site and/or have other appropriate treatment at the investigator's discretion. The DSWs will be followed till 100% re-epithelialization.

4. To prevent the itchiness and skin reaction caused by the long-term usage of Tegaderm™, Vaseline Gauze or Non-Stick Gauze such as silastic foam dressings can be used on and after Day 14 at the investigator's discretion.

4.2 Randomization and Blinding

Permuted block randomization method stratified by site will be applied to generate randomization codes, detailed in the randomization plan. Each randomization number will be assigned to individual patients according to the time-sequence for screened patient becoming eligible.

Blinding to patients and the investigator will be performed in this study. Besides, the evaluator blinding on wound healing evaluation will also be performed that an additional evaluator who is not aware of the treatment given will assess based on the photos of the wound. A second additional evaluator, who is also blinded, will be requested when the discrepancy occurs between the investigator and the first additional evaluator in the determination of 100% re-epithelialization.

At the initiation of the study, the study center will be instructed on the method for breaking the blind. The emergency key (individual random code envelope) will be kept by the investigator. Study drug treatment may be revealed only for reasons relating to the subject's safety and when critical therapeutic decisions are contingent on knowing the assigned study drug, including conditions listed in Section 4.3.1 and 4.3.2. Withdrawal of a subject from the study is not a sufficient reason to break the blind.

The reason to break the blind must be discussed with the Sponsor prior to breaking the blind. Investigator can request this by using the "Emergency Key Open Request Form" and sending it to the sponsor's representative with the rationale described. After receiving authorization for unblinding from the Sponsor, the investigator will acknowledge with his/her signature and the date on the Emergency Key envelope, then open to unblind the specific subject's treatment assignment. When the blinding code is broken, the reason must be fully documented as a written entry in the source document.

Key information will be recorded in the "Emergency Key Open Request Form", including the subject number, the date the blind was broken, the rationale, the person who requested the breaking of the blind, and the signatures of the Sponsor representative contacted, and the person who broke the blind. The incidence of blind broken should be documented in the subject's case report form (CRF), but no emergency key should be revealed.

4.3 Stopping rules and unscheduled visits

4.3.1 Stop the study

The study will be stopped when > 1/3 of patients in the phase I have developed study drug related grade 2 or above SAEs defined as in Section 8. The investigator will determine if SAEs are study drug related without breaking the blind. If the cause of SAE is inconclusive, the investigator can request to break the blind following the procedure stated in Section 4.2.

4.3.2 Discontinue the study product

Patients who experience > Grade 2 skin allergic reaction or > Grade 2 systemic allergic reaction related to the product or placebo must not receive any further TWB-

103 or placebo treatment. If a patient should develop infection at DSW site before Day 10, he/she will stop the TWB-103 or placebo application at the investigator's discretion. Patients with the aforementioned conditions, before or at Visit 8, should finish the scheduled assessments (except that application of TWB-103/placebo is stopped; that the application and dispensation of Tegaderm™ will be at the investigator's discretion; and that the return of Tegaderm™ will be asked if applicable). Patients with allergic reaction or infection may receive appropriate treatments at the PI's discretion, will be monitored throughout the healing process (including the recovery from allergic reaction or infection, and the complete closure of DSW) and will continue the remaining visits (application of TWB-103 or placebo will be stopped if planned originally). In these cases of TWB-103/placebo discontinuation, wound assessments performed after onset of allergic reaction or infection will be excluded from statistical analysis.

4.3.3 Withdraw from the study

Patients may be withdrawn from the study voluntarily or at the investigator's discretion. Refer to Section 3.4 for details.

4.3.4 Unscheduled visits

Unscheduled visits can be requested when patients require the investigator's medical attention, e.g. the reopen of DSW but self-care is insufficient, infection, or allergic reaction. Patients should finish the assessments of Day 14 (except that the completion of hemogram and serum biochemistry as well as the application and dispensation of Tegaderm™ will be at the investigator's discretion; and that the return of Tegaderm™ is not required) during the unscheduled visit. Patients will resume the original planned visits and/or come in additional unscheduled visits at the

investigator's discretion. The option to choose Vaseline Gauze or Non-Stick Gauze such as silastic foam dressings only can be selected on or after Day 14.

5. TRIAL MATERIALS

5.1 Trial Product (s)

TWB-103 is supplied as a two-component therapeutics consisting of one vial of living allogeneic fibroblasts and one vial of gelatin-based hydrogel. The two components are stored separately as the cells need to stay frozen in a -80^{o}C freezer (with temperature not higher than -70^{o}C) and the hydrogel will require a proper storage in a 4^{o}C refrigerator (with temperature at 2~6^{o}C). The cell vial and placebo vial can be stored approximately up to six months after receiving. The expiration date of IP is printed on the label attached to the package of IP as well as the data sheet companying with IP.

5.2 Dosage and Administration

Patients who meet all eligibility requirements for entry into the study will be randomized into one of the treatment group or control group in 1:1 ratio as shown below:

Treatment Group:

TWB-103 add-on Tegaderm^{TM} till 100% re-epithelialization or up to 10 days, whichever comes first, followed by Tegaderm^{TM} alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10. If 100% re-epithelialization is not observed on Day 14 (the end of treatment), patients will have application of Tegaderm^{TM} up to Day 28.

Control Group:

Placebo+Tegaderm^{TM} till 100% re-epithelialization or up to 10 days, whichever comes first, followed by Tegaderm^{TM} alone application from Day 10 to Day 14 if failing to achieve 100% re-epithelialization by Day 10. If 100% re-epithelialization is not

observed on Day 14 (the end of treatment), patients will have application of Tegaderm™ up to Day 28.

Note:

1.Tegaderm™ will be renewed at each visit between Visit 3 (Day 3) to Visit 7 (Day 28) if 100% re-epithelialization is not observed. Whenever Tegaderm™ falls off from DSW site, new Tegaderm™ should be applied immediately. If necessary, drainage is allowed, but re-application of TWB-103 or placebo is not necessary in this case.

2. If the first 100% re-epithelialization is observed on Day 28, patients will be scheduled Day 42 follow-up and dispensed with Tegaderm™.

3. If the first 100% re-epithelialization is not observed on Day 28, patients will receive the application of Tegaderm™ on site for protection of wound site and/or have other appropriate treatment at the investigator's discretion. The DSWs will be followed till 100% re-epithelialization.

4. To prevent the itchiness and skin reaction caused by the long-term usage of Tegaderm™, Vaseline Gauze or Non-Stick Gauze such as silastic foam dressings can be used on and after Day 14 at the investigator's discretion.

After the creation of DSW (Day 0), the wound site will be covered with gauze containing epinephrine solution (1:100000) for a few minutes and then TWB-103+Tegaderm™ or placebo+Tegaderm™ will be applied to DSW site immediately after. Bipolar electrocautery can be used to stop bleeding in some spots if bleeding continues after applying epinephrine and compression for 15 minutes. Dressing will be changed every 3~4 days (on Day 3, 7, and 10) following the procedure stated below.

(1) Remove the Tegaderm™. The wound is properly cleaned by gentle wiping with gauze pad or cotton swab wetted with normal saline or by rinsing the wound with normal saline. The wound is then touched with dry gauze pad or cotton swab to remove excessive fluid or moisture.

(2) Perform wound assessment.

(3) Thaw TWB-102 Cells (the treatment group) or freezing solution (control group) at 37°C water bath for 60~80 seconds.

(4) Taking 0.4 mL cells (the treatment group) or freezing solution (control group) mixed with 4.6 ml gel hydrogel (pre-melted 37°C water bath for ~20 minutes) in one syringe.

(5) The final mixture will be applied to the target wounds (0.05 mL mixture/cm^2 wound).

(6) Cover the wound area with Tegaderm™.

5.3 Package and Labeling

The investigational product (IP) will be packaged in vials for each administration. All vials will be labeled for study number, vial identifier, prescription instructions, the investigator's name, storage conditions, expiry date, and the descriptions of "Clinical trial use only" and "Keep out of the reach of children".

5.4 Storage and Drug Accountability

The IP shipping is to be arranged by the Sponsor to the study site and to be handled by the investigator or the designated pharmacist for management and administration. The two components are stored separately as the cells need to stay frozen in a -80°C freezer and the hydrogel will require a proper storage at 2~6°C. TWB-103/placebo can be stored up to six months before clinical application.

5.5 Product Accountability

All patients are administered IP or control material at the clinical site (Visit 2~4). All of the unused IP and control material will be asked to be destroyed on site or returned from the clinical site to the sponsor. Each IP and control material shipped, used, and

returned will be recorded with a date in order to keep track of the IP and control material in precise details.

5.6 Assessment of Compliance

The IP or control material will be administered at the study site at scheduled visits (Visit 2~4). Patient compliance should not be a severe issue. However, the study monitor will assure the patient's compliance with the study protocol.

5.7 Treatment for Investigational Product Overdose

Product overdose will not be of concern as the dosing regimen of TWB-103/placebo in this study is to be administered at the site by site medical staff and believed to be safe. If over dosage should occur, the patient or the person in charge of caring for the patient should contact the investigator as early to determine if any immediate medical treatment is needed. The patient should also be arranged as soon as possible for evaluation before any further IP treatment can be proceeded. This post-overdose visit can be an un-scheduled or a regular study visit. The study monitor appointed by the sponsor should be contacted by the investigator of any over-dose report as soon as being aware of the event. Any unfavorable effects caused by the overdose event must be reported as an AE and even SAE.

5.8 Other Consideration for Investigational Product

Because nicotine interferes the wound closure, smoking is not allowed from one week prior to Day 0 till Day 14.

6. STUDY ASSESSMENTS

6.1 Informed Consent

All patients must provide signed informed consent at the Screening visit, prior to any study-related procedures. Only the institutional review board (IRB) approved informed consent form can be used.

6.2 Demographics

Demographic data, including age, gender, weight and height information will be obtained at the Screening visit.

6.3 Pregnancy Test and Contraception

Patient with childbearing potential must be confirmed of not being pregnant at the Screening visit. The pregnancy test should be done at the screening visit, which is within 2 weeks prior the DSW creation and the treatment. Both male and female patients should also be informed that defined contraceptive methods must be used from signing informed consent to 30 days after the last dose administration.

Acceptable contraceptive forms include:

a. Established use of oral, injected or implanted hormonal methods of contraception

b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

c. Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps)

6.4 Eligibility

Eligibility should be thoroughly checked by the investigator at Screening Visit. See Sections 3.2 and 3.3 for detailed eligibility criteria.

6.5 Physical Examinations

The patient will be examined at each scheduled visit by standard physical examination items including general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, other body systems if applicable for describing the status of the patient's health.

6.6 Medication History

Previous medications are categorized into therapies relevant or not related to cutaneous wound/ulcer at the Screening Visit. The cutaneous wound/ulcer-irrelevant therapy should only be recorded up to 4 weeks before study entry. The cutaneous wound/ulcer therapy (all kinds of modality) should be recorded for at least 3 months prior to Screening Visit.

6.7 Medical History

The general medical history up to 3 months of study entry should be recorded at the Screening Visit. The medical history should include procedural within a 1 year time and major surgical history for the life time base. The history of cutaneous wound/ulcer for the coming DSW creation will be recorded in the "cutaneous wound/ulcer history" part of the CRF, separately. Medical history and cutaneous wound/ulcer history will include date of onset, location, and diagnosis, prior therapies, and current status. The cutaneous wound/ulcer history should be recorded for lifetime of the patient.

6.8 Vital Signs

Patient will be measured of blood pressures, pulse rate and body temperature at all scheduled visits.

6.9 Hematologic and Biochemical Indexes

The hematologic and biochemical indexes will be measured at Visit 1~8. For Visit 2, the hematologic and biochemical tests conducted within 7 days prior to Day 0 are acceptable. The items to be measured include the following:

Hematology: hemoglobin, hematocrit, Red blood cell (RBC), platelet, White blood cell (WBC) with differential counts, Absolute neutrophil count (ANC)

Biochemistry: aspartate transaminase (AST), alanine transaminase (ALT), serum creatinine, blood urea nitrogen (BUN), albumin, total bilirubin, gamma-glutamyl transferase (γ-GT), alkaline phosphatase (Alk-P)

6.10 Investigational Product

Investigational drugs will be administered to eligible patients at Visit 2~4, starting with the Administration visit (Day 0). Drug accountability and inventory will be recorded in the CRFs and the relevant study log.

6.11 Wound assessment

The wound assessment will be measured at all scheduled visits except the Screening Visit.

From Visit 2 (Day 0) to Visit 8 (Day 42), the investigator will determine the end of treatment based on the healing progress. Wound healing will be assessed based on the wound observation by the investigator and an additional evaluator. An additional evaluator who is not aware of the treatment given will evaluate based on photos of the wound. The additional evaluator will receive photos of the wound from CRO and will return the assessment to CRO. A second additional evaluator, who is also blinded, will

be requested when the discrepancy occurs between investigator and the first additional evaluator in the determination of 100% re-epithelialization.

The photos of wound will be taken under the following guidelines.

(a) Cameras and rulers with the same brand and model will be used throughout the study.

(b) The study staff who are trained will be in charge of taking photos following the guidelines for each study center.

(c) Two different photos will be taken for each wound at each visit: one for the calculation of wound healing and the other as the reference of the wound location relative to the body part.

(d) The wound area shown in the photo specific for calculation purpose, along with the provided ruler, should have sufficient size and quality for evaluation.

(e) Images will be processed by the software, Image J.

(f) The investigator and evaluator(s) will select the boundary of said wound in the photo manually and by the wand tool in Image J.

(g) Calculate the wound size by Image J based on the area selected.

(h) The healing percentage of wounds will be calculated by the ratio of healing area and original area (Day 0).

Complete wound closure is defined as skin 100% re-epithelialization without drainage or dressing requirements. Wound closure should be re-confirmed on Day 28 when the complete wound closure occurs by Day 14, or on Day 42 in the case that complete wound closure occurs at some point between Day14 and Day 28.

During the 360 days of follow-up (Visit 9~12), recording of 100% re-epithelialization and the area of target wound are not required. Instead, potential long-term adverse

events will be determined and recorded, including scar assessment (Vancouver Scar Scale and if necessary, additional comments on scar elasticity, scar color and pigmentation), skin texture (relationship to surrounding skin, texture, margins, size and multiplicity), pain assessment (see section 6.12) and any altered sensations.

6.12 Pain assessment

The pain assessment will be measured by employing short-form McGill pain questionnaire and will be performed at all scheduled visits, expect Visit 2 (Day 0), starting from the Screening visit. Patients should evaluate pain level at the (future) DSW site.

6.13 Exit of Study

The patient should complete the last follow-up (Visit 12) before exiting from the study, regardless of the treatment groups and the wound healing outcome.

6.14 Panel reactive antibodies (PRA) test

All patients (Phase I + Phase II) will be tested with Class I HLA on Day 0 and Day 28. The same testing kit should be employed for all labs. For Visit 2, the PRA test conducted within 7 days prior to Day 0 is acceptable.

Note: HLA = Human leukocyte antigen

6.15 Tegaderm™ dispensing and return

The size of Tegaderm™ to be used for each patient will be determined by the investigator based on the size of DSW. Sufficient amount of Tegaderm™ will be dispensed to patients. The amount of Tegaderm™ dispensed should be adequate for patient's use till next visit. Patients are advised to apply Tegaderm™ to DSW site if the wound open remains or reappears, and to re-apply new Tegaderm™ every 2~3

days till next visit or wound closure. Whenever Tegaderm™ falls off from DSW site, new Tegaderm™ should be applied immediately. Unused Tegaderm™ will be returned to the clinical site at the next visit. Re-dispensing of unused Tegaderm™ to the same patient is allowed when the primary package of Tegaderm™ remains intact.

Tegaderm™ will be dispensed to patients from Visit 2 (Day 0) to Visit 7 (Day 28). However, at Visit 7 (Day 28), Tegaderm™ is dispensed only when Visit 8 (Day 42) is scheduled. To prevent the itchiness and skin reaction caused by the long-term usage of Tegaderm™, Vaseline Gauze or Non-Stick Gauze such as silastic foam dressings can be used on and after Day 14 at the investigator's discretion.

7. STUDY SCHEDULE

7.1 Screening visit

(Visit 1: within 2 weeks prior to DSW creation)

- Explain the nature of the study and have patients to read and sign an Informed Consent Form
- Assign patient screening number
- Obtain demographic characteristics
- Obtain medical history
- Obtain vital signs
- Perform physical examinations
- Perform pregnancy test for applicable patients
- Obtain blood samples for hemogram and biochemical tests
- Screen patients for inclusion/exclusion criteria
- Pain questionnaire
- Record adverse events
- Record prior/concomitant treatments
- Randomization (before DSW creation but after all baseline procedures are completed and the subject has been deemed eligible for the study)

7.2 Administration Visit

(Visit 2: Day 0)

Before DSW creation

- Perform physical examinations
- Obtain vital signs
- Obtain blood samples for hemogram and biochemical tests (the hematologic and biochemical tests conducted within 7 days prior to Day 0 are acceptable)
- Obtain blood samples for PRA test (the PRA test conducted within 7 days prior to Day 0 is acceptable)

After DSW creation

- Wound assessment (including the thickness of DSW)
- Apply study medications (treatment group: TWB-103+ Tegaderm™; control group: placebo+Tegaderm™)
- Dispense Tegaderm™ to patients
- Record adverse events
- Record concomitant treatments

7.3 Evaluation Visits

7.3.1 Visit 3: Day 3 ± 1 day

- Perform physical examinations
- Obtain vital signs
- Obtain blood samples for hemogram and biochemical tests
- Pain questionnaire
- Wound assessment

- Apply study medications (if not 100% re-epithelialization. Treatment group: TWB-103+ Tegaderm™; control group: placebo+Tegaderm™)
- Dispense Tegaderm™ to patients
- Return unused Tegaderm™ (if received at previous visit)
- Record adverse events
- Record concomitant treatments

7.3.2 Visit 4: Day 7 ± 1 day

- Perform physical examinations
- Obtain vital signs
- Obtain blood samples for hemogram and biochemical tests
- Pain questionnaire
- Wound assessment
- Apply study medications (if not 100% re-epithelialization. Treatment group: TWB-103+ Tegaderm™; control group: placebo+Tegaderm™)
- Dispense Tegaderm™ to patients
- Return unused Tegaderm™ (if received at previous visit)
- Record adverse events
- Record concomitant treatments

7.3.3 Visit 5: Day 10 ± 1 day

- Perform physical examinations
- Obtain vital signs

- Obtain blood samples for hemogram and biochemical tests
- Pain questionnaire
- Wound assessment
- Apply Tegaderm™ (if not 100% re-epithelialization, for both treatment and control group)
- Dispense Tegaderm™ to patients
- Return unused Tegaderm™
- Record adverse events
- Record concomitant treatments

7.4 The end of treatment visit

(Visit 6: Day 14 days ± 2 days)

- Perform physical examinations
- Obtain vital signs
- Obtain blood samples for hemogram and biochemical tests
- Pain questionnaire
- Wound assessment
- Apply Tegaderm™, Vaseline Gauze or Non-Stick Gauze (if not 100% re-epithelialization, for both treatment and control group)
- Dispense Tegaderm™, Vaseline Gauze or Non-Stick Gauze to patients
- Return unused Tegaderm™
- Record adverse events

- Record concomitant treatments

7.5 Follow-up visits

7.5.1 Visit 7: Day 28 ± 3 days

- Perform physical examinations
- Obtain vital signs
- Obtain blood samples for hemogram and biochemical tests
- Obtain blood samples for PRA test
- Pain questionnaire
- Wound assessment
- Apply Tegaderm™, Vaseline Gauze or Non-Stick Gauze (if not 100% re-epithelialization, for both treatment and control group)
- Dispense Tegaderm™, Vaseline Gauze or Non-Stick Gauze to patients (only for patients who have Day 42 Visit)
- Return unused Tegaderm™, Vaseline Gauze or Non-Stick Gauze
- Record adverse events
- Record concomitant treatments

7.5.2 Visit 8: Day 42 ± 3 days

(Only scheduled when the wound closure is not completed by Day14 but is observed on Day 28)

- Perform physical examinations
- Obtain vital signs

- Obtain blood samples for hemogram and biochemical tests
- Pain questionnaire
- Wound assessment
- Return unused Tegaderm™, Vaseline Gauze or Non-Stick Gauze
- Record adverse events
- Record concomitant treatments

7.5.3 Visit 9~12 (90, 180, 270, 360 days ± 14 days after Visit 7 (if no visit 8) or Visit 8)

- Perform physical examinations
- Obtain vital signs
- Pain questionnaire
- Wound assessment (scar assessment, skin texture and any altered sensations, see details in section 6.11)
- Record adverse events (only TWB-103/placebo-relative and DSWs-relative adverse events will be recorded)
- Exit of study (Visit 12)

8. ADVERSE EVENTS

8.1 Definitions

- Adverse Event (AE):

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a study medication and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study medication, whether or not related to the study medication. Laboratory abnormalities should not be recorded as AEs unless determined to be clinically significant by the Investigator.

- Expected AE:

Expected AE are defined as any event, the specificity or severity of which is consistent with the current investigator brochure.

- Unexpected AE:

Unexpected AE is defined as any event, the specificity or severity of which is not consistent with the current investigator brochure. "Unexpected", as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

- Serious Adverse Event (SAE):

Serious Adverse Event (SAE): A Serious Adverse Event is defined as an AE meeting one of the following conditions:

- Death during the period of protocol defined surveillance
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.2 AE/SAE Intensity and Relationship Assignment

- AE/SAE Intensity

The investigator must rate the intensity for all AEs that occur during the study using the grades based on CTCAE (v4.03) provided below:

- Grade 1 (Mild):

  Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2 (Moderate):

  Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

- Grade 3 (Severe or medically significant but not immediately life-threatening):

  Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

- Grade 4 (Life threatening consequences):

  Urgent intervention indicated.

- Grade 5 (Death related to AE)

  Note: Activities of Daily Living (ADL)

  *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

  **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Adverse events observed during the study will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by dose level and overall by System/Organ/Class (SOC) classified in MedDRA as appropriate.

- AE/SAE Relationship Assessment

The investigator will be asked to assess all AEs with respect to their causal relationship to the study drug according to the following classification:

- Definitely Related

  There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study

agent/intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study agent/intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- Probably Related

  There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study agent/intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Possibly Related

  There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possible" soon after discovery, it can be flagged as requiring more information and later be upgraded to probable or certain as appropriate.

- Unlikely

  A clinical event, including an abnormal laboratory test result, whose temporal relationship to study agent/intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time

after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

- Not related

The AE is completely independent of study agent/intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician Expected Events Related to Disease Process: Provide explicit definitions of the type(s), grade(s), and duration(s) of adverse event(s) that will be considered disease related.

8.3 Collecting, Recording and Reporting of Adverse Events

8.3.1 Collecting and Reporting of AE

AEs may be volunteered spontaneously by the study subject, discovered as a result of general questioning by the study staff, or determined by physical examination. All AEs will be recorded on the CRF. For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. AEs should be reported starting from signing ICF to the end of study (Visit 12) or to the last visit patients finish before withdrawal. Follow-up of the AE, even after the date of study drug discontinuation, is required if the AE persists. The study subject will be followed until the event resolves or stabilizes at a level acceptable to the investigator.

8.3.2 Reporting of SAE

Serious, alarming and/or unusual adverse events must be reported to the sponsor/CRO contact within 24 hours of the investigator's knowledge of the event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

The investigator is responsible to communicate details of medical emergencies in trial subjects to the Ethics Committee. Reporting of adverse events will comply with US federal regulations, Japanese regulations and Taiwanese regulations for IND safety reporting. Sponsor/CRO is responsible to inform the events to FDA, PMDA and TFDA.

Fatal or life-threatening, suspected unexpected ADRs should be notified to Local ADR Reporting Center by sponsor/CRO as soon as possible, but no later than 7 calendar days, after first acknowledged by the sponsor, and a complete report should be followed 8 additional calendar days. This report must include an assessment of the importance and implication of the findings and/or previous experience on the same or similar medical products. Serious, unexpected ADRs that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first acknowledged by the investigator that a case qualifies.

The information which sponsor/CRO evaluates as threatening the safety of the subject and having impact on the ongoing study should be urgently (as soon as possible and within 1 business day following the information receipt date) transmitted to the investigators/trial sites via e-mail, etc. from the study monitor or person responsible for monitoring out of the safety information to be reported to the regulatory authority. In unexpected serious adverse events to be reported to the regulatory authority, the information which sponsor/CRO considers to be highly emergent safety information (per case) should be transmitted to the investigators/trial sites within 30 days following the information receipt date. Other serious events to be reported to the regulatory authority should be transmitted to the investigators/trial sites as monthly periodic report or annual report within 30 days following the transmission request date via e-mail, etc. from the study monitor or person responsible for monitoring.

8.3.3 Reporting of Pregnancy

Any patient or patient's partner who becomes pregnant during the treatment period should be recorded and the information regarding this pregnancy should be collected. Any pregnancy occurs during the 30 days following the last dose of investigational product should also be reported and accompanied information should also be collected. When female patient or male patient's partner suspects a pregnancy during the treatment period or within 30 days of the last dose, a pregnancy test should be conducted. Once pregnancy is confirmed, the patient should stop the administration of investigation product

immediately, if patient is still during the treatment period. The pregnancy should be reported to the sponsor using the pregnancy report form. The Obstetrician/Gynecologist of the female patient or male patient's partner should be notified the trial information. Because information of specific tests regarding this investigational product is not clear yet, whenever possible, a pregnancy should be followed to term or to any premature terminations reported. Additionally, the status of the mother and child should be reported to the sponsor after delivery. Although pregnancy occurring during the trial is not considered as an adverse event, any pregnancy complications should be recorded as AEs or SAEs.

9. DATA ANALYSIS

9.1 Data Quality Assurance

The PI/CRO will provide paper CRFs or electronic CRFs (via EDC system) for the recording and collection of subject data and for the collection of data. All CRFs will be completed as soon as possible after the subject's visit. Corrections to data on the CRFs will be documented or traced. The investigator will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the investigator will need to again sign the investigator signature page or approve electronically. Designated source documents will be signed and dated by the appropriate study personnel.

9.2 Clinical Data Management

The investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

The sponsor/CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the sponsor/CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines and the sponsor/CRO's SOPs as well as provisions of the study-specific Data Management Plan if any.

10. SAMPLE SIZE AND STATISTICAL METHODS

10.1 Determination of Sample Size

The target number will be up to 30 evaluable subjects. Approximately up to 36 patients will be recruited and to complete a total of 30 evaluable patients. In this study, evaluable population will be per-protocol (PP) population defined in Section 10.2. The determination of sample size is arbitrary as there is no historical data can be referred.

10.2 Statistical and Analytical Plans

10.2.1 Analysis Population

Two populations will be introduced for statistical analysis:

Intent-to-treat (ITT) population:

- Patients randomized
- Patients ever treated by at least one dose of trial medication
- Patients with any post-treatment evaluation

Per-protocol (PP) population:

- Dosed with planned dosing regimen of investigational product
- With efficacy endpoint measurement at wound assessment (with first 100% re-epithelialization or complete Day 14 visit evaluation)
- Fulfilling all inclusion and exclusion criteria
- Without taking prohibited medication

Since the dosing regimen designed in Phase I are exactly those designed for Phase II, and the procedures/schedules of assessment that patients receive are

identical in both phases, the data collected in Phase I portion will be combined with those in the Phase II portion for statistical analysis.

Primary endpoints and secondary efficacy endpoints in Phase I/II will be analyzed on ITT and PP population. Non-primary safety endpoints, demographics and baseline characteristics will be analyzed on ITT population. Conclusion of primary endpoint in Phase I will be made based on ITT population analysis results and that in Phase II will be made according to the result of ITT population analysis.

10.2.2 Analysis methods

For all assessments, the baseline will be defined as the most recently available data before the administration of 1st dose treatment.

Descriptive statistics will be provided by treatment group/country and by all for all of the endpoints, including primary and secondary ones. Frequency table will be provided for categorical data, while mean, standard deviation, maximum, minimum, median, inter-quartile range (IQR), and 95% two-sided confidence interval will be calculated for continuous measurements.

AEs and SAEs will be reported by treatment group/country and physiological systems as appropriate. The incidence of treatment-related AEs and SAEs between treatments will be analyzed by Cochran-Mantel-Haenszel test (CMH) test.

Incidence of AEs and SAEs will be analyzed by CMH test. Changes in physical examinations will be displayed for each individual system. Net changes from pre-treatment laboratory test results and vital signs will be analyzed by descriptive statistics.

Healing time from DSW creation to 100% re-epithelialization will be estimated by using Kaplan-Meier methods and compared between groups by using log-rank test. The healing time is defined as from DSW creation to the first 100% re-epithelialization with confirmation for at least 10 days apart, observed by the investigator and the first additional evaluator.

If the first 100% re-epithelialization is observed at any visit by Day 28 with confirmation for at least 10 days apart, the healing time is noted as the duration from the Day of DSW creation to the day of the first 100% re-epithelialization. The fulfilling of the visits and/or follow-ups after the 100% re-epithelialization date will not be taken into account to determine the healing time. If the 100% re-epithelialization is not observed by Day 28 visit, the healing time will be censored on day of the last visit up to Day 28 visit. If the 100% re-epithelialization is observed by Day 28 visit but no confirmation is made, the healing time will be censored on day of the last visit up to Day 28 visit. The censoring rules will be applied immediately once patients leave the study regardless the participation and/or completion of the long-term (360 days) follow-ups.

If patient develops grade 2 or above SAEs and should exit the study prematurely before Day 14, he/she should be excluded from the primary efficacy analysis, because early censor will result in under estimation of the healing time while treatment group (TWB-103+Tegaderm^{TM}) is prone to have higher risk of developing treatment related SAE.

In the cases of TWB-103/placebo discontinuation due to allergic reaction or infection, wound assessments performed after onset of allergic reaction or infection will be excluded from statistical analysis.

Healing rates (complete wound closure) of patients at Days 7, 10 and 14 after DSW creation will be analyzed by CMH test. Healing percentage of wounds (ratio of healing and original areas) at Days 7, 10 and 14 after DSW creation will be analyzed by Analysis of variance (ANOVA) model with treatment group and country as factor. Score on short-form McGill pain questionnaire will be analyzed by using Analysis of covariance (ANCOVA) model with treatment group and country as factor and baseline characteristics as covariate. Vancouver Scar Scale will be analyzed by Wilcoxon ranked sum test. The score in each category (pigmentation, vascularity, pliability and height) and the sum score of all category in Vancouver Scar Scale will be analyzed.

All treatment group comparisons will be conducted with significance level of 0.05, using 2-tailed tests.

Demographics and baseline characteristics will be summarized for each group/country by using descriptive statistics.

10.2.3 Interim analyses

There is no planned interim analysis for this study. The statistical analysis and clinical study report writing will be done based on the collected data from the study.

10.2.4 Data and safety monitoring board

Independent Data and Safety Monitoring Board (DSMB) will not be held.

10.2.5 Missing data estimation

No missing data imputation will be applied for this study.

11. ETHICAL CONSIDERATIONS

11.1 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants and their families.

Consent forms will be IRB approved and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.2 IRB review

This protocol and the associated informed consent documents must be submitted to the IRB for review and approval. The study will not be initiated until the IRB provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and CRO.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when

necessary to eliminate immediate hazards to the study participants or when the change involves only logistics or administration. Any significant deviation from the protocol when no approved amendment exists will be regarded as a protocol violation, and will be addressed as such during the reporting of the study.

11.3 Confidentiality of Data and Patient Records

Include procedures for maintaining participant confidentiality, any special data security requirements, and record retention per the sponsor's requirements.

Participant confidentiality is strictly held in trust by the participating investigators, and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating patients.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

If applicable, the study monitor or other authorized representatives may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The information provided by sponsor in this protocol and the associated Clinical Investigator's Brochure and the data generated by this clinical study is to be considered as confidential property of the sponsor.

12. PUBLICATIONS

The data and information associated with this study may be used by sponsor now and in the future for the purposes of presentation, publication at the discretion of the sponsor or for submission to regulatory agencies. In addition, relative to the release of any proprietary information, sponsor reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the investigator agrees to the release of the data from this study and acknowledges the above publication policy.

13. RETENTION OF TRIAL DOCUMENTS

Records of all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation should be retained by the PI in a secure storage facility. The records should be accessible for inspection and copying by authorized authorities.

All study documentation at the clinical site and PI records will be archived in accordance with ICH GCP, applicable regulations. Study records should not be destroyed without prior written agreement between sponsor/CRO and the study investigator.

14. REFERENCES

1 Beldon P. What you need to know about skin grafts and donor site wounds. *Wound Essentials* 2007; **2**: 149–155.

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3 Demirtas Y, Yagmur C, Soylemez F, Ozturk N, Demir A. Management of split-thickness skin graft donor site: A prospective clinical trial for comparison of five different dressing materials. *Burns* 2010; **36**: 999–1005.

15. PROTOCOL AMENDMENT HISTORY

The protocol amendment history is made after version 1.6.

Version	Date	Description of Change	Brief Rationale
1.6	25-Jan-2017		
1.8	18-Apr-2017	**1.** Correct the name of solution, the items in the label and typos. **2.** Add the rationale for the inclusion criteria and exclusion criteria. **3.** Include male patients to exclusion criteria #1 and add the human serum albumin to exclusion criteria #12. **4.** Revise the period of contraceptive use. **5.** Revise the wound photo guideline. **6.** Revise the source of AE definitions. **7.** Add the reporting procedure of SAE and pregnancy.	**1., 6.** Changes are made to avoid confusion. **2.** Changes are made to assist the understanding of eligibility criteria. **3-4.** Changes are made to ensure safety of patients. **5.** Changes are made to ensure the quality of wound assessment. **7.** Changes are made to ensure the safety of patients and the quality of the study.
2.0	25-Sep-2017	**1.** Revise the window days for Day 28 and Day 42 Visits. **2.** Revise inclusion/exclusion criteria including the thickness of DSW, tobacco use and the limitation of serum albumin. **3.** Define the prohibited medications (d) that are specific for DSW. **4.** Redefine the assessments for unscheduled visit. **5.** Revise the storage condition of trial products. **6.** Revise procedures after the creation of DSW but before the wound assessment, including the treatment of bleeding and the cleaning of wound. **7.** Revise the duration of tobacco use in this study. **8.** Define the window days for hematologic, biochemical and PRA tests of Visit 2. **9.** Revise the wound photo	**1., 6.** Changes are made to accommodate clinical practice at three study sites. **2-3., 7., 11., 14.** Changes are made to ensure safety of patients and to minimize the complexity of efficacy evaluation. **4., 8.** Changes are made to reduce unnecessary blood samples. **5.** Changes are made to ensure the proper storage of the trail products. **9.** Changes are made to ensure the quality of wound assessment. **10.** Changes are made to ensure the accuracy of pain assessment. **12-13.** Changes are made for data analysis.

		guideline. **10.** Revise pain assessment, including required visits and evaluating body part. **11.** Revise the use of Tegaderm™, including the visits of dispensing and two additional dressing options for Day 14 and later. **12.** Correct the AE grading guidelines and the use of MedDRA. **13.** Define the baseline for all assessments. **14.** Revise withdrawal procedures.	
3.0	11-Apr-2019	**1.** The number of evaluable subjects remains unchanged (30), but "(20 from Taiwan and 10 from Japan)" is deleted**.** **2.** The number of recruited subjects remains unchanged (approx. 36), but "(24 from Taiwan, 12 from Japan)" is deleted.	To facilitate patient recruitment.