ONENESS BIOTECH
合一生技股份有限公司

Randomized Controlled Study to Evaluate the Efficacy and Safety of ON101 Cream for the Treatment of Chronic Diabetic Foot Ulcers

Protocol for Phase III Study of ON101 Cream

Sponsor: Oneness Biotech Co., Ltd.

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I. INVESTIGATOR SIGNATURES PAGE

Randomized Controlled Study to Evaluated the Efficacy and Safety of ON101 Cream for the Treatment of Chronic Diabetic Foot Ulcers

Protocol Number: ON101CLCT02

Protocol Version: 20190925 v6.0

I have read all pages of this clinical study protocol for which Oneness Biotech Co., Ltd. is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.
Principal Investigator: Signature: ---------- <*Insert name and qualifications of the Investigator*> Date Printed Name: ---------- Address: ---------- ----------

I. SPONSOR INFORMATION PAGE AND SIGNATURES

Randomized Controlled Study to Evaluated the Efficacy and Safety of ON101 Cream for the Treatment of Chronic Diabetic Foot Ulcers

Protocol Number: ON101CLCT02

Protocol Version: 20190925 v6.0

Sponsor: Oneness Biotech Co., Ltd

Shan-Ney Huang	Date

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II. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALT	Alanine Aminotransferase (GPT)
AST	Aspartate Aminotransferase (GOT)
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
DM	Diabetes Mellitus
DFU	Diabetic Foot Ulcer
ECG	Electrocardiogram
FAS	Full Analysis Set
GCP	Good Clinical Practice
HbA1c	Glycated Hemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDF	International Diabetes Federation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PPS	Per Protocol Set
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Sprague-Dawley
SOP	Standard Operating Procedure
STZ	Streptozotocin
SUSAR	Suspected Unexpected Serious Adverse Reactions
WBC	White Blood Cell
WHO	World Health Organization

List of Key Study Terms

Terms	Definition of terms
Baseline	1) Observed values/findings which are regarded as calibrated zero status in the present study, 2) Time when 'Baseline' is observed
Discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a trial by an enrolled subject. Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) investigator-initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis. "Termination" has a history of synonymous use, but is now considered non-standard.
Enroll	To register or enter into a clinical trial; transitive and intransitive. Informed consent precedes enrollment, which precedes or is contemporaneous with randomization.
Intervention	The drug, device, therapy or process under investigation in a clinical trial which has an effect on outcome of interest in a study: e.g., health-related quality of life, efficacy, safety, pharmacoeconomics.
Randomization	Action to allocate a subject to the treatment group or treatment cohort. Depending on the type of rules for handling for study drugs, 'Randomization' is usually executed just before entering the 'investigational period'
Screening	1). Process for retrieving candidates for the study. 2). Process for checking the eligibility of subjects usually done during the "pre-investigational period"
Screening failure	Screened subject, but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive randomized or open label study treatment, or decided not to participate anymore (withdrew consent) prior to completing pre-investigational period
Study period	Period of time from start to end of the study.
Subject	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Title of Study	Randomized Controlled Study to Evaluate the Efficacy and Safety of ON101 Cream for the Treatment of Chronic Diabetic Foot Ulcers
Study Objective(s)	The primary objective of this study is to evaluate the efficacy of the new treatment of ON101 Cream compared to Aquacel® Hydrofiber® dressing, applied to chronic diabetic foot ulcers for up to 16 weeks. An additional objective of this study is to collect safety information including adverse events and clinical laboratory abnormalities.
Design and Methodology	This trial is designed as a randomized, evaluator blinded, active-controlled, multi-center study comparing the efficacy and safety of ON101 cream and Aquacel® Hydrofiber® dressing in the treatment of diabetic foot ulcers. An independent evaluators who blinded to subjects' treatment will evaluate whether the wound has healed. Eligible subjects will be randomized to receive either ON101 cream or Aquacel® Hydrofiber® dressing in a 1:1 allocation. The study treatment will be applied to the selected ulcer for a maximum period of 16 weeks, until the wound/ulcer closure (wound size of 0) for two consecutive visits at least 2 weeks apart, or until the subject exited the study as treatment failure. After that, all subjects regardless of wound healing at the end of comparison period will be followed for 12 weeks to investigate durability. During the follow-up period, Aquacel® Hydrofiber® dressing will be applied for subjects who have unhealed or with recurrent wound. Each target ulcer with wound photographs for blind assessment will be monitored at each scheduled visit. Two interim analyses are planned at about 118 and 212 subjects completed the comparison period or early withdrawn from study intervention. This will be about 50% and 90% of the total number of subjects will be randomized. The final analysis will be conducted at the end of the study.
Number of Subjects Planned	236 eligible subjects will be randomized; 118 in ON101 cream group and 118 in Aquacel® Hydrofiber® dressing group Ensuring at least 212 subjects.
Number of Study Sites Planned	There will be around 15 study centers in Taiwan, US, and China. Other countries may be added.
Selection Criteria (Inclusion)	1. Has signed a written informed consent prior to the first study evaluation 2. Male or female is at least 20 and < 80 years of age 3. Diabetes mellitus (type 1 or 2) with an HbA1c < 12.0% measured during screening or within three months prior to randomization 4. An ankle brachial index on the target limb at least 0.8 measured

	during screening or within three months prior to randomization 5. The target ulcer must have the following characteristics: a、 Grade 1 or 2 per Wagner Ulcer Classification System b、 No higher than the ankle c、 No active infection d、 A cross-sectional area of between 1 and 25 cm^2 post-debridement e、 Present for at least 4 weeks before randomization 6. If female and of childbearing potential has a negative pregnancy test and is not breastfeeding at screening visit 7. Able and willing to attend the scheduled visits and comply with study procedures
Selection Criteria (Exclusion)	1. Presence of necrosis, purulence or sinus tracts that cannot be removed by debridement 2. Acute Charcot's neuroarthropathy as determined by clinical and/or radiographic examination 3. Has undergone revascularization procedure aimed at increasing blood flow in the treatment target limb < 4 weeks prior to randomization 4. Poor nutritional status defined as an albumin < 2.5 g/dL 5. AST and/or ALT >3 × the normal upper limit 6. Serum Creatinine >2 × the normal upper limit 7. Treatment with immunosuppressive or chemotherapeutic agents, radiotherapy or systemic corticosteroids within the 4 weeks before randomization 8. Use of any investigational drug or therapy within the 4 weeks prior to randomization 9. A psychiatric condition (e.g., suicidal ideation), current or chronic alcohol or drug abuse problem, determined from the subject's medical history, which, in the opinion of the Investigator, may pose a threat to subject compliance 10. Judged by the investigator not to be suitable for the study for any other reason
Discontinuation Criteria	1. Violation and/or significant deviation of study protocol 2. Lack of efficacy satisfactory (defined as a worsening of Wagner grade to level of 3) 3. Safety concerns 4. Lost to follow-up 5. Withdrawal consent 6. In the Investigator's opinion, it is in the patient's best interest 7. Termination of study by the sponsor
Test Intervention	ON101 cream (extracts of *Plectranthus amboinicus* and *Centella Asiatica*) 1.25% ON101-DS in cream base, 15g cream per tube Twice daily for up to 16 weeks

Reference Therapy	Aquacel® Hydrofiber® dressing
Primary Variable	The primary efficacy outcome is the comparison of the incidence of complete healing of the target ulcer between the two treatment groups at the end of treatment.
Secondary Variables	· Time to complete ulcer healing, · Percentage change in ulcer surface area from baseline, · Percentage of subjects with a 50% reduction of ulcer surface area, · Incidence of infection of the target ulcer. Safety outcomes include assessment of the incidence of treatment-emergent adverse events, clinical laboratory values, and vital signs.
Exploratory Variable	Recurrence of the target ulcer within follow-up period evaluated in those subjects who demonstrated complete wound healing at the end of comparison period.
Statistical Methods	The primary efficacy analysis, the rate of complete healing, will be based on the logistic regression model for the binary response that will be used to test for the differences in the treatment efficacy between ON101 cream and Aquacel® Hydrofiber® dressing. The logistic model will include treatment group and the following prognostic factors: baseline wound size and baseline Wagner grade. The comparison between the two treatment groups will be presented in term of the odd ratios, with p-values and associated 95% confidence intervals of the odds ratio. Two interim analyses will be conducted at about 118 and 212 subjects complete the comparison period or early withdraw from study intervention on a sequential basis. This will be about 50% and 90% of the total number of subjects that will be randomized. The final analysis will be conducted at the end of study. The futility/superiority of ON101 cream will be assessed using the Lan-DeMets approach which the boundaries are determined by the type of O'Brien-Fleming spending function. The wound size will be compared between groups by means of analysis of co-variance (ANCOVA). The method of Kaplan and Meier will be used to summarize the time to event data. The difference in time to complete ulcer healing between the treatment groups will be analyzed by the log-rank test. For the safety parameters, numerical comparisons between treatment groups in adverse events (AEs), vital signs and safety laboratory results based on change from baseline will be provided.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

Obtaining informed consent		Screening Period		Confirmation of entry criteria		Randomization		Administration period (up to 16 weeks)	Follow-Up (up to 28 weeks)
	→	Standard Care	→		→		→	ON101 cream (BID)	Aquacel® Hydrofiber® dressing (for non-healing wound)
							→	Aquacel® Hydrofiber® dressing	

Schedule of Assessments

Assessments	Screening	Baseline	Comparative Period (up to 16 weeks)								Follow-Up@			
Visit Number	1	2#	3	4	5	6	7	8	9	10&	11	12	13	14
Visit Weeks	-1		2	4	6	8	10	12	14	16	18	20	24	28
Visit Days	-7	1*	15	29	43	57	71	85	99	113	127	141	169	197
Allowed visit window(days)	-3		±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7
Informed consent	X													
Randomization		X												
Apply test medication or comparative intervention		X	X	X	X	X	X	X	X	X@	X@	X@	X@	X@
Standard ulcer care	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X													
Inclusion/Exclusion criteria	X	X												
Disease status	X	X												
Pregnancy test	X													
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ulcer assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X									X				X
X-Rays	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X			X		X		X		X				X
Medical history	X	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

*: Day 1 should normally be the day of first treatment intake. The day before should normally be Day -1 and there is no Day 0.
This approach is in accordance with CDISC.

#: Subject may proceed to Visit 2 as soon as Visit 1 procedures are completed, that means the day of Visit 1 could be same as Visit 2.

&: Visit 10 indicates as the end of study treatment or prematurely discontinuation of study treatment.

@: During the follow-up period, Aquacel® Hydrofiber® dressing will be applied for subjects who have unhealed or with recurrence wound.

1 INTRODUCTION

1.1 Background

Current statistical data from the International Diabetes Federation (IDF) and the World Health Organization (WHO) show a dramatic worldwide increase in diabetes mellitus (DM). In 2000, nearly 250 million people were affected by DM. This corresponds with a global prevalence that is estimated to be 2.8%; a near doubling of this number -- to 400 million (a projected prevalence of 4.4%) -- is expected in the next two decades [1]. Because of its secondary complications, the life expectancy of diabetic patients is on average 10 years shorter than non-diabetics [2]. Diabetic foot ulcer (DFU) is a common secondary complication of DM, with an estimated 15% of patients with diabetes expected to develop a foot ulcer within their lifetime [3]. More importantly, DFU as the most common cause of hospitalization in diabetic patients [4], resulting in lower extremity amputations in about 15% of cases [3].

DFUs are the result of various etiological factors and are characterized by an inability to self-repair in a timely and orderly manner [5]. DFU occurs as a consequence of the interaction of several contributory factors, which may be divided schematically into intrinsic (neuropathy, peripheral vascular disease, and diabetes severity) and extrinsic (wound infection, callus formation, and excessive pressure to the site) [6]. Several studies have examined the risk factors for the development of DFU. Most agree that a triad of factors contributes to ulceration. These include the presence of peripheral neuropathy, foot deformities, and acute or chronic repetitive trauma. In addition to the triad of risk factors described in the literature, impaired wound healing has been implicated as a significant cause for poor healing in the DFU. Other causes of poor wound healing in DFU include infection and ischemia.

The cornerstones of DFU treatment have long been advocated as including: regular debridement, wound-pressure off-loading, re-vascularization when appropriate, adequate treatment of infection, and wound care. A fundamental tool in the management of DFU is the assessment of the wound area, either by measuring the maximal width and length of the ulcer [7] or through wound tracings [7]. Despite this current multifaceted approach, only a portion of ulcers (up to 50%) will be healed after 12 - 20 weeks [7]. Furthermore, compelling evidence suggests that DFU that fail to heal within 20 weeks are more likely to result in a prolonged and protracted healing process. Failure of normal wound healing in a DFU is the most prevalent pathophysiological component cause leading to lower extremity amputations in individuals with diabetes mellitus. Healing a foot wound lowers the risk of amputation. Moreover, patients who have had one amputation are at high risk of successive amputations with considerable morbidity, mortality and financial cost [8]. As a result, treatments that address the underlying structural and functional impairments that contribute to prolonged wound healing are being investigated for their diagnostic and therapeutic

benefits. Future therapies need to rely on the successful integration of mediators of different pathways involved in wound healing, such as the impaired microvascular function, diminished activity of growth factors, cytokines, neuropeptides, and the hypoxic tissue environment.

1.2 Non-clinical and Clinical Data

ON101, containing extracts of *Plectranthus amboinicus* and *Centella Asiatica*, is developed for the ulcer healing of patients with lower extremity diabetic ulcers.

Plectranthus amboinicus was known to contain carvacrol, p-cymene, γ-terpinene, limonene, linalool, myrcene, thymol, α-amorphene, and β-cubebene. The essential oils of *Plectranthus amboinicus* were demonstrated to have growth inhibitory effect on bacteria and fungi. Extracts from *Plectranthus amboinicus* were also reported to have antioxidant and anticlastogenic effects. *Plectranthus amboinicus* leave juice was traditionally used topically to treat burns, insect bites, crack at the corner of the mouth, and skin allergy.

The chemical constituents of *Centella asiatica* were known to include triterpene, terpenoid, pentacyclic compound, asiaticoside and asiatic acid. The leaves of *Centella asiatica* were traditionally used in folk medicine to treat leprosy, cancer, arthritis, hemorrhoids, asthma, bronchitis, and tuberculosis. Active extracts from *Centella asiatica* had been proven to be able to enhance wound healing, possible by increasing the antioxidant level of wound tissues, stimulating the production of type-I collagen in fibroblast cells and by increasing the remodeling of the collagen matrix in the wound. The products of TTFCA (total triterpenic fraction of Centella asiatica) functioning at wound healing had been commercial available in the market.

Eight pharmacological studies were conducted by the Developmental Center for Biotechnology, Taiwan, to test for the effectiveness and mechanism of action of ON101. Streptozotocin (STZ) was used to induce diabetic animals to establish the ulcer-healing model. In another diabetic animal model, db/db rat, ON101 also showed ulcer-healing effects.

From the histology study in ulcer tissues, the collagen contents in ulcers treated with the active ingredients of ON101 were significantly lower than those treated with placebo. Tissues treated with ON101 showed no inflammation and a very thin granulation tissue. In histopathology study, the intensities of positive CD71 (the marker of transit amplifying cell and an index of ulcer healing signal) in tissues treated with ON101 were significantly higher than those treated with placebo. These results revealed that ON101 could enhance cell renovation ability in ulcers.

Seven GLP-compliant toxicity studies of ON101 were conducted at the Development Center for Biotechnology, Taiwan. And under the test conditions used, ON101 did not show any abnormal or positive response in three genotoxicity tests. In dermal irritability test, ON101 is neither an irritant nor a sensitizer in wounded skin. In acute toxicity study, ON101 drug

substance exerted no adverse toxic effects in Sprague-Dawley (SD) rats at the dose level up to 5000 mg/kg via oral route. Oral administration of ON101 drug substance up 3000 mg/kg/day to SD rats did not induce any adverse effect during the 28-day repeating dose study. Therefore, the 28-day NOAEL for rats orally ingesting of ON101 drug substance is 3000 mg/kg/day.

In a clinical research trial conducted at National Taiwan University Hospital in 11 subjects with Wagner-grade-3 chronic diabetic foot ulcers, treatment with ON101 for 2 weeks resulted in approximately 20% reduction of wound size and no serious adverse effects have been reported. Of the 11 evaluable subjects, the mean wound size at baseline was 359 mm^2 (20 – 2352 mm^2), and decrease to 293 mm^2 after 2 weeks of ON101.

Another clinical trial was carried out 30 subjects with Wagner-grade-1 chronic diabetic foot ulcers treated with ON101 for up to 12 weeks. The results showed that the incidence of healing by 12 weeks was 50.0% and the time of 50% subjects reached healing was approximately 10 weeks. Of the 30 subjects, treatment with ON101 for up to 12 weeks resulted in approximately 70% reduction of wound size. The average wound size at baseline was 577 mm^2 (303 - 1225 mm^2), and decrease to 163 mm^2 for up to 12 weeks of ON101.

1.3 Summary of Key Safety Information for Study Drugs

Both previous trials did not show any adverse events caused by ON101, as expected, ON101 cream is safe and well tolerated to the subjects with diabetic foot ulcer.

1.4 Rationale for Trial Design

New treatments that improve the number of ulcers that heal and/or speed up healing are urgently needed. The main purpose of our clinical trial is to demonstrate superiority of ON101 vs. Aquacel® Hydrofiber® in wound healing. Previous studies with ON101 showed that ON101 is associated with wound size reduction and improved healing rate. However, these studies were not adequately powered for wound healing rate as primary endpoint. This comparative study is important because the results may inform the choice in managing the DFU. The proposed study will provide 16 weeks data on wound healing rate in order to demonstrate superior benefits of ON101 compared to Aquacel® Hydrofiber® dressing on a clinically important outcome. Clinical healing and safety will be compared in diabetic patients with Wagner Grade 1 or 2 DFUs managed with either of two primary treatments: ON101 cream or Aquacel® Hydrofiber® dressing, both used within similar standard care including appropriate lower extremity off-loading.

2 STUDY OBJECTIVE(S), DESIGN AND VARIABLES

2.1 Study Objectives

The primary objective of this study is to evaluate the efficacy of the new treatment of ON101 cream compared to Aquacel® Hydrofiber® dressing applied to chronic diabetic foot ulcers for up to 16 weeks.

An additional objective of this study is to collect safety information including adverse events and clinical laboratory abnormalities.

2.2 Study Design and Dose Rationale

2.2.1 Study Design and Rationale

This trial is designed as a randomized, evaluator blinded, active-controlled, multi-center study comparing the efficacy and safety of ON101 cream and Aquacel® Hydrofiber® dressing in the treatment of diabetic foot ulcers. An independent evaluators who blinded to subjects' treatment will evaluate whether the wound has healed, defined as epithelialization wound. Subject with Type 1 or 2 diabetes mellitus (DM) and with Wagner Grade 1 or 2 diabetic foot ulcer (DFU) of neuropathic or neuro-ischemic etiology will be included in this study. If there is more than one ulcer on the foot, the most severity then largest ulcer that confirmed to the inclusion/exclusion criteria will be selected for study evaluation. Eligible subjects will be randomized to receive either ON101 cream or Aquacel® Hydrofiber® dressing in a 1:1 allocation. The study treatment will be applied to the selected ulcer for a maximum period of 16 weeks, until the wound/ulcer closure (wound size of 0) for two consecutive visits at least 2 weeks apart, or until the subject exited the study as treatment failure. After that, all subjects regardless of wound healing at the end of comparison period will be followed for 12 weeks to investigate durability. During the follow-up period, Aquacel® Hydrofiber® will be applied for subjects who have unhealed or with recurrence wound. Each target ulcer with wound photographs for blind assessment will be monitored at each scheduled visit.

Two interim analyses will be conducted at around 50% and 90% of study information; the final analysis will be conducted at the end of the study. The futility/superiority of ON101 cream will be assessed using the Lan-DeMets method with O'Brien-Fleming spending boundaries.

2.2.2 Dose Rationale

The study treatment, ON101 (1.25%), will be applied two times daily. Data of preclinical studies using active components and ON101 can well justify the recommended dosing regimen of this study. In a sub-acute repeating dose study, the results indicated that SD rats ingested ON101 drug substance at 3000 mg/kg for 28 consecutive days did not develop any observable adverse

effects. The final product is for topical use and dermal irritation study in rabbit and guinea pig demonstrated the product to be nonirritant and does not cause any erythema or edema.

Aquacel® Hydrofiber® dressing (ConvaTec) is a moisture retention dressing that consists of soft non-woven sodium carboxymethyl cellulose fibers which form a gel on contact with wound fluid. Dressings will be changed daily, on alternate days or three times a week according to need, but not longer than 7 days.

2.3 Variables

2.3.1 Primary Variable

The primary variable is the number of target ulcers healed in each group within 16 weeks. The primary efficacy outcome is the comparison of the incidence of complete healing of the target ulcer between the two treatment groups at the end of treatment.

For the purpose of this study a complete healing will be defined as complete epithelialization which is maintained with no drainage for at least 2 weeks and is confirmed by a blinded independent evaluator.

2.3.2 Secondary Variables

The secondary efficacy outcomes are:

- ✓ Time to complete ulcer healing,
  The time of the original healing will be taken as the time to healing.
- ✓ Percentage change in ulcer surface area from baseline,
- ✓ Percentage of subjects with a 50% reduction of ulcer surface area,
- ✓ Incidence of infection of the target ulcer.

Safety outcomes include assessment of the incidence of treatment-emergent adverse events, clinical laboratory values, and vital signs.

2.3.3 Exploratory Variable

The exploratory endpoint is recurrence of the target ulcer within follow-up period evaluated in those subjects who demonstrated complete wound healing at the end of comparison period.

3 STUDY POPULATION

3.1 Selection of Study Population

A total of 236 subjects will be randomized to ensure that approximately 212 subjects are evaluable. Evaluable subjects for this study mean all randomized subjects taking at least one dose of study treatment. The study will be conducted as multi-center trial. All sites will maintain a log of subjects screened for study entry and will document the reasons for exclusion for each subject not entered. The log of all subjects screened will be maintained in the Investigator Site File at the investigational site.

Additional sites may be initiated and non-productive sites may be closed to ensure sponsor timelines. Subjects who were already randomized in the study are not allowed to reenter.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Has signed a written informed consent prior to the first study evaluation
2. Male or female is at least 20 and < 80 years of age
3. Diabetes mellitus (type 1 or 2) with an HbA1c < 12.0% measured during screening or within three months prior to randomization
4. An ankle brachial index on the target limb at least 0.8 measured during screening or within three months prior to randomization
5. The target ulcer must have the following characteristics:
   a、 Grade 1 or 2 per Wagner Ulcer Classification System
   b、 No higher than the ankle
   c、 No active infection
   d、 A cross-sectional area of between 1 and 25 cm^2 post-debridement
   e、 Present for at least 4 weeks before randomization
6. If female and of childbearing potential has a negative pregnancy test and is not breastfeeding at screening visit
7. Able and willing to attend the scheduled visits and comply with study procedures

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Presence of necrosis, purulence or sinus tracts that cannot be removed by debridement
2. Acute Charcot's neuroarthropathy as determined by clinical and/or radiographic examination

3. Has undergone revascularization procedure aimed at increasing blood flow in the treatment target limb < 4 weeks prior to randomization
4. Poor nutritional status defined as an albumin < 2.5 g/dL
5. AST and/or ALT >3 × the normal upper limit
6. Serum Creatinine >2 × the normal upper limit
7. Treatment with immunosuppressive or chemotherapeutic agents, radiotherapy or systemic corticosteroids within the 4 weeks before randomization
8. Use of any investigational drug or therapy within the 4 weeks prior to randomization
9. A psychiatric condition (e.g., suicidal ideation), current or chronic alcohol or drug abuse problem, determined from the subject's medical history, which, in the opinion of the Investigator, may pose a threat to subject compliance
10. Judged by the investigator to be not suitable for the study for any other reason

3.4 Discontinuation Criteria for Individual Subjects

A discontinuation is a subject who is randomized into the study and for whom study treatment is terminated prematurely for any reason.

The subject is free to withdraw from the study intervention and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

Discontinuation Criteria for Individual Subjects:

1. Violation and/or significant deviation of study protocol
2. Lack of efficacy satisfactory (defined as a worsening of Wagner grade to level of 3)
3. Safety concerns
4. Lost to follow-up
5. Withdrawal consent;
6. In the Investigator’s opinion, it is in the patient’s best interest;
7. Termination of study by the sponsor.

In all cases, the reason for and date of withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. The subject must be followed up to establish whether the

reason was an adverse event, and, if so, this must be reported in accordance with the adverse events reporting procedures.

If a subject withdraws from the study or the study intervention is discontinued prematurely, all procedures as scheduled at the end of the trial should be included on the case report form.

There will be no replacement of withdrawn subjects, regardless of the reason for withdrawal. All subjects who experience adverse event which is ongoing either at the time of withdrawal or at the post study visit, must be followed-up at appropriate time intervals until the adverse event is resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

4 STUDY TREATMENTS

4.1 Description of Study Interventions

4.1.1 Test Intervention

The study intervention is ON101, containing 1.25% of extracts of *Plectranthus amboinicus* and *Centella Asiatica*, available as cream for topical administration.

The following described the composition of ON101 cream.

Code Name	ON101 cream
Component	Dry extracts of PA-F4 and S1 (1:4 ratio) <Cream Base: Cetostearyl alcohol, ~~Ireine,~~ Liquid petrolatum, Methyl paraben Propyl paraben, Span 60, Tween 60, White petrolatum, water and pigments>
Amount per tube	1.25% ON101-DS in cream base, 15g cream per tube

4.1.2 Comparative Intervention

As a comparator, Aquacel® Hydrofiber® dressing (ConvaTec) is used. Aquacel® Hydrofiber® dressing maintains a moist wound environment for optimal healing, debridement and easy removal. Innovative dressing composed of sodium carboxy-methylcellulose fibers for the management of exudating wounds. This dressing is soft, nonwoven, conformable and highly absorbent.

4.2 Packaging and Labeling

All interventions used in this study will be packed, and labeled under the responsibility of a qualified person at Oneness Biotech Co., Ltd. and/or the designee in accordance with Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization guidelines for Good Clinical Practice (ICH GCP) guidelines, and applicable local laws/regulations.

4.3 Study Intervention Handling

Current ICH GCP Guidelines require the investigator to ensure that study medication deliveries from the sponsor are received by a responsible person (e.g. pharmacist), and

- that such deliveries are recorded;
- that study intervention is handled and stored safely and properly;
- that study intervention is only dispensed to study subjects in accordance with the protocol;
- that any unused study intervention is returned to the sponsor or standard procedures for the alternative disposition of unused study drug are followed.

Treatment inventory and accountability records for the study medication will be kept by the investigator/pharmacist. Study medication accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study interventions to any persons except the subjects in this study.
- The investigator/pharmacist will keep the study interventions in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test treatment.
- A study treatment inventory will be maintained by the investigator/pharmacist. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator/pharmacist agrees to conduct a final intervention supply inventory and to record the results of this inventory on the Treatment Accountability Record. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.
- Used or unused study intervention may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted by the Sponsor or representative, only if agreed upon by the Sponsor. A copy of the standard institutional procedure for destroying investigational treatment will be provided to the Sponsor or designee upon request. Unused study interventions not destroyed at the site must be returned to the Sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

The investigator and research staff will not know the randomization assignment at the time of subject be screened to ensure they do not accidentally notify the subject of their assignment. After obtained a signed written informed consent and all study entry criteria has been confirmed, the investigator will be informed of the randomized treatment assignment by opening the individual treatment code envelope.

However, this study is developed as evaluator blind. A blinded independent evaluator, blinded to subjects' treatment, will evaluate the digital photograph on whether the wound has healed, defined as epithelialization wound. The results by a blinded independent evaluator will be used for primary analysis in this study.

4.5 Assignment and Allocation

Subjects who meet the inclusion and exclusion criteria will be randomly assigned to receive ON101 cream or Aquacel® Hydrofiber® dressing using a 1:1 randomization schedule. The schedule will be designed to balance the treatment arms by assigning eligible subjects from each study site in block randomization scheme. Individual investigators are blinded to the size of the block, eliminating the possibility that a prospective subject's assignment could be determined before randomization. Subject numbers assigned to subjects that do not receive study intervention will not be reused.

5 TREATMENTS AND EVALUATION

The following sections describe the procedures to be completed at screening and during the study. Subjects are to be assessed by the same investigator or site personnel whenever possible.

The following table details the study schedule of procedures for study period:

Schedule of Assessments

Assessments	Screening	Baseline	Comparative Period (up to 16 weeks)								Follow-Up[@]			
Visit Number	1	2[#]	3	4	5	6	7	8	9	10[&]	11	12	13	14
Visit Weeks	-1		2	4	6	8	10	12	14	16	18	20	24	28
Visit Days	-7	1*	15	29	43	57	71	85	99	113	127	141	169	197
Allowed visit window(days)	-3		±4	±4	±4	±4	±4	±4	±4	±4	±4	±7	±7	±7
Informed consent	X													
Randomization		X												
Apply test medication or comparative intervention		X	X	X	X	X	X	X	X	X[@]	X[@]	X[@]	X[@]	X[@]
Standard ulcer care	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X													
Inclusion/Exclusion criteria	X	X												
Disease status	X	X												
Pregnancy test	X													
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ulcer assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X									X				X
X-Rays	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X			X		X		X		X				X
Medical history,	X	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

[*] : Day 1 should normally be the day of first treatment intake. The day before should normally be Day -1 and there is no Day 0.
This approach is in accordance with CDISC.

[#] : Subject may proceed to Visit 2 as soon as Visit 1 procedures are completed, that means the day of Visit 1 could be same as Visit 2.

[&] : Visit 10 indicates as the end of study treatment or prematurely discontinuation of study treatment.

[@]: During the follow-up period, Aquacel® Hydrofiber® dressing will be applied for subjects who have unhealed or with recurrence wound.

5.1 Visit Schedule Summary

5.1.1 Screening Period

(Visit 1: Between Day -7 to Day 1)

Before screening assessments are conducted, the patient must be given a complete explanation of the purpose and evaluations of the study. Subsequently, the patient must sign and receive a copy of the ICF that was approved by the Independent Ethics Committee (IEC) and an authorization for

use and disclosure of protected health information before any study-specific procedure is performed. An original signed consent form will be retained in the patient's source documentation at the study site, and a copy will be provided for the patient to take home. Screening will occur within 7 days before treatment administration. Potential patients will be evaluated for entry into the study according to the stated inclusion and exclusion criteria. Individuals who are identified during this screening as not eligible for study enrollment need not complete all screening procedures. The reason for ineligible status will be recorded. Re-screening of patients is permissible if they fulfill the inclusion and exclusion criteria.

The following procedures will be performed to assess the patient's eligibility for the study:

- Explain the nature of the study and have subjects to read and sign an informed consent form
- Assign subject identifier - screen number
- Obtain demographic characteristics and vital signs
- Perform Physical examinations
- Perform foot X-Rays
- Perform assessment of target diabetic foot status
- Perform assessment of foot ulcer status and photography
- Standard ulcer care
- Record medical history including specific chronic complications
- Perform laboratory tests including hematology and biochemistry
- Perform pregnancy test for women of childbearing potential only
- Perform 12 Lead Electrocardiogram (ECG)
- Screen subject for inclusion/exclusion criteria
- Record medical history and concomitant medications

5.1.2 Baseline Visit

(Visit 2: Day 1)

The following procedures will be performed in this visit:

- Confirm subject eligibility
- Obtain the assignment of randomized study treatment (ON101 cream or Aquacel® Hydrofiber® dressing)
- Assign subject identifier - randomization number

- Apply test medication or comparative intervention according to randomization result
- Perform physical examinations and obtain vital signs
- Perform assessment of foot ulcer status and photography
- Standard ulcer care
- Perform assessment of adverse events
- Record medical history and concomitant medications

5.1.3 Comparative Period

(Visit 3-Visit 10: Day 15 to Day 113)

The following procedures will be performed in this period:

- Apply test medication or comparative intervention

  If complete wound healing by the judgment of independent reviewer happens before Visit 10, the applied test medication (ON101 cream) or comparative intervention (Aquacel® Hydrofiber® dressing) will be stopped at next scheduled visit which will be deemed as V10.

  If the wound is unhealed at Visit 10, only Aquacel® Hydrofiber® dressing will be applied.
- Perform physical examinations and obtain vital signs
- Perform laboratory tests including hematology and biochemistry at Visit 4, Visit 6, Visit 8, Visit 10 and at the visit of early permanent discontinuation of study treatment
- 12 Lead ECG examination will be performed at Visit 10 or at the visit of prematurely discontinuation of study treatment
- Perform assessment of foot ulcer status and photography
- Standard ulcer care
- Perform assessment of adverse events
- Record concomitant medication

5.1.4 Follow-up Period

(Visit 11-Visit 14: Day 127 to Day 197)

The following procedures will be performed in this period:

- Apply Aquacel® Hydrofiber® dressing to the subjects whose wounds are unhealed or recurrent
- Perform physical examinations and obtain vital signs

- Laboratory tests including hematology and biochemistry will be performed at Visit 14 (Week 28) or Visit of early permanent discontinuation during the follow-up period
- 12 Lead ECG examination will be performed at visit 14 (Week 28) or visit of early permanent discontinuation during the follow-up period
- Perform assessment of foot ulcer status and photography
- Standard ulcer care
- Perform assessment of adverse events
- Record concomitant medication

5.2 Dosing and Administration of Study Treatments and Other Medications

5.2.1 Dose/Dose Regimen and Administration Period

The investigator will select the treatment area for each subject at the baseline visit. During the treatment period, subject will apply the study medication (ON101 cream) to the selected treatment area only. The study cream will be applied two times daily for a maximum period of 16 weeks, until the wound/ulcer closure (wound size of 0) for two consecutive visits at least 2 weeks apart, or until the study subject exited the study as lack of efficacy satisfactory (defined as a worsening of Wagner grade to level of 3).

The surface area of the ulcer will be estimated at each clinical visit in the following manner. Length is the longest edge-to-edge measurement of the ulcer; width is taken from a perpendicular axis to the length. The study drugs will be applied in an amount to fully cover the ulcer area. The maximum amount of ON101 cream applied on the wound must not exceed 2 millimeter in thickness (or 1 cc for ulcer size of $5cm^2$). The investigator/study coordinator will give a demonstration and will train the patients how to apply the medication at each clinical visit.

Aquacel® dressing offers the unique gelling action of Hydrofiber® technology that absorbs and locks in exudate and bacteria. It provides excellent absorption and retention capabilities for moderate to highly exuding wounds, confirms to the wound surface to form an intimate contact, supporting wound healing by providing a moist wound healing environment. The Aquacel® Hydrofiber® dressing will be left in place for up to 7 days or changed earlier, depending on the extent of the exudate produced by the wound.

Both treatment groups will be covered by several layers of gauze, and subjects received accommodative footwear for non-plantar ulcers and off-loading for plantar ulcers to relieve the pressure from the ulcerated foot; the products used are not specified.

5.2.2 Previous and Concomitant Medication (Drugs and Therapies)

5.2.2.1 Previous Medication (Drugs and Therapies)

All previous medications, which are used within 4 weeks prior to the randomization, will be recorded in the source documents and CRF.

5.2.2.2 Concomitant Medication (Drugs and Therapies)

If the administration of any concomitant treatment becomes necessary, it must be reported in the case report form and in the subject's medical records. As far as possible, minimum changes (dose, frequency) should be made to the concomitant treatment during the study. However, concomitant medications should be kept to a minimum during the study. The sponsor must be consulted if there is any doubt, and a decision to withdraw the subject must be made jointly by the sponsor and the investigator.

Permitted concomitant medication

Oral and/or intravenous antimicrobial agents are allowed for treatment of presumed infection.

Prohibited concomitant medication

Topical antimicrobials and agents known to affect wound healing are not allowed during the study treatment period.

5.2.3 Treatment Compliance

The amount of returned study medication (ON101) from each subject will be recorded in the CRF at each visit.

5.2.4 Emergency Procedures and Management of Overdose

No specific advice is available for treatment of overdose of ON101, other than supportive treatment. No specific antidote has been identified to date.

In emergency situations during study, the investigator will perform adequate procedures to ensure the health and safety of study subject. All emergencies and serious adverse events should be reported by telephone immediately to Sponsor.

5.2.5 Restrictions During the Study

Subjects shall prevent from causing any pregnancy during the study period.

If any treatment (drugs, therapies) becomes necessary, subjects should inform study site before receiving treatment and ask the Investigator or sub-investigator for their instructions.

5.3 Demographics and Baseline Characteristics

5.3.1 Demographics

The following demographic data will be collected at screening.

- Sex
- Birthday
- Height, body weight
- Ankle-brachial index on target foot, determined by dividing the highest ankle systolic measure by the highest brachial systolic measure
- Diabetes type and duration
- History of previous medications and therapies (within 4 weeks prior randomization)
- History of smoking and alcohol use

Baseline characteristics will be collected at Screening or on Day 1 (before administration of study intervention) in accordance with the schedule as detailed in the Schedule of Assessments.

5.3.2 Medical History

A complete medical history will be recorded in the source documents and CRF. All details (including information related to the duration, i.e., the number of months or years), especially those regarding chronic and recurring illness will be recorded on the medical history page with special emphasis on medical history of the last 12 months prior to randomization. In addition, the following history on chronic complications will be collected separately: coronary artery disease (CAD), diabetic neuropathy (DN), diabetic kidney disease (DKD), diabetic retinopathy (DR), diabetic peripheral arterial disease (PAD).

5.3.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

Please refer to "Diabetic Foot Disorders: A Clinical Practice Guideline (2006 revision)" as Appendix 1.

The following target ulcer characteristics should be collected before randomization:

- Duration of diabetic foot ulcer
- Ulcer severity (Wagner grade)
- Ulcer etiology (Neuropathic, Neuro-ischemic)
- Ulcer location (Plantar, Non-plantar)

Although no single system has been universally adopted, the classification system most often used was described and popularized by Wagner. In the Wagner system, foot lesions are divided into six grades based on the depth of the wound and extent of tissue necrosis.

Grade 0: No open lesion, may have deformity or cellulitis

Grade 1: Superficial ulcer

Grade 2: Deep ulcer to tendon or joint capsule

Grade 3: Deep ulcer with abscess, osteomyelitis, or joint sepsis

Grade 4: Local gangrene – forefoot or heel

Grade 5: Gangrene of entire foot

The major aetiologies of DFUs are neuropathy (nerve damage), neuroischaemia and peripheral vascular (arterial) disease. Some 40–70% of DFUs are caused by neuropathy, 15–24% by peripheral vascular disease and 15–45% by neuroischaemia.

The neuropathic foot is typically warm to touch with good perfusion and palpable pulses. The skin may be anyhdrotic (dry) and prone to fissuring and callosities. Ulcers often occur on the plantar surface, principally under the metatarsal heads in the forefoot. They are round and surrounded by callus.

The neuroischaemic foot is typically cool to touch and has poor perfusion, characterized by diminished or absent foot pulses. The skin is usually atrophic, anyhdrotic and shiny. Hair growth is often minimal and atrophy of the subcutaneous tissues is apparent. Ischaemic ulcers often occur on the digits and heels, and are usually dry with vertical walls. Necrotic tissue may be present.

5.4 Efficacy Assessment

The efficacy assessment is based on the subject's wound size. It will be conducted at clinic by digital planimetry method at baseline and every 2 weeks after study intervention until wound closure (wound size of 0) has confirmed 2 weeks apart, or until the study subject exited the study as lack of efficacy satisfactory.

The digital planimetry method involves applying a two-layer transparent acetate over the wound and tracing the perimeter with a permanent pen. The contact layer is then discarded into clinical waste and the top layer stored within the subject notes. The top layer is placed on a digital tablet, and the border is re-traced using a stylus. The underlying sensor then calculates the wound area.

For the purpose of this study a complete healing will be defined as complete epithelialization which is maintained with no drainage for at least 2 weeks and is confirmed by a blinded independent evaluator. At each clinic visit after study intervention, digital photographs should be taken of study wound after the area had been carefully shaved to visualize the wound margin and for better visualization of epithelialization and granulation tissue area.

5.5 Safety Assessment

5.5.1 Vital Signs

Vital signs (including temperature, blood pressure, heart rate and respiratory rate, all measured after 5 minutes in the sitting position) and weight will be taken at each scheduled visit or early permanently discontinued study intervention. The subject's height will be recorded at the baseline visit. Significant adverse changes in vital signs occurring after the subject randomized into this study will be recorded as adverse events.

5.5.2 Adverse Events

Adverse event collection will begin after study intervention initialed and continue through the entire study visit. All observed or spontaneously reported AEs will be recorded in the source documents and CRFs. Data to be recorded includes a description of the event, date of onset and end of the event, severity, action with respect to study intervention, treatment required, relationship to study intervention, and outcome of the event.

5.5.3 Laboratory Assessments

Blood samples for the laboratory tests will be collected at specified visit, i.e., Screening, Week 4, Week 8, Week 12, Week 16, Week 28 or early permanently discontinued study intervention. All the measurements will be conducted in the laboratory at the study site.

Laboratory reports must be signed and dated by the principal investigator or sub-investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

The following is a list of laboratory evaluations to be performed during the course of the study according to the local laboratory instructions.

Hematology: hemoglobin, white blood cell (WBC) count total and differential, platelet count, red blood cell (RBC)

Biochemistry: glycated hemoglobin (HbA1c), serum glutamyl-oxaloacetic transaminase (AST), serum glutamic-pyruvic transaminase (ALT), albumin, creatinine, blood urea nitrogen (BUN), fasting plasma glucose

Urine or serum pregnancy test will be performed on women with child bearing potential at screening visit.

Note: According to the changing of regional practice, the BUN test can't be conducted in local laboratory in Mainland China. The BUN test will be waived in Mainland China.

5.5.4 Physical Examination

A physical examination including vascular, neurological, and musculoskeletal status will be performed at screening, baseline visit, each bi-weekly visit (during comparative period), and scheduled visits during follow-up period.

5.5.5 Electrocardiogram (ECG)

An ECG will be performed at screening, week 16 and week 28 or early permanently discontinued study intervention.

5.5.6 X-ray

The foot X-ray will be performed at screening visit.

5.6 Adverse Events and Other Safety Aspects

5.6.1 Definition of Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study treatment
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

Beginning when the subject randomized, the investigator will closely monitor each subject for evidence of treatment intolerance and for the development of clinical or laboratory evidence of adverse events.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”).

5.6.2 Definition of Serious Adverse Events (SAEs)

A serious AE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening (an event in which the <subject> is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe),
- Results in persistent or significant disability/incapacity,
- Results in congenital anomaly, or birth defect,
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious).
- Other medically important events.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-

threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse 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.

5.6.3 Criteria for Causal Relationship to the Study Treatment

The investigator will also evaluate the relationship of each adverse event to study intervention according to the definitions as follows. Adverse events that fall under either "Unlikely", "Possible" or "Probable" or "Definitely" should be defined as "adverse events whose relationship to the study treatments could not be ruled out".

- Not related: Adverse reactions associated with drug usage are clearly not related.
- Unlikely: Adverse reactions and drug usage on the timing is not reasonable (but not impossible), and the patients ' own illness or medicines (chemicals) indicated more reasonable explanation for this event.
- Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Probable: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).
- Definitely: Adverse reaction associated with medication usage is time sequential, which is credible and cannot be reasonably counted to the patients ' own illness or medicines (chemicals). The reaction after stopping the medication reflects the credible basis on pharmacology or pathology, as well as precise pharmacological phenomena or disease state, it appears similar reaction if re-dosing.

5.6.4 Criteria for Defining the Severity of an Adverse Event

The following standard with 3 grades is to be used to measure the severity of adverse events, including abnormal clinical laboratory values.

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

5.6.5 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator must contact the sponsor immediately (within 24 hours of their knowledge of the event or at the earliest possible time point).

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be signed by investigator. The initial report of a serious adverse event may be made by email. It is preferable that serious adverse events be reported via email. A report of a serious adverse event must be followed by a completed Serious Adverse Event Form from the investigator.

In addition, the suspected unexpected serious adverse reactions (SUSAR) should also forward to IRB and health authority by the sponsor within the time frame according to the regulation of the health authority.

5.6.6 Follow-up to Adverse Events

All adverse events occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized (all follow-up results are to be reported to the sponsor).

Since it is unpredictable how long such a follow-up will take, data from this follow-up generated after the subject's post study visit will be recorded by the investigator. Full details regarding this follow-up will be described in the study report, whenever necessary.

If during adverse event follow-up, the adverse event progresses to an "SAE", or if a subject experiences a new SAE whose relationship to the study drug(s) cannot be ruled out, the investigator must immediately report the information to the sponsor.

Even if the subject does not return to normal or to his or her previous state, the follow-up can be considered finished when the following procedures have been taken:

- The investigator judges that the follow-up of the subject concerned is no longer necessary based on the progress made during the follow-up,
- The reason for such a judgment is entered as a comment on the case report form for the follow-up, and
- The sponsor judges that the reason is acceptable with regard to the safety of the subject concerned.

5.6.7 Procedure in Case of Pregnancy

If it is subsequently discovered that a subject is pregnant during the study period, study treatment will be permanently discontinued in an appropriate manner.The Investigator must notify sponsor or its designee of this event within 24 hours of awareness. The pregnancy events require immediate notification to sponsor or its designee starting from the date of randomization until the last follow up visit. For the subject who withdraws the study during the treatment period, the pregnancy events should be reported to sponsor until 28 days after the last administration of study treatment.In addition, the Investigator must report to sponsor or its designee follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome.

5.6.8 Supply of New Information Affecting the Conduct of the Study

When new information necessary for conducting the clinical study properly is obtained, the sponsor should inform all investigators involved in the clinical study, IRB/IEC, as well as the regulatory authorities of such information, and when needed, should amend the subject information, written informed consent form and/or protocol on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB should be sent to the IRB.

5.6.9 Deviations from the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

- Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the sponsor and the head of the study site. Keep a copy of the notice.
- Consult with the sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the sponsor.

6 TERMINATION OF THE CLINICAL STUDY

- When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the investigator.
- If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor of the discontinuation and the reason for it.

7 STATISTICAL METHODOLOGY

7.1 Sample Size

The recent phase 2 clinical trial was carried out 30 subjects with Wagner-grade-1 chronic diabetic foot ulcers treated with ON101 for up to 12 weeks. The results showed that the incidence of healing by 12 weeks was 50% and the time of 50% subjects reached healing was approximately 10 weeks. Of the 30 subjects, treatment with ON101 for up to 12 weeks resulted in approximately 70% reduction of wound size. The average wound size at baseline was 577 mm^2 (303 - 1225 mm^2), and decrease to 163 mm^2 for up to 12 weeks of ON101.

Sample size calculation is performed by the superiority test based on the incidence of complete healing of the target ulcer between the two treatment groups within 16 weeks. The ON101 cream will be considered to be effective if the complete healing rate is superior to the corresponding endpoint of the Aquacel® Hydrofiber® dressing at two-sided 5% significance level. The hypothesized complete healing rate difference between two treatment groups is 20%, assuming the rates are 50% for ON101 cream and 30% for Aquacel® Hydrofiber® dressing. This study is also planned two interim and 1 final analysis at around 50%, 90%, and 100% of study information, and the futility/superiority of ON101 cream will be assessed using the Lan-DeMets alpha-spending approach with an O'Brien-Fleming boundary.

Under the assumption described above and with a 1:1 randomization ratio of the two groups, a minimal 212 evaluable subjects will be required to achieve at least 80% power to detect a significant difference in complete healing rate using a 2-sided alternative at the 5% nominal significance level. Assuming the non-evaluability rate is 10%, a total of 236 subjects (118 subjects for ON101 cream and 118 subjects for Aquacel® Hydrofiber® dressing) will be enrolled into this trial.

7.2 Analysis Sets

In accordance with ICH recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses. Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan (SAP).

7.2.1 Full Analysis Set (FAS)

The intent-to-treat (ITT) principal will be applied on the "full analysis set (FAS)". The FAS includes all subjects who are randomized, irrespective of actual receipt of study intervention. This set will be the primary analyses population for all efficacy data. Under the ITT principle, all participants once randomized are analyzed according to the condition to which they were originally assigned, regardless of adherence with the protocol or the occurrence of adverse events. Thus, using the ITT principle, participants who were randomly assigned to the ON101 cream group but who received partial or none of the ON101 cream, would still be followed and analyzed

as if the participant received the ON101 cream. Participants randomly assigned to the Aquacel® Hydrofiber® dressing group but who received the ON101 cream would be retained in the Aquacel® Hydrofiber® dressing group and analyzed as if they received only the Aquacel® Hydrofiber® dressing.

7.2.2 Safety Analysis Set (SAF)

The "safety analysis set (SAF)" will include all randomized patients who received study intervention to the selected treatment area. This set will be used for the analyses of safety data. Safety will be assessed according to the treatment subjects actually received at least one dose of ON101 cream or Aquacel® Hydrofiber® dressing.

7.2.3 Supportive Analysis Population

Subjects in FAS with eligible target ulcer at baseline will be included as modified ITT (mITT) population. mITT will be used for supportive analyses of efficacy data as appropriate.

7.3 Demographics and Other Baseline Characteristics

The demographics and baseline wound characteristics (ulcer severity, etiology, location and size) of subjects will be collected at screening period or Day 1 (before study intervention applied). These variables will be summarized by descriptive statistics for two treatment groups. For continuous variables, the number, mean, standard deviation, median, minimum, and maximum values will be presented. Besides, an analysis of variance (ANOVA) test will also be performed for continuous variables to test the comparability for two randomized groups.

For categorical variables, the numbers and percentages of subjects in each class will be listed, and the Fisher's exact test for two treatment group comparison will also be performed.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Variable

The primary efficacy variable is the proportion of subjects whose target ulcer is complete healing. The definition of complete healing for the target ulcer is complete epithelialization which is maintained with no drainage for at least 2 weeks and is confirmed by a blinded independent evaluator.

This will be a multi-center study. It is anticipated that the number of participating centers can be large and the number of subjects enrolled at each center could be small. As a result, the data from all centers will be pooled for statistical analyses.

The hypothesis for the comparison is given as follows:

H_0: The healing rates on ON101 cream and Aquacel® Hydrofiber® dressing are the same

H_1: The healing rates on ON101 cream and Aquacel® Hydrofiber® dressing are not the same

The number of percentage of subjects achieving the efficacy endpoints will be summarized by visit and ON101 cream group will be compared to the Aquacel® Hydrofiber® dressing group with Chi-square test. The logistic regression model with treatment/intervention as fixed factor, and baseline wound size and Wagner grade as covariates will be applied to the primary analysis of primary endpoint. The results of the logistic regression model will be presented in terms of the odd ratio (ON101 cream versus Aquacel® Hydrofiber® dressing), with p-values and associated 95% confidence intervals of the odds ratio.

The test intervention (ON101 cream) will be concluded to be superior to the control (Aquacel® Hydrofiber® dressing) in average if the null hypothesis (H_0) is rejected and the odds ratio higher than 1. To reflect the interim analysis, final analyses will be based on a Type I error rate (two-sided) of 0.039611.

7.4.2 Analysis of Secondary Variables

The secondary efficacy variables will be analyzed using FAS population.

- Time to complete ulcer healing:

  Time to complete ulcer healing will be calculated for all subjects from the day of the first study medication applied until the day that original healing of target ulcer is first observed. Subjects who could not achieve complete ulcer healing at the last evaluation time point will be censored (non-healing) at the date of last evaluation. The median time to complete ulcer healing will be estimated by Kaplan-Meier method and two-sided 95% confidence interval will be reported. The log-rank test will be performed for comparing time to complete ulcer healing among two groups.

- Percentage change in ulcer surface area from baseline:

  Summary statistics of the measured wound size and the percentage change from baseline will be obtained for each group by observation time point and their changes over time will also be graphically presented.

  For the analysis on the ulcer surface area, the percentage change from baseline at each visit will be calculated using the actual wound size. The wound size percentage change will be compared between groups by means of analysis of co-variance (ANCOVA) adjusted with baseline measurement of sizes and baseline Wagner grade.

- Percentage of subjects with a 50% reduction of ulcer surface area:

  The proportion of subjects who achieve 50% reduction of wound size from baseline to interim visit will be calculated for two groups and analyzed by a logistic regression model with treatment as factor, and baseline wound size and Wagner grade as covariates.

- Incidence of infection of the target ulcer:

The incidence of infection of the target ulcer will be summarized and tabulated by two treatment groups at the final ulcer assessment. The incidence of infection of target ulcer between two groups will be compared using Fisher's exact test.

7.4.3 Analysis of Exploratory Variables

The exploratory variable will be analyzed for those subjects whose target ulcer complete healed at the end of comparative period, the recurrences of target ulcer within 3-month follow-up period will be compared between two groups by Fisher's exact test.

7.5 Analysis of Safety

Adverse events will be regarded as Treatment Emergent (TEAE) if they started on or after the date and time of administration of the first dose of study intervention or if they were present prior to the administration of the first dose of study intervention and increased in severity during the study.

Adverse Events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) dictionary and grouped by system organ class and preferred term and events. TEAEs will be summarized by frequency and proportion of total subjects, by system organ class and preferred terms. If appropriate, the incidence of adverse events (preferred terms and system organ class) will be compared for each of the two treatment groups using Fisher's exact test.

For the clinical laboratory and vital signs data, the data will be tabulated by treatment group for raw data and for change from baseline to evaluated time points; descriptive statistics to be provided include: n, mean, median, standard deviation, minimum and maximum. The differences between groups will be analyzed by analysis of covariance (ANCOVA) with factor being fitted for treatment, and baseline value fitted as a covariate. Subjects with laboratory data outside the normal range will be listed and abnormal values will be flagged.

7.6 Interim Analysis (and Early Discontinuation of the Clinical Study)

7.6.1 Early Discontinuation

The Independent Data Monitoring Committee (IDMC) will review the results of the interim analysis for a possible early termination of the trial. The statutes of the IDMC will be defined in advance and will be included in a separate charter. To avoid possible bias, unless a decision is made to terminate the trial, the IDMC will not disclose any results other than the recommendation to continue the trial.

7.6.2 Interim Analysis

Two Interim Analyses will be conducted when 118, and 212 subjects complete the comparison period or early withdraw from study intervention on a sequential basis. This will be about 50% and 90% of the total number of subjects that will be randomized.

The independent Data Monitoring Committee (IDMC) will review the results of the interim analyses for a possible early termination of the trial due to an overwhelming efficacy results based on pre-defined alpha specified based on O'Brien-Fleming alpha-spending function specified in this protocol and detailed in the Statistical Analysis Plan(SAP). The statutes of the IDMC will be defined in advance and will be included in a separate charter.

The Lan and DeMets version (Lan and DeMets, 1983) of the O'Brien-Fleming alpha-spending function is used to calculate the Type I Error rate alpha, to maintain the trial-wise 5% type I error. Because the 1st interim analysis has been conucted at 124 subjects who complete the comparision period, the alpha boundary will be estimated base on 53% information for the 1st interim analysis. The proportion of the overall number of target subjects (a total of 236 subjects) included in the analyses at each point and alpha boundaries used to assess significance at each analysis are as follows.

Analysis number	% of randomized subjects	Alpha Boundary
1. Interim Analysis 1	53%	0.003957
2. Interim Analysis 2	90%	0.034760
3. Final	100%	0.039611

As the 1st IA failed to meet the boundary of (0.003957); a 2nd IA will be conducted. Based on the above mentioned boundary for the 2nd IA, the IDMC can stop the trial if the observed p-value is less than 0.034760, the alpha presented above.

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7.7 Handling of Missing Data

All available data will be displayed and utilized in data analysis. Under the ITT principle, the subject will be considered as "non-healing" if no available data for post-baseline wound/ulcer healing assessment. Otherwise, the method of last observation carry forward (LOCF) will be used to account for incomplete observation.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or designee must record all protocol-required data in the provided Case Report Form (CRF). In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) onto the CRF as soon as possible after the subject visit. CRFs and any supporting documents should be available for retrieval by the sponsor/delegated CRO at any given time. The investigator should keep a copy of the CRFs and submit the original CRFs to the sponsor/delegated CRO.

The monitor should verify the data in the CRFs with source documents to confirm that there are no inconsistencies between them. If the monitor finds no inconsistencies, the appropriate CRFs are collected.

If any inconsistency is detected on the collected CRFs, the monitor or data manager should query the investigator/sub-investigator using the query resolution form. Resolution of the query should be prepared by the investigator/sub-investigator or site designee and provided to the sponsor.

The monitor should verify the revised data of the CRFs with source documents and confirm that there are no inconsistencies between them, and also check that appropriate records on the correction/addition of data are maintained.

For screening failures, the minimum demographic data (sex, age, race and screening date) and reason for screening failure will be collected in screening failure log (SFL), if applicable.

The investigator is responsible to ensure that all data in the CRFs, and data correction report are accurate, complete and legible, and that all entries are verifiable with source documents. Copies of these documents should be appropriately maintained on submission.

Laboratory tests are performed at local laboratory in each study site.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and signed and dated informed consent forms
- Visit dates

- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events and concomitant medication (if applicable)
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)

8.1.3 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data management will be coordinated by the sponsor or delegated CRO in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. CRF retrieval and correction process will be referenced in the CRF instructions. Coding of medical terms will be performed using MedDRA.

In the interest of collecting data in the most efficient manner, the investigator or designee should enter data (including laboratory values if applicable) into the CRF immediately after the subject visit. CRFs and any supporting documents should be available for retrieval at any given time.

The study database will be soft-locked when all data that are specified in the study protocol to be collected have been received and cleaned according to applicable SOPs. It will be hard-locked when a (blind) data review meeting has been held, and all data related decisions have been made and reflected in the database.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The study will start only after written approval from an IRB/IEC, which operates according to ICH GCP guidelines. Documentation of the IRB/IEC initial and continued study approval or the withdrawal of such approval will be immediately forwarded to the Sponsor.

8.2.2 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to GCP, ICH Guidelines and the applicable laws and regulations.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

Prior to execution of the clinical study, the investigator should prepare the written informed consent form and other written information in collaboration with the sponsor and revise the information whenever necessary. The written informed consent form and any other written information should be submitted to the sponsor and be subject to prior approval by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

- The investigator/sub-investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects, using the written information, and for obtaining their full understanding and written consent to participate in the study of their own free will.
- The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the written information, or write down his/her name, and date the form.
- Informed consent must be obtained by the time that the first observations / examinations of the pre-investigational period are performed. Guardian consent should be obtained from the proxy consenter, before start of pre-investigational period.
- The investigator or other responsible personnel must give a copy of the signed consent form to the subject and store the original appropriately in accordance with the rules at the study site concerned.
- The investigator or other responsible personnel should note the following when obtaining consent from subjects:
    - No subject may be subjected to undue influence, such as compulsory enrollment into a study.

- The language and expressions used in the written information should be as plain and understandable as possible. Subjects should be given the opportunity to ask questions and receive satisfactory answers to the inquiry, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator/sub-investigator, collaborators, or the sponsor from liability for negligence.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

- The investigator/sub-investigator will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study (e.g., report of serious adverse drug reactions). The communication should be documented in the subject's medical records, and it should be confirmed whether the subject is willing to remain in the study or not.
- If the investigator recognizes the necessity to revise the written information in the terms and conditions applicable to paragraph 1, the written information should be revised immediately based upon the newly available information, and be re-approved by the IRB/IEC.
- The investigator/sub-investigator should obtain written informed consent to continue participation with the revised written information defined in paragraph 2, even if subjects are already informed of the relevant information orally. The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the informed consent form, or write down his/her name and date the form. The investigator or other responsible personnel should give a copy of the signed informed consent form to the subject who had given consent with the written information and store the original appropriately as done for the previous informed consent.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

The study will be considered for publication or presentation at (scientific) symposia and congresses. The investigator will be entitled to publish or disclose the data generated at their respective study site only after allowing the sponsor to review all transcripts, texts of presentations, and abstracts related to the study at least 90 days prior to the intended submission for publication or any other disclosure. This is necessary to prevent premature disclosure of trade secrets or patent-protected information and is in no way intended to restrict publication of facts or opinions formulated by the investigator. The sponsor will inform the investigator in writing of any objection or question arising within 30 days of receipt of the proposed publication material. The manuscript can be published only after agreement between investigator(s) and sponsor.

8.3.2 Documents and Records Related to the Clinical Study

The sponsor will provide the investigator, etc. and study site with the following documents:

- Study protocol (and amendments, as applicable)
- Investigator's Brochure (and amendments, as applicable)
- CRFs and SAE Report Worksheet
- Study drug with all necessary documentation
- Study contract
- Protocol approval of regulatory authority

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Agreement with the investigator concerning the protocol and CRF
- Curricula vitae of all investigators and subinvestigators

- Copies of notifications from the IRB/IEC(including a list of participating board members) concerning the protocol and protocol amendments (if applicable)
- Executed Study contract
- Laboratory normal values and ranges(including amendment or revised versions); (if applicable, signed and dated by the responsible laboratory employee)
- Signed confidentiality agreement
- Medical/Laboratory/Technical procedures/tests certifications or accreditations or established quality control or other validation, where required.

At the end of the study, the sponsor is responsible for the collection of:

- Unused CRFs and other study documentation,
- Unused study treatment

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. It is recommended, however, that records be retained for at least five years in the event follow-up is necessary to help determine any potential hazards to subjects who took part in the study.

The sponsor will notify the investigator if the NDA is approved or if the development is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on CRFs supplied for each subject.

The documents of the Efficacy and Safety Evaluation Committee (minutes and standard operating procedures and others) and the judgment committee outside the study sites (minutes and standard operating procedures and others) shall be retained by the sponsor.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments and/or revisions. Depending on the nature of the amendment and/or administrative change, either IRB/IEC approval or notification is required. The changes will become effective only after the approval of the sponsor, the investigator, and the IRB/IEC (if applicable). Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Insurance of Subjects and Others

The sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

9 QUALITY ASSURANCE

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to inspect/audit the clinical study at any or all investigational sites. The auditor is independent from the clinical monitoring and project management team at the Sponsor. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

The sponsor will establish all the duties related to the clinical study before requesting implementation of the study by the study sites and allocate suitable personnel to the study.

10.1 Independent Data-Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed to evaluate the outcome and safety and tolerability issues that may arise during the conduct of the study according to the IDMC Charter. The IDMC will consist of 3 members. Two members will constitute a quorum. The IDMC includes experts in or representatives of the fields of clinical medicine, in particular expertise related to the disease being studied, clinical trial methodology, including safety review, assessment, and reporting biostatistics. It is essential that the judgment of members of the IDMC not be influenced by factors other than those necessary to maintain subject safety and to preserve the integrity of the trial. Independence is essential to ensure that IDMC members are objective and capable of an unbiased assessment of the trial‘s safety and efficacy data.

The IDMC will review two formal interim efficacy and safety analyses at the time when the 118 and 212 subjects (50% and 90% of the total number of randomized subjects) have completed the comparison period or early withdrawn from study intervention. During the randomized portion of the study, the trial may be stopped early if the ON101 cream arm appears to be insufficiently efficacious, significantly more efficacious, or if there are unacceptable toxicities.

The critical nature of interim decision means that the investigators and the sponsor must provide complete, timely and accurate interim data. Following the interim review, the IDMC will forward to the sponsor its recommendation regarding whether to continue the study as planned.

Apart from these formal interim analyses, the IDMC may periodically monitor the overall safety results. To avoid possible bias, unless a decision is made to terminate the trial, the IDMC will not disclose any results other than the recommendation to continue the trial.

10.2 Independent Evaluator

An independent evaluator who is blinded to subjects’ treatment will evaluate the wound healing status, especially on epithelialization wound, that may arise during the conduct of the study. The independent evaluator who will be from outside of the sponsor company and outside of the study sites (investigators), and is an expert in the respective disciplines of the fields of clinical medicine, in particular expertise related to the disease being studied.

All photographs sent to the independent evaluator will be under the blinded matter. On the photographs used for wound healing status there will be no information available regarding treatment group, subject background data (eg, gender, age) and the time of photo. The photographs will be re-labeled according to the randomization list for photos before they are sent to the independent evaluator for evaluation. The randomization process will also ensure that the independent evaluator does not receive the time sequence on photographs of the same subject consecutively.

11 REFERENCES

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12 APPENDICES

APPENDIX 1. Diabetic Foot Disorders: A Clinical Practice Guideline (2006 revision)