A PROSPECTIVE, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF A GEL FORMULATION OF ESMOLOL HYDROCHLORIDE (GALNOBAX®) IN TREATING DIABETIC FOOT ULCERS

Protocol Number: NG-A16

IND Number: 102371

IND Sponsor: NovaLead Pharma Pvt. Ltd.

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Version Number: v 2.1

28 Nov 2019

Summary of Changes from Protocol Version 1.0 to Protocol Version 2.0

Affected Section(s)	Summary of Revisions Made	Rationale
Section 1.1 **Page 2 and** **Section 5.1** **Page 19**	**Original Text** 1. Subjects, male or female, aged 18 to 65 years (inclusive) with Type 1 or Type 2 diabetes undergoing therapy for glycemic control Modified Text **1.** Subjects, male or female, aged 18 to 75 years (inclusive) with Type 1 or Type 2 diabetes undergoing therapy for glycemic control	Many participating sites reported that several potential patients are being denied treatment due to upper age limit of 65 years in the current protocol. The life expectancy of India is about 69 years. In a community based cross-sectional study carried out in India, the average age of subjects with diabetic foot ulcer (DFU) is more than 60 years and 75% patients are with age more than 60 years as reported in a recent clinical study (Vibha et al. BMC Endocrine Disorders (2018) 18:43). Compared to patients with age < 50 years, the odds of developing DFU among patients in age group of 61-70 years was 4.4 and in age group of >70 years was 11.6. Thus, more non-healing ulcers are seen in the elderly or geriatric population than in young population. By including patients up to 75 years will establish safety and efficacy of Galnobax in geriatric population and such sub-population analysis will be carried out. The Galnobax treatment provided in this study is a topical treatment over the wound and hence not expected to lead to any severe side effects because of low systemic circulation of drug.

Summary of Changes from Protocol Version 2.0 to Protocol Version 2.1

Affected Section(s)	Summary of Revisions Made	Rationale
Section 6.3	**New Text Added** In case the Subject is staying far from the site (i.e. 40 km or more from the site) and/or Nurse is unable to visit every week to the site for treatment compliance check, following procedure will be followed for IP transport and compliance check: IP will be issued to the study Nurse at the time of the randomization visit along with study diary in an aluminum box having a lock. One key of this lock will be with the study Nurse and other with the unblinded CRC at the site. At the time of weekly site visit of the Subject, study Nurse will keep used IP tubes and Study diary in this box which will be locked and sent to the site with the Subject. Site unblinded CRC will take aluminum box from the subject and will check IP compliance as well as study diary. The IP will be reissued to the nurse after weighing the tubes and new study diary will also be issued (through which new dose of the subject will be conveyed to the Nurse). These materials will be kept in the aluminum box which will be locked and given to the Subject for handing over it to the study Nurse. This process will continue during all treatment visits.	In order to make convenient for the subjects and study Nurse residing far-off from the study site.
Contact Details, **Section 1.1 Page No 6,** **Section 4.1 Page No 16 and** **Section 9.4.1 Page No 43**	Original Text Total number of participating sites: - 20 Modified Text Total number of participating sites: - 40	In order to meet recruitment target for study

CONTACT DETAILS	
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Clinical Research Organization	**JSS Medical Research India Private Limited** Address: Plot 12/2, 6th Floor, Vatika Mindscapes Tower- B, Sarai Khwaja Metro Station, NH-2, Mathura Road, Sector 27 D, Faridabad, Haryana-121003, India Phone: +91 11 129 6613500 Fax: +91 11 129 6613520
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Biostatistician	**Mr. Santosh Kumar** Address: JSS Medical Research India Private Limited Plot 12/2, .6th Floor, Vatika Mindscapes Tower-B Sarai Khwaja Metro Station, NH-2, Mathura Road Sector 27 D, Faridabad, Haryana-121003, India Phone: +91 11 129 6613500 E-mail: *santosh1.kumar@jssresearch.com*
Investigator Responsible for Conducting the Study	This information is documented separately in the dossier to be submitted to the regulatory authority.
Clinical Laboratory and other Medical and Technical Department(s) and Institutions involved in the Study	This information is documented separately in the dossier to be submitted to the regulatory authority.
Total number of participating sites	40

SPONSOR'S DECLARATION

I, on behalf of NovaLead Pharma Pvt. Ltd., have read, understood & approved this Protocol. I agree to comply with all requirements regarding the obligations of Sponsor and all other pertinent requirements of the International Conference on Harmonization (ICH) of technical requirements for registration of Pharmaceuticals for human use guideline for Good Clinical Practice ICH E6 (amended version), in accordance with Declaration of Helsinki (amended version), Good Clinical Laboratory practice, and applicable regulatory guidelines.

Sponsor's Representative:

Name: **Dr. Sudhir Kulkarni**

Address: **NovaLead Pharma Pvt. Ltd.**
Anaahat, Plot No. 5, Ram Indu Park,
S.No. 131/1b/2/11, Baner Road,
Pune 411 045, INDIA
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Signature: 

Date: 27/12/2019

CRO Approval Page

I have prepared version 2.1 of Study protocol (ID: NG-A16), dated 28 Nov 2019.

To the best of my knowledge, the protocol is accurate and complete. I approve this version as the final copy and consider it acceptable for regulatory submission.

Protocol Author:

Dr. Neha Pawar

JSS Medical Research India Private Limited
Plot 12/2, 6th Floor, Vatika Mindscapes Tower-B
Sarai Khwaja Metro Station, NH-2, Mathura Road
Sector 27 D, Faridabad, Haryana-121003, India

Signature:

Date: 30 Dec 2019

Study Biostatistician:

Mr. Santosh Kumar

JSS Medical Research India Private Limited
Plot 12/2, 6th Floor, Vatika Mindscapes Tower-B
Sarai Khwaja Metro Station, NH-2, Mathura Road
Sector 27 D, Faridabad, Haryana-121003, India

Signature:

Date: 30 Dec 2019

INVESTIGATOR'S DECLARATION

I, the undersigned, declare that I have read and understood this protocol and hereby agree to conduct the Study in accordance with this protocol and to comply with all requirements regarding the obligations of investigators and all other pertinent requirements of the International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use guideline for Good Clinical Practice ICH E6 (amended version), in accordance with Declaration of Helsinki (amended version), principles on Good Laboratory Practice, and all regulatory requirements for including all elements required for an Institutional Review Board to assess Study risks and benefits.

I further agree to ensure that all associates assisting in the conduct of Study are informed regarding their obligations.

I agree to comply with all relevant standard operating procedures required for the conduct of this Study and would document any significant deviation occurring during the Study.

Principal Investigator:
Name:

Signature:

Date:

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Definitions

Term	Definition
Diabetic Foot Ulcer (DFU)	Diabetic foot ulceration is full-thickness penetration of the dermis of the foot in a person with diabetes.
Standard of Care (SoC)	Wound cleaning by normal saline, maintenance of moist wound environment and off-loading of the Target Ulcer. In addition, during Site Visits removal of necrotic, infected and/or nonviable tissue by debridement and management of infection to be done by the Investigator, if required.
Target Ulcer Closure	100% re-epithelialization without drainage or dressing requirement (except if recommended by the Investigator for covering of the closed wound) to be confirmed by two consecutive site visits two weeks apart from first observation of closure.
Time to Target Ulcer Closure	Duration of first observation of closure from Baseline visit for those Target Ulcers for which conditions for Target Ulcer Closure were satisfied.
Intent to Treat (ITT) Population (Safety Evaluable Population)	All Subjects who are randomized and received at least one dose of Study medication will be included in ITT Population.
Full Analysis Set (FAS) Population (Efficacy Evaluable Population)	All randomized Subjects who had at least 6 weekly Site Visits for the assessments of Target Ulcer Closure or had Target Ulcer closed earlier than 6 weeks.
Per Protocol (PP) Population	All randomized Subjects who have completed the Study without any major protocol deviation.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council for Harmonization Good Clinical Practice (ICH GCP), Declaration of Helsinki and GCP guidelines as per Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services (DGHS), Government of India. The Principal Investigator will ensure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this Study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the EC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the Study. All changes to the consent form will be EC approved and a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Prospective, Multicenter, Randomized, Double-Blind, Phase 3 Study to Evaluate the Safety and Efficacy of a Gel Formulation of Esmolol Hydrochloride (Galnobax®) in Treating Diabetic Foot Ulcers
Study Description:	The purpose of the current Study is to determine the safety and effectiveness of Galnobax® plus Standard of Care versus only Standard of Care, in treating DFU. In addition, Study is designed to investigate the safety of Galnobax® vehicle for establishing non-deleterious effects of Vehicle on wound healing in the Subjects with DFU.
Objectives:	The objective of this Study is to evaluate efficacy and safety of Galnobax® gel (14% twice daily application) plus Standard of Care treatment versus only Standard of Care for healing of DFU.
	Primary Objective: 1. To assess the efficacy of Galnobax® in terms of proportion of Subjects achieving Target Ulcer Closure within 12-week Treatment Phase upon application of Galnobax® plus Standard of Care as against only Standard of Care treatment, as assessed by the blinded Investigator.
	Secondary Objectives: 1. To compare Time to Target Ulcer Closure within the 12-week Treatment Phase, upon application of Galnobax® plus Standard of Care as against only Standard of Care treatment, as assessed by the blinded Investigator. 2. To compare proportion of Subjects achieving Target Ulcer Closure till End of Study upon application of Galnobax® plus Standard of Care as against only Standard of Care treatment, as assessed by the blinded Investigator.

	Safety Objectives: 1. To investigate the safety of Galnobax® treatment during the Study. 2. To investigate the safety of Galnobax® vehicle for establishing non-deleterious effects of Vehicle on wound healing.
Endpoints:	Primary Endpoint: Efficacy endpoint: The efficacy assessment will involve Galnobax® plus Standard of Care and only Standard of Care groups 1. Proportion of Subjects achieving Target Ulcer Closure within 12-week Treatment Phase, as assessed by blinded Investigator. Secondary Endpoints: Efficacy endpoints: 1. Time to Target Ulcer Closure during the 12-week Treatment Phase, as assessed by the blinded Investigator. 2. Proportion of Subjects achieving Target Ulcer Closure till End of Study, as assessed by the blinded Investigator. Safety endpoints: 1. Proportion of Subjects with treatment emergent adverse events (TEAEs). 2. Proportion of Subjects with events related to the local wound assessment of Target Ulcer in Vehicle plus Standard of Care group.
Study Population:	A maximum of 350 Subjects will be randomized for this Phase 3 clinical Study who have DFU and satisfy eligibility criteria given below and in *Section 5*. The break-up of these 350 Subjects is as follows: Group 1: Galnobax® + SoC such that minimum number of Subjects in this group is 120. Group 2: SoC alone such that minimum number of Subjects in this group is 120. Provision for drop-outs in Groups 1 and 2: 20% i.e. 60 Subjects Group 3: Vehicle + SoC such that the maximum number of Subjects in this group is 50 to evaluate the safety of Galnobax® vehicle. **Eligibility Criteria** **a. Inclusion criteria** The Subjects who satisfy all the following inclusion criteria will be enrolled in the Study and subsequently randomized:

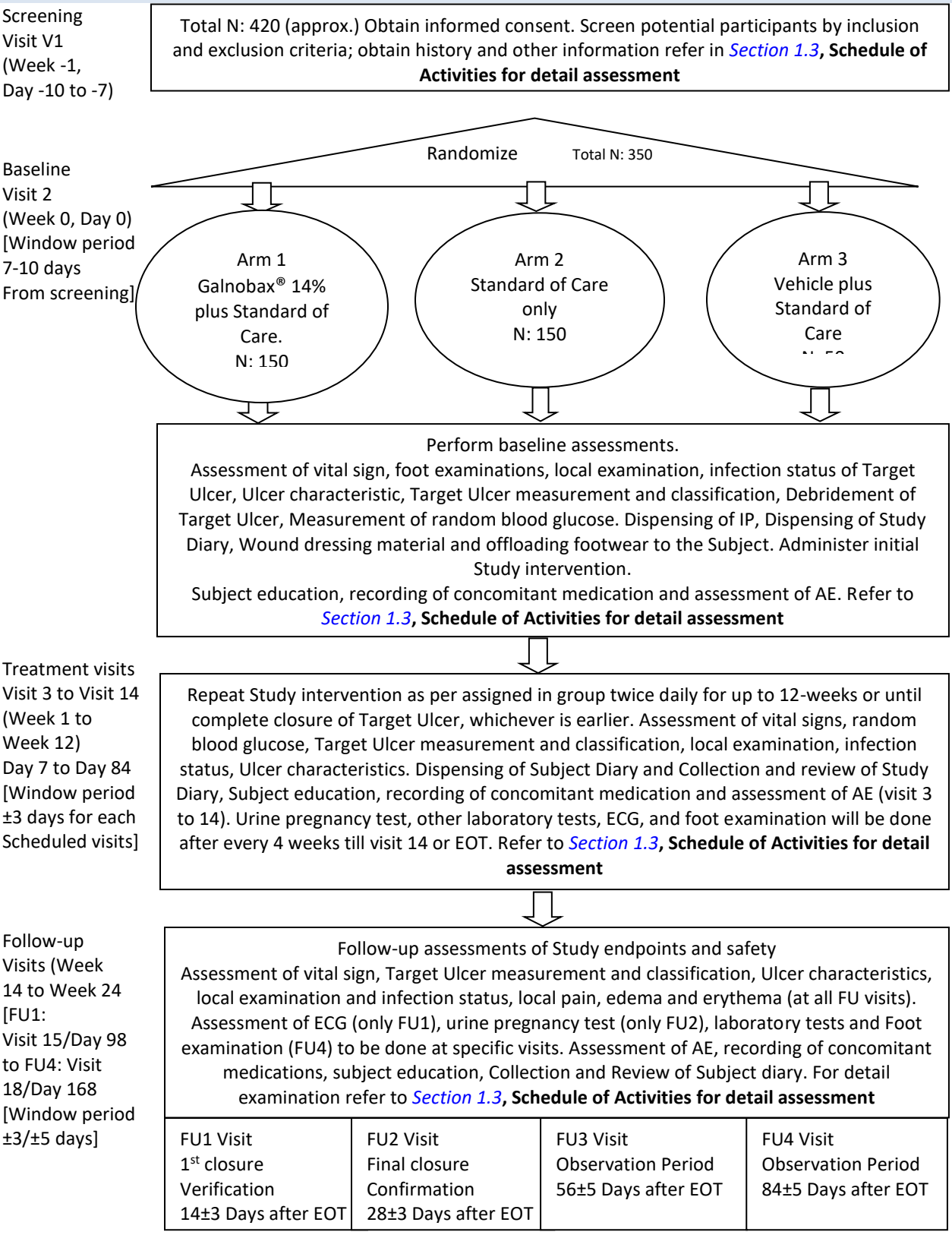
	1. Subjects, male or female, aged 18 to 75 years (inclusive) with Type 1 or Type 2 diabetes undergoing therapy for glycemic control 2. Subject has glycosylated hemoglobin, $HbA1_C$, ≤ 12% 3. Subject with diagnosis of neuropathic foot ulcer by 10g monofilament test 4. Subject has adequate vascular perfusion of the affected limb, confirmed by Ankle-Brachial Index (ABI) ≥ 0.65 and ≤ 1.3 ***Note**: If the ABI measurement is >1.30 one of the following confirmatory tests must be performed for subject to be considered eligible. Prior documented flow Study within the last 3 months of the Screening Visit is acceptable.* *a. Great Toe pressure (plethysmography) > 40 mm Hg;* *b. Transcutaneous partial pressure oxygen (TcPO2) at the foot > 40 mm Hg;* *c. Skin Perfusion Pressure (SPP) > 40 mm Hg;* *d. Doppler ultrasound (biphasic or triphasic waveforms) consistent with adequate blood flow to the affected extremity, as determined by the standard practices of the Investigator and the site* 5. Presence of at least one DFU that meets all of the following criteria: *a. A full-thickness ulcer of Grade A1 as per Texas classification system;* *b. Ulcer is located below or up to 5 cm above the malleoli (excluding ulcers between the toes);* *c. Ulcer size (area) is ≥ 2 cm^2 and ≤ 15 cm^2 (post-debridement);* *d. There is a minimum 3 cm margin between the qualifying Target Ulcer and any other ulcers on the specified foot, post-debridement;* *e. No exposed bone, tendon, muscle, ligament or joint capsule, and no tunneling, undermining, or sinus tracts;* *f. Unresponsive to ulcer care and open for at least 6 weeks at the time of the Screening Visit;* *g. Ulcer is non-infected as determined by clinical assessment and complete hemogram;* *h. Ulcer has a clean, granulating base free of adherent slough to the greatest extent possible as per Investigator;* *i. Ulcer area reduction < 30% from the Screening Visit to Baseline visit* ***Note**: Criterion 4(i) will be evaluated at the time of randomization. If the subject has more than one qualifying DFU, the ulcer designated as*

	the Target Ulcer should be the ulcer preferably on the plantar region which is older, deeper and with a larger area. 6. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Investigator 7. Subject, if female of child-bearing potential, has a negative urine pregnancy test at Screening and willing to use acceptable methods of contraception (birth control pills, barriers) or abstinence throughout the Study 8. Subject is able and willing to comply with Study procedures including the use of an off-loading device (as applicable for the location of the ulcer) and adhere to protocol during the Study in the opinion of Investigator *9.* A Subject or LAR agrees to sign informed consent form and allow audio visual recording of consent, if applicable **b. Exclusion criteria** Subjects will not be eligible for enrolment in the Study if they meet any of the exclusion criteria listed below: 1. Actively infected ulcers with or without purulent discharge, ulcers with exposed bone or associated with osteomyelitis *Note: The osteomyelitis should be ruled out by clinical examination and X-ray findings where found necessary by the Investigator. If the Investigator is unable to ascertain the condition of osteomyelitis by probing of the Target Ulcer or digital X-ray then Investigator may use other techniques such as MRI, bone scintigraphy, leukocyte scanning or bone biopsy to rule out the presence of osteomyelitis based on availability of the investigation facility at the clinical sites.* *Note: If foot has more than one ulcers and one of them is infected, then Target Ulcer should not be selected from this foot unless all ulcers on the foot are free of infection. If subject has ulcers on both foots and infection is seen in the ulcer on non-target foot, subject may be included in the Study with prescribing oral antibiotic treatment for non-Target Ulcer.*

	2. Subjects with more than three ulcers below knee 3. Subjects with Target Ulcer requiring off-loading that cannot be effectively off-loaded; or unable to tolerate the off-loading method 4. Subject has ulcers caused by a disease other than diabetes, e.g., fungal ulcerations, malignant ulcerations, and ulcerations due to venous or arterial insufficiency, or due to hematological disorders, in the opinion of the Investigator 5. Ulcer, about which the Investigator is suspicious for cancer *Note: In case of such suspicion, ulcer present more than 1 year will require a 3-mm punch biopsy to rule out malignancy. Prior documented negative ulcer biopsy within the last 1 year of the Screening Visit is acceptable*. 6. Subjects with a gangrenous or ischemic ulcer 7. Subject with ulcer that in the opinion of the Investigator, may need amputation 8. Subject with Target ulcer where wound measurement is not possible, such as ulcers between toes 9. Body mass index (BMI) > 40 kg/m^2 10. Laboratory values at Screening of: *a) Hemoglobin < 10.0 g/dL* *b) White Blood Cells (WBC) < 2.0 X 10^9 cells/L* *c) Liver function studies [Total bilirubin, aspartate aminotransferase (AST) and alanine transaminase (ALT)] > 3x the upper limit of normal* *d) Albumin < 2.5 g/dL* *e) eGFR < 25 mL/min* 11. Presence of any existing clinically significant medical condition(s) that, in the opinion of the Investigator, could interfere with wound healing, including but not limited to the following: *a) Vasculitis or connective tissue disease* *b) Buerger's disease, Raynaud's or other peripheral vascular disease* *c) Clinically significant claudication or peripheral edema on the affected limb* *d) Acute or unstable Charcot foot* *e) Aplastic anemia or exacerbation of sickle cell anemia* *f) Current sepsis* *g) Congestive heart failure (NYHA Class III or IV), coronary heart disease with ST segment elevation, myocardial infarction, or coronary artery bypass graft or percutaneous transluminal coronary angioplasty within the last 6 months* *h) End-stage renal disease* *i) Immunosuppression* *j) Acquired immune deficiency syndrome (AIDS) or HIV positive*

	k) Any malignancy history 12. Subject has received or is currently receiving or scheduled to receive any of following medication or therapies during the course of the Study *a) Immunosuppressants (chronic systemic corticosteroids) within 30 days of randomization visit* *b) Revascularization surgery (e.g., angioplasty, coronary artery bypass surgery, transmyocardial revascularization) within 30 days of randomization visit* *c) Growth factors within 30 days of randomization visit* *d) Hyperbaric oxygen therapy (HBOT) within last 7 days of randomization visit* *e) Negative pressure wound therapy (NPWT) within last 7 days of randomization visit* *f) Bioengineered tissue or skin substitutes within 30 days of randomization visit* *g) Application of topical steroids to the ulcer surface within 30 days of randomization visit* *h) Use of any investigational drug(s) or therapies within 30 days of randomization visit* 13. Subject with intolerance to β-blockers at any time in the past 14. Has any other factor which may, in the opinion of the Investigator, compromise participation and/or follow-up in the Study
Phase:	3
Description of Sites/Facilities Enrolling Participants:	This Study will be conducted at 40 sites across India with competitive recruitment amongst sites.
Description of Study Intervention:	Galnobax® 14% gel, Twice daily, Topically
Study Duration:	*16 months*
Participant Duration:	*6 months*

1.2 SCHEMA


Screening Visit V1 (Week -1, Day -10 to -7)
Total N: 420 (approx.) Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history and other information refer in Section 1.3, Schedule of Activities for detail assessment
Baseline Visit 2 (Week 0, Day 0) [Window period 7-10 days From screening]
Randomize
Total N: 350
Arm 1 Galnobax® 14% plus Standard of Care. N: 150
Arm 2 Standard of Care only N: 150
Arm 3 Vehicle plus Standard of Care
Perform baseline assessments.
Assessment of vital sign, foot examinations, local examination, infection status of Target Ulcer, Ulcer characteristic, Target Ulcer measurement and classification, Debridement of Target Ulcer, Measurement of random blood glucose. Dispensing of IP, Dispensing of Study Diary, Wound dressing material and offloading footwear to the Subject. Administer initial Study intervention.
Subject education, recording of concomitant medication and assessment of AE. Refer to Section 1.3, Schedule of Activities for detail assessment
Treatment visits Visit 3 to Visit 14 (Week 1 to Week 12) Day 7 to Day 84 [Window period ±3 days for each Scheduled visits]
Repeat Study intervention as per assigned in group twice daily for up to 12-weeks or until complete closure of Target Ulcer, whichever is earlier. Assessment of vital signs, random blood glucose, Target Ulcer measurement and classification, local examination, infection status, Ulcer characteristics. Dispensing of Subject Diary and Collection and review of Study Diary, Subject education, recording of concomitant medication and assessment of AE (visit 3 to 14). Urine pregnancy test, other laboratory tests, ECG, and foot examination will be done after every 4 weeks till visit 14 or EOT. Refer to Section 1.3, Schedule of Activities for detail assessment
Follow-up Visits (Week 14 to Week 24 [FU1: Visit 15/Day 98 to FU4: Visit 18/Day 168 [Window period ±3/±5 days]
Follow-up assessments of Study endpoints and safety
Assessment of vital sign, Target Ulcer measurement and classification, Ulcer characteristics, local examination and infection status, local pain, edema and erythema (at all FU visits). Assessment of ECG (only FU1), urine pregnancy test (only FU2), laboratory tests and Foot examination (FU4) to be done at specific visits. Assessment of AE, recording of concomitant medications, subject education, Collection and Review of Subject diary. For detail examination refer to Section 1.3, Schedule of Activities for detail assessment
FU1 Visit 1st closure Verification 14±3 Days after EOT
FU2 Visit Final closure Confirmation 28±3 Days after EOT
FU3 Visit Observation Period 56±5 Days after EOT
FU4 Visit Observation Period 84±5 Days after EOT

1.3 SCHEDULE OF ACTIVITIES (SOA)

		Screening visit	**Baseline visit**	**Treatment visit[o]**												**Follow-up visit[p]**			
Week		-1	0	1	2	3	4	5	6	7	8	9	10	11	12/EOT[r]	14	16	20	24/EOS[s]
Day		-10 to -7	0	7	14	21	28	35	42	49	56	63	70	77	84	98	112	140	168
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15/FU1	16/FU2	17/FU3	18/FU4
Window period (days)			7-10[q]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±5	±5[t]
ICF		X																	
Inclusion/exclusion criteria		X	X																
Demography		X																	
Urine Pregnancy test		X					X				X				X		X		
Medical history[a]		X																	
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination with body weight		X					X				X				X				X
Laboratory tests[b]	Hematology tests	X					X				X				X				X
	Biochemistry tests	X					X				X				X				X
	HbA_{1C}	X													X				X
	Random blood glucose		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG/EKG or 2-D ECHO[c]		X					X				X				X	X			
Dispensing Study Diary			X																
Dispensing Subject Diary															X				
Collection and review of Study Diary[d]				X	X	X	X	X	X	X	X	X	X	X	X				
Collection and review of Subject Diary[e]																X	X	X	X
Treatment compliance check				X	X	X	X	X	X	X	X	X	X	X	X				
Offloading, dressing compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ankle brachial index[f] + monofilament test		X																	
Dispensing of Offloading footwear			X																
X-Ray[g]		X																	
Foot Examination for (Vascular, neurological, dermatological & musculoskeletal assessment)		X	X				X				X				X				X
Target Ulcer classification		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local examination, infection status of Target Ulcer		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Ulcer characteristics (Edge, color, peri-ulcer, drainage, granulation etc.)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Target Ulcer measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[h]		X																
Dispensing of IP[i]		X																
Treatment application		X	X	X	X	X	X	X	X	X	X	X	X	X				
Subject Education[j]	X																	
Recording of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE recording[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Debridement of Target Ulcer[l]	X																	
Nutritional information[m]	X																	
Photographs of both legs from various angles (medial, lateral, dorsal and plantar)[n]	X	X																
Clinical assessment of infection status of non-study ulcer(s)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of local pain		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of local edema		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of local erythema		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispensing of Wound dressing material*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] Medical and ulcer history will also include foot specific history such as location and duration of the selected ulcer and other medical conditions of the Subject. Events occurring prior to application of first dose of IP will be recorded as medical history and events occurring after the application of first dose of IP will be recorded as adverse events

[b] Laboratory tests will be performed at Screening Visit V1, V6, V10, V14 or EOT and during follow-up only at V18 or EOS and will include:

- Hematology parameters: CBC: WBC, RBC, Hematocrit, Hemoglobin, MCV, MCH, MCHC, RDW, Platelet Count, Mean Platelet Volume.
- Biochemistry parameters: Glucose, Calcium, Albumin, Total Protein, Sodium, Potassium, CO_2, Chloride, BUN, eGFR, ALP, ALT, AST, Bilirubin.
- HbA_{1C}
- Urine pregnancy test will be done in women of child bearing potential at Screening Visit V1, V6, V10, V14 or EOT and during follow-up only at V16/FU2 throughout the Study

[c] ECG will be done at Screening Visit V1, V6, V10, and V14 or EOT and during follow-up only at V15/FU1

[d] Study Diary review will be done by unblinded Investigator during Study Nurse visit to the site

[e] Subject Diary review will be done by blinded Investigator for all subjects in follow up Phase

[f] Ankle Brachial Index and 5.0 SW monofilament test will be performed at the Screening Visit V1

[g] X-ray of the foot under Study will be performed at the Screening Visit and further at the Investigator's discretion to rule out osteomyelitis.

[h] The Investigator will re-assess Subject eligibility at Baseline Visit V2, with emphasis on reduction of ulcer size since Screening Visit V1. If a potential Target Ulcer has decreased ≥30% between the Screening and Baseline visits, then this potential Target Ulcer cannot be designated as Target Ulcer. If none of the potential Target Ulcer(s) meet eligibility criteria at the Baseline V2, Subject will be considered as screen failure and exit the Study without further evaluation. If the Subject has more than one qualifying ulcer, the ulcer designated as the Target Ulcer should be the ulcer on the plantar region which is older, deeper and with a larger area

[i] Re-dispensing of IP may occur as and when required during Treatment Phase

[j] Subject Education and training on Diabetes management and use of off-loading device will be done as and when required

[k] The AE reporting will begin from the application of the first dose of the IP from the Baseline Visit

[l] Debridement of ulcer as and when necessary during site visit

[m] Nutritional information should be provided to Subject as and when necessary

[n] Photographs of both the legs will be taken from various angles to ensure that there are no more than three ulcers on both the legs

[o] In case the ulcer/wound closes within 12-weeks of Treatment Phase, the Subject will immediately enter the 12-weeks of Follow-Up Phase. In case of the Subject, whose Target Ulcer reopens during 12-weeks of Treatment Phase (within 84 days from Baseline) which is prior to the confirmation of Target Ulcer closure, the Subject would be given the treatment to complete 12-week of Treatment Phase

[p] During Follow-Up Phase, if the Target Ulcer has reopened after confirmation of its closure, the Subject will still be continued with the Follow-up assessment.

[q] This window period is from the Screening Visit

[r] EOT is at week 12 visit or any visit on which first observation of Target Ulcer closure has happened or treatment is Stopped

[s] EOS is at week 24 visit or any visit on which the Subject exits the Study

[t] Window period of ±3 days will be allowed for each Treatment visit as well as FU1 and FU2 visits and window period of ±5 will be allowed for FU3 and FU4

Note: [*]Dispensing of Wound dressing material will be provided as long as required

2 INTRODUCTION

2.1 STUDY RATIONALE

The scourge of DFU is expected to increase given the increasing global prevalence of type 2 diabetes mellitus (T2DM). The diabetic population in India which presently is 69.2 million is expected to increase to 123.5 million by 2040.[1] Among different diabetes related complications, DFU is second most common affecting approximately 15% of diabetic patients during their lifetime.[2] It has been reported that 14% - 24% of DFU patients require amputation. Moreover, recurrence of DFU in a subject is reported in more than 50% cases in a span of 2-5 years.[3 4] Even after 20 weeks of standard care treatment, DFUs remain unhealed at 67% time.[5] Notably, diabetes is responsible for more than 1 million amputations annually with every 30 seconds a leg is amputated for DFU.[6] About 85% of lower limb amputations in India as well in USA are preceded by a DFU.[7-9] Individuals with lower-limb amputations are at risk for developing concomitant medical ailments, report a diminished quality of life, and are more likely to die than other individuals with diabetes.[10 11] Following an amputation, the chance for another amputation is approximately 50% within 5 years of period.[9] The 5-year mortality rate after lower limb amputation ranges from 39% to 68%.[12] The cost of DFU treatment in India is about $650-$3250 and every episode of infection in DFU costs $1000 in India.[13]

DFU can develop because of acute or chronic cutaneous compromise of the skin, arterial insufficiency, peripheral neuropathy, or a combination of these factors.[14] Despite several treatment modalities that have been reported, including advanced moist wound therapy (AMWT), bioengineered tissue or skin substitutes, growth factors, electric stimulation and negative pressure wound therapy (NPWT), DFU generally does not respond well to treatment.[15-18] In its absence, the current Standard of care (SoC) for DFU involves pressure relief (off-loading), wound debridement, treatment of infection and ischemia, local wound-care comprising cleansing with saline and the use of modern wound dressings that promote a moist environment.[19]

These statistical data as discussed above provide the rationale for Galnobax® to be investigated as there is an urgent need for new treatment options for DFU.

Galnobax® has potential to provide a safer, effective and affordable treatment option for DFU Subjects. This Phase 3 Study of Galnobax® will be conducted with the objective of assessing the efficacy of Galnobax® gel in Subjects suffering from DFU from Baseline to Week 12 or wound closure whichever is earlier, in a larger population to obtain a statistically significant outcome. The Study design maintains same treatment period (12-weeks), same follow-up period (12-weeks), similar inclusion and exclusion criteria and similar SoC as in previously conducted Phase 1/2 Study.

2.2 BACKGROUND

Investigational drug product - Galnobax®

Galnobax® is a new gel formulation to be administered topically containing a pharmaceutically approved drug substance Esmolol hydrochloride. Esmolol hydrochloride is a beta1-selective (cardioselective) adrenergic receptor blocking agent with a short duration of action (elimination half-life is approx. 9 minutes) and no intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Esmolol hydrochloride inhibits the beta1 receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit beta2 receptors located chiefly in the bronchial and vascular musculature. Esmolol hydrochloride is metabolized by esterase from erythrocytes and is not metabolized by liver or kidney.[20]

Non-clinical Studies

The non-clinical studies on the drug substance of Galnobax® demonstrates that it is capable of pleiotropic actions to heal DFU such as:[21]

- Aldose reductase inhibition
- Inhibition of sorbitol accumulation in erythrocytes and inhibition of Advanced Glycosylated End products formation
- Faster wound closure in scratch assay under high glucose environment

The non-clinical studies on Galnobax® using globally accepted animal models for evaluating pharmacological parameters for healing of DFU such as diabetic Lewis Rats (for pharmacokinetic studies) and diabetic Hairless rats have demonstrated that;

a. Galnobax® closes the diabetic wound faster than the control group for up to 10 days.

b. While the wound epithelialization in the treatment groups is like the control groups, it is amply demonstrated that the Galnobax® group had improved induction of internal healing processes such as endogenous nitric oxide production in inflammatory and proliferative phase and higher collagen formation and deposition in the remodeling phase of diabetic wound healing than the control group resulting in better quality of wound healing.

c. Better healing in Galnobax® treated wounds is also demonstrated by laser Doppler studies which show higher average flux of blood flow in vehicle treated groups.

d. Galnobax® has multiple therapeutic actions such as Nitric oxide induction, Collagen turnover at the wound site, neo-vascularization and anti-oxidant effects contribute to faster healing and closure compared to the control.

Additionally, the non-clinical PK studies evidence that by application of Galnobax®, Esmolol hydrochloride is minimally absorbed (less than 10 ng/mL in rats and average maximum concentration of 30 ng/mL in minipigs) into systemic circulation, thereby evidencing that Galnobax® is safe to use in the treatment of DFU. The above observations and the fact that Esmolol hydrochloride is a pharmaceutically approved drug with well elucidated safety profile, suggest that Galnobax® has significantly favorable risk/benefit profile.[21]

Clinical Studies

The efficacy analysis of Phase 1/2 clinical Study of Galnobax® numerically establishes that Galnobax® 14% treatment has advantage in terms of area and volume reduction over the Vehicle and Galnobax® 20%. This advantage of Galnobax® 14% is more pronounced in hard to heal DFU:

- **In plantar DFU:** Galnobax® 14% showed 98.1% area closure Vs 75.8% for Placebo. The median time for complete wound closure was 35 days for Galnobax® 14% Vs 64 days for Placebo[21]
- **In older DFU:** On DFUs older than 8 weeks at baseline, Galnobax® 14% group showed complete closure in 75% Subjects Vs 43% in Placebo group[21]

The safety analysis of Phase 1/2 clinical Study establishes and reconfirms the findings of the non-clinical studies that Galnobax® is safe for long term use (tested for 12-weeks) in both 14% and 20% concentrations. Overall 29 adverse events (AEs) were observed in the Study and only two were related to the Study treatment. These two AEs were local mild allergic reactions which were found to be reversible. The safety of Galnobax® is further reinforced by the pharmacokinetic analysis of Phase 1/2 clinical Study which establishes that the systemic concentration of its drug substance (Esmolol hydrochloride) was below quantification limit (10 ng/mL) at any time during the

treatment period, irrespective of wounds of different sizes and doses of Galnobax®. This observation is significantly lower than:

- Systemic concentration of 868-1470 ng/mL observed for approved doses of intravenous Esmolol hydrochoride
- Human peak plasma concentration of 500, 1200 and 2500 ng/mL respectively observed for the infusion of Esmolol hydrochloride at the rate of 100, 250 and 500 µg/kg/min[22]

Considering the above facts, it is proposed to investigate Galnobax® 14% in a Phase 3 Study to establish safety and efficacy with statistical significance.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Phase 1/2 study of Galnobax® on 44 DFU Subjects reported the following:

a. No deaths were reported during the study.

b. There were 4 SAEs (arthritis bacterial, infected skin ulcer, gastroenteritis, and cellulitis) reported during the study, all in the Galnobax® 20% group and none determined by the Investigator as related to the study drug. All these SAEs were resolved during the study.

c. There were 29 AEs of which only 2 were determined by the Investigator as related to the Study drug (TEAEs) with 1 Subject each in the Galnobax® 14% [TEAE: skin discoloration] and Galnobax® 20% [TEAE: erythema] groups. Both these events were non-serious and mild in intensity which were reversible on discontinuation of drug. None of the vital signs and Electrocardiogram (ECG) abnormalities were reported as TEAEs.

d. Furthermore, the drug substance used in Galnobax® (Esmolol hydrochloride) is approved for intravenous application with all reported AEs being mild, transient and reported to be reversible after discontinuation of dosing in spite of systemic concentration of 868-1470 ng/mL [23] and human peak plasma concentration of 500, 1200 and 2500 ng/mL respectively at the infusion rate of 100, 250 and 500 µg/kg/min[22]. As against this, the clinical pharmacokinetic (PK) studies of Galnobax® conducted as part of the Phase 1/2 study demonstrated that the systemic concentration of its drug substance (Esmolol hydrochloride) through topical administration was below quantification limit (10 ng/mL) at any time during the treatment period, irrespective of wounds of different sizes and doses of Galnobax®. This low systemic absorption and localized action is also substantiated by non-clinical PK studies conducted in Lewis rats and in minipigs.[21]

The non-clinical toxicity studies of Galnobax® showed slight irritation in rabbit model which was found to be reversible and did not elicit skin sensitization in guinea pig model.

All of the above is sufficient to conclude that Galnobax® with no deaths, no SAEs related to the drug, only 2 drug related AEs which were reversible and minimal systemic absorption (way below approved tolerated concentrations) as established in Phase 1/2 study has a favorable human safety profile.[21]

2.3.2 KNOWN POTENTIAL BENEFITS

Basic science and translational investigation are intensively researching the key abnormalities responsible for altering the wound-healing process in DM.[24] Yet, in spite of some available therapies, DFU still remains ineffectively treated in 67% of the cases resulting in lower extremity

amputations in about 15% of the cases.[25] Thus, DFU continues to be a strong medical unmet need and calls for a new drug which can comprehensively address the underlying structural and functional abnormalities through which DM impairs wound healing. There is a dire need to improve the clinical outcomes and improve the quality of life of Subjects with DFUs.

14% Galnobax®, a gel formulation for topical administration with an approved drug substance (Esmolol hydrochloride) with favorable data from the Phase 1/2 clinical study and non-clinical studies has not only been found safe, demonstrated more comprehensive ability to address the underlying structural and functional abnormalities through which DM impairs would healing but has also demonstrated potential to be more effective in delivering better outcomes namely:[21]

a. Complete closure in older non-healing DFUs compared to the Vehicle (75% v/s 43%)
b. Faster complete closure compared to the Vehicle (35 days v/s 64 days)
c. Higher area reduction over Vehicle in 12-weeks treatment (98.1% v/s 75.8%)
d. No local reaction or risk of long term use of drug is anticipated

In addition, Galnobax® provides a tissue adherent thermo-reversible polymeric gel suitable for application on chronic wounds.[21]

Therefore, there are sufficient known and well evidenced benefits of Galnobax® for the treatment of DFU.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The fundamentals of good clinical care include adequate off-loading, frequent debridement, moist wound care, treatment of infection, and revascularization of ischemic limbs. Even when properly managed, the wounds may not heal in a timely fashion thereby leaving them open to getting complicated by intervening infection, hospitalization, amputation and, thus, to be costlier because of the increased utilization of healthcare resources.[26]

Considering the clinically beneficial outcomes established in Phase 1/2 study, findings of non-clinical pharmacological and toxicological information and ample existing human safety data on its drug substance (Esmolol hydrochloride), positions Galnobax® as having a favorable Risk / Benefit profile to necessitate the proposed clinical Phase 3 study.

In this Phase 3 Study, care has been taken to ensure that in the event of any drug related adverse event, the Investigator will assess risk/benefit of Galnobax® to the Subject before deciding continuation of treatment. In addition, the treatment will be administered to the Subject by a trained Nurse, which will further minimize risk to the Subject, if any.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
• To assess the efficacy of Galnobax® in terms of proportion of Subjects achieving Target Ulcer Closure within 12-week Treatment Phase upon application of Galnobax® plus Standard of Care as against only Standard of Care treatment, as assessed by the blinded Investigator	The efficacy assessment will involve Galnobax® plus Standard of Care and only Standard of Care groups Efficacy endpoints: Proportion of subjects achieving Target Ulcer Closure within 12-week Treatment Phase, as assessed by blinded Investigator	Complete wound closure of a chronic, nonhealing wound is one of the most important objective and clinically meaningful wound healing endpoint
Secondary		
Efficacy	Efficacy endpoints	
• To compare Time to Target Ulcer Closure within the 12-week Treatment Phase, upon application of Galnobax® plus Standard of Care as against only Standard of Care treatment, as assessed by the blinded Investigator	• Time to Target Ulcer Closure during the 12-week Treatment Phase, as assessed by the blinded Investigator	This endpoint evaluates clinically meaningful reduction in the time to Target Ulcer Closure using a time-to-event analysis (the event being first observation of complete closure)
• To compare proportion of Subjects achieving Target Ulcer Closure till End of Study upon application of Galnobax® plus Standard of Care as against only Standard of Care treatment, as assessed by the blinded Investigator	• Proportion of Subjects achieving Target Ulcer Closure till End of Study, as assessed by the blinded Investigator	This endpoint is for evaluating sustained effect of the treatment post its discontinuation
Safety		
• To investigate the safety of Galnobax® treatment during the Study	• Proportion of Subjects with treatment emergent adverse events (TEAEs)	This endpoint evaluates safety of Galnobax® by assessing TEAEs

• To investigate the safety of Galnobax® vehicle for establishing non-deleterious effects of Vehicle on wound healing	• Proportion of Subjects with events related to the local wound assessment of Target Ulcer in Vehicle plus Standard of Care group	This endpoint evaluates events related to local wound assessment of Target Ulcer in Vehicle plus Standard of Care group

4 STUDY DESIGN

4.1 OVERALL DESIGN

This Study is a Phase 3, multicenter, randomized, double-blind, parallel-group Study designed to evaluate the safety and efficacy of Galnobax® plus SoC versus only SoC, in treating DFU in adults with diabetes mellitus (DM). In addition, Study is designed to evaluate safety of Vehicle plus SoC versus only SoC in Subjects with DFU to investigate deleterious effects of Vehicle on wound healing, is any.

For this purpose, the Subjects will be randomized in 3:3:1 ratio into one of the following groups:

- Group 1: Galnobax® 14% gel plus SoC
- Group 2: SoC only
- Group 3: Vehicle plus SoC

Total number of Subjects in the Study: This Study will have FAS Population (Efficacy Evaluable Population) of a minimum of 240 Subjects in Group 1 and Group 2 (minimum of 120 in each Group). To ensure this and assuming 20% drop out rate, the population of two groups would be maximum of 300 Subjects. In addition, for investigating the effect of vehicle on wound healing, Vehicle plus SoC group will recruit up to 50 Subjects. Thus, overall 350 Subjects will be recruited in the Study.

No. of investigational sites: This Study will be conducted at approximately 40 sites across India with competitive recruitment amongst sites.

Maximum duration of a Subject in the Study: The maximum total duration of Subject in the Study will be 25 weeks spread over three phases in following sequence:

1. Screening Phase of 1-week (7 + 3 days)
2. Treatment Phase of a maximum of 12-weeks (84±3 days) starting with Baseline visit
3. Follow-Up Phase of 12-weeks (84±5 days). This will comprise of Closure Confirmation period of 4 weeks (28±3 days) and Observation period of 8 weeks (56±5 days).

Subject Number Assignment: The Subjects will be assigned randomization number using an interactive web-based randomization system (IWRS). Prior to randomization, Subjects will be stratified by location (plantar or non-plantar) and size (<5 cm^2 or ≥ 5 cm^2) of the Target Ulcer solely for the purpose of bringing homogeneity among the three treatment Groups in proportionately. Once a randomization number has been assigned, it cannot be re-assigned to any other Subject.

Application of Treatment: Subjects in the Study will receive treatment twice daily during the 12-weeks of Treatment Phase or up to the Target Ulcer Closure, whichever is earlier. During this period, the twice daily treatment to the Subjects in all the arms of the Study will be administered

by the Study Nurse. Unless recommended by the Investigator otherwise, SoC during the Follow-Up Phase will be self-administered by the Subject.

Visit Schedule of the Subjects: Subjects in the Study will visit investigational site once a week during the 12-week Treatment Phase for wound measurement and for completing Study related assessments and procedures. In the Follow-Up (FU) Phase, the Subjects will visit investigational site at week 14, 16, 20 and 24.

Rules for Subject progression in the Study

The Subject progression in the Study will happen as per rules given in Table 1

Table 1 Subject progression as per condition of Target Ulcer

Sr. No.	Target Ulcer Closure within Treatment Phase	Reopened in Closure Confirmation period?	Action to be taken in the Study
1	Not closed	Not applicable	Proceed to Follow-Up Phase
2	Closed	No	Continue the Follow-Up Phase
		Yes	If reopened within 12-weeks from Baseline visit, continue treatment till EOT or Target Ulcer Closure, whichever is earlier and then proceed to Follow-Up Phase. If reopened after 12-weeks from Baseline visit, continue the Follow-Up Phase

The nomenclature used of various Study visits will be as follows:

Screening Visit: V1 or Day -10 to -7 (minus ten to minus seven) or Week -1 (minus one)

Treatment Visits:

V2 or Day 0 or Week 0 (also referred to as Baseline visit)
V3 or Day 7 or Week 1
V4 or Day 14 or Week 2
V5 or Day 21 or Week 3
V6 or Day 28 or Week 4
V7 or Day 35 or Week 5
V8 or Day 42 or Week 6
V9 or Day 49 or Week 7
V10 or Day 56 or Week 8
V11 or Day 63 or Week 9
V12 or Day 70 or Week 10
V13 or Day 77 or Week 11
V14 or Day 84 or Week 12 or End of Treatment (EOT)

Follow-Up (FU) Visits:

FU1 or V15 or Day 98 or Week 14 (also referred to as Closure Verification visit)
FU2 or V16 or Day 112 or Week 16 (also referred to as Closure Confirmation visit)
FU3 or V17 or Day 140 or Week 20
FU4 or V18 or Day 168 or Week 24 or End of Study (EOS)

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The Study consists of about one week (7 to 10 days) of Screening period to confirm the suitability of Subject for the Study and to restrict recruitment of Subjects having healing ulcers. The Study has Treatment Phase of up to 12-weeks (84 ± 3 days) or the Target Ulcer Closure, whichever happens earlier as the Investigational Product (IP) requires 12-weeks of treatment to establish its efficacy. In view of this, if the Target Ulcer re-opens within these 84 days, the Subject will resume the treatment, up to completion of the Treatment Phase or the Target Ulcer Closure, whichever is earlier. If Target Ulcer closes prior to 12-week, then the Subject enters the 12-week Follow-Up phase immediately. The 12-week Follow-Up is required to confirm Target Ulcer closure, assess strength of closed Target Ulcer, assess progression of open wounds post Treatment Phase in terms of wound size and AEs, if any.

In this trial, Subjects will be randomized in three Groups viz, Galnobax® plus SoC, only SoC, and Vehicle plus SoC in 3:3:1 ratio. A large population is required to achieve statistically significant efficacy endpoint for wound closure, whereas relatively smaller number of Subjects are sufficient to assess non-deleterious effects of Vehicle gel. During randomization, the Subjects will be stratified based on location as well as size of the Target Ulcer to have a proportional population in the three groups. Since SoC only is the treatment of choice used in clinical setting for DFU presently, this trial uses SoC only as comparator arm to Galnobax® plus SoC treatment for efficacy analysis. The parameters of Vehicle plus SoC arm will be compared with only SoC arm to check if Vehicle has any deleterious effects on wound healing.

The FAS Population (Efficacy Evaluable Population) will include all randomized Subjects who have at least 6 weekly assessments for Target Ulcer Closure or has Target Ulcer closed earlier than 6 weeks. The efficacy analysis in this Study will use FAS Population in order to ensure that Subjects have received reasonable treatment, and are assessed for Target Ulcer Closure by blinded Investigator.

4.3 JUSTIFICATION FOR DOSE

Phase 1/2 clinical study of Galnobax® established that Galnobax® is safe for long term use (tested for 12-weeks) in both 14% and 20% concentrations. The efficacy analysis showed that Galnobax® treatment has advantage in terms of area and volume reduction over Placebo. The advantage of Galnobax® 14% is even more pronounced in hard to heal wounds. Considering this fact, this study has been planned to investigate Galnobax® 14% in a phase 3 trial to establish safety and efficacy in a larger number of Subjects for statistical significance.

Each eligible Study Subject will be assigned to one of the three treatment groups as described in Table 2 and will receive the next available consecutive randomization number.

Table 2 Dosing schedule

Gr. No.	Study group	Treatment frequency
1	Standard of Care + Galnobax® gel	Twice daily
2	Standard of Care	Twice daily
3	Standard of Care + Vehicle gel	Twice daily

Dose Modification for Study Drug

If any adverse reaction potentially related to Study drug is observed in terms of hypersensitivity or local allergic reaction at or around the Target Ulcer site, Investigator may decide to discontinue the

study drug administration to the Subject or adjust the frequency per the requirement for a limited period.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the Study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial. In addition, if Subject is discontinued or withdrawn from the Study, the last recorded visit of such Subject shall be considered as the End of Study.

5 STUDY POPULATION

The Subjects included in this Phase 3 clinical study are those having DFU which has not healed for at least 6 weeks and satisfy eligibility criteria described below. It is made explicitly clear that there will be only one Target Ulcer per patient.

5.1 INCLUSION CRITERIA

The Subjects would be included in the Study if they satisfy all of the following inclusion criteria: Potential Subjects are required to meet all of the following criteria for enrollment into the Study and subsequent randomization:

1. Subjects, male or female, aged 18 to 75 years (inclusive) with Type 1 or Type 2 diabetes undergoing therapy for glycemic control
2. Subject has glycosylated hemoglobin, $HbA1_C$, ≤ 12%
3. Subject with diagnosis of neuropathic foot ulcer by 10g monofilament test
4. Subject has adequate vascular perfusion of the affected limb, confirmed by Ankle-Brachial Index (ABI) ≥ 0.65 and ≤ 1.3

Note: If the ABI measurement is >1.30 one of the following confirmatory tests must be performed for Subject to be considered eligible. Prior documented flow study within the last 3 months of the Screening Visit is acceptable

   a) Great Toe pressure (plethysmography) > 40 mm Hg;
   b) Transcutaneous partial pressure oxygen (TcPO2) at the foot > 40 mm Hg;
   c) Skin Perfusion Pressure (SPP) > 40 mm Hg;
   d) Doppler ultrasound (biphasic or triphasic waveforms) consistent with adequate blood flow to the affected extremity, as determined by the standard practices of the Investigator and the site

5. Presence of at least one DFU that meets all of the following criteria:
   a) A full-thickness ulcer of Grade A1 as per Texas classification system;
   b) Ulcer is located below or up to 5 cm above the malleoli (excluding ulcers between the toes);
   c) Ulcer size (area) is ≥ 2 cm^2 and ≤ 15 cm^2 (post-debridement);
   d) There is a minimum 3 cm margin between the qualifying Target Ulcer and any other ulcers on the specified foot, post-debridement;
   e) No exposed bone, tendon, muscle, ligament or joint capsule, and no tunneling, undermining, or sinus tracts;
   f) Unresponsive to ulcer care and open for at least 6 weeks at the time of the Screening Visit;
   g) Ulcer is non-infected as determined by clinical assessment and complete hemogram;

h) Ulcer has a clean, granulating base free of adherent slough to the greatest extent possible as per Investigator;

i) Ulcer area reduction < 30% from the Screening Visit to Baseline visit

Note: Criterion 4(i) will be evaluated at the time of randomization. If the Subject has more than one qualifying DFU, the ulcer designated as the Target Ulcer should be the ulcer preferably on the plantar region which is older, deeper and with a larger area.

6. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Investigator
7. Subject, if female of child-bearing potential, has a negative urine pregnancy test at Screening and willing to use acceptable methods of contraception (birth control pills, barriers) or abstinence throughout the Study
8. Subject is able and willing to comply with Study procedures including the use of an off-loading device (as applicable for the location of the ulcer) and adhere to protocol during the Study in the opinion of Investigator
9. A Subject or LAR agrees to sign informed consent form and allow audio visual recording of consent, if applicable

5.2 EXCLUSION CRITERIA

Subjects will not be eligible for enrolment in the Study if they meet any of the exclusion criteria listed below:

1. Actively infected ulcers with or without purulent discharge, ulcers with exposed bone or associated with osteomyelitis

Note: The osteomyelitis should be ruled out by clinical examination and X-ray findings where found necessary by the Investigator. If the Investigator is unable to ascertain the condition of osteomyelitis by probing of the Target Ulcer or digital X-ray then Investigator may use other techniques such as MRI, bone scintigraphy, leukocyte scanning or bone biopsy to rule out the presence of osteomyelitis based on availability of the investigation facility at the clinical sites.

Note: If foot has more than one ulcers and one of them is infected, then Target Ulcer should not be selected from this foot unless all ulcers on the foot are free of infection. If Subject has ulcers on both foots and infection is seen in the ulcer on non-target foot, Subject may be included in the Study with prescribing oral antibiotic treatment for non-Target Ulcer.

2. Subjects with more than three ulcers below knee
3. Subjects with Target Ulcer requiring off-loading that cannot be effectively off-loaded; or unable to tolerate the off-loading method
4. Subject has ulcers caused by a disease other than diabetes, e.g., fungal ulcerations, malignant ulcerations, and ulcerations due to venous or arterial insufficiency, or due to hematological disorders, in the opinion of the Investigator
5. Ulcer, about which the Investigator is suspicious for cancer

Note: In case of such suspicion, ulcer present more than 1 year will require a 3 mm punch biopsy to rule out malignancy. Prior documented negative ulcer biopsy within the last 1 year of the Screening Visit is acceptable

6. Subjects with a gangrenous or ischemic ulcer
7. Subject with ulcer that in the opinion of the Investigator, may need amputation
8. Subject with Target ulcer where wound measurement is not possible, such as ulcers between toes
9. Body mass index (BMI) > 40 kg/m^2
10. Laboratory values at Screening of:
    a) Hemoglobin < 10.0 g/dL

b) White Blood Cells (WBC) < 2.0 X 10^9 cells/L
c) Liver function studies [Total bilirubin, aspartate aminotransferase (AST) and alanine transaminase (ALT)] > 3x the upper limit of normal
d) Albumin < 2.5 g/dL
e) eGFR < 25 mL/min

11. Presence of any existing clinically significant medical condition(s) that, in the opinion of the Investigator, could interfere with wound healing, including but not limited to the following:
    a) Vasculitis or connective tissue disease
    b) Buerger's disease, Raynaud's or other peripheral vascular disease
    c) Clinically significant claudication or peripheral edema on the affected limb
    d) Acute or unstable Charcot foot
    e) Aplastic anemia or exacerbation of sickle cell anemia
    f) Current sepsis
    g) Congestive heart failure (NYHA Class III or IV), coronary heart disease with ST segment elevation, myocardial infarction, or coronary artery bypass graft or percutaneous transluminal coronary angioplasty within the last 6 months
    h) End-stage renal disease
    i) Immunosuppression
    j) Acquired immune deficiency syndrome (AIDS) or HIV positive
    k) Any malignancy history
12. Subject has received or is currently receiving or scheduled to receive any of following medication or therapies during the course of the Study
    a) Immunosuppressants (chronic systemic corticosteroids) within 30 days of randomization visit
    b) Revascularization surgery (e.g., angioplasty, coronary artery bypass surgery, transmyocardial revascularization) within 30 days of randomization visit
    c) Growth factors within 30 days of randomization visit
    d) Hyperbaric oxygen therapy (HBOT) within last 7 days of randomization visit
    e) Negative pressure wound therapy (NPWT) within last 7 days of randomization visit
    f) Bioengineered tissue or skin substitutes within 30 days of randomization visit
    g) Application of topical steroids to the ulcer surface within 30 days of randomization visit
    h) Use of any investigational drug(s) or therapies within 30 days of randomization visit
13. Subject with intolerance to β-blockers at any time in the past
14. Has any other factor which may, in the opinion of the Investigator, compromise participation and/or follow-up in the Study

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. This will occur to those Subject who did not meet the eligibility criteria at Baseline Visit or whose Target Ulcer reduces in area by ≥30% during the Screening period. Such Subject is considered screen failed

and will exit from the Study without any further evaluation. Subject who has screen-failed once may be rescreened at an appropriate time as decided by the Investigator. Only one such re-screening is allowed for any Subject during the study.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment and retention strategies would be detailed in the clinical trial management plan (CTMP) and monitoring plan (MP) including the site-specific plans as per the site-specific standard operating procedure (SOP). The considerations for recruitment and retention strategies would include the following but not limited to:

- Target study sample size as consistent with information contained in **Sample Size Determination**
- Anticipated accrual rate
- Anticipated number of sites and participants to be enrolled for the study
- Source of participants
- Recruitment venues
- How potential participants will be identified and approached
- Types of recruitment strategies planned
- Procedures to enhance retention of patient in the study
- Participants compensation/incentives for the study

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Test IP (Galnobax®)

Galnobax® is a topical gel containing 14% Esmolol hydrochloride. The gel will be packaged into lacquered aluminium tube in the quantity of 15 g per tube for both morning and evening application on the Target Ulcer. *The composition of the Galnobax® gel is as shown in Table 3*

Table 3 Composition of Galnobax®

INGREDIENTS
Active Ingredient
Esmolol hydrochloride
Inactive Ingredients
Benzalkonium chloride solution
Poloxamer 338
Sodium Acetate Trihydrate
Glacial Acetic Acid
Concentrated Hydrochloric Acid
Purified water

Vehicle gel

The Vehicle gel to match the IP will be supplied by the Sponsor. The Vehicle gel will be without active ingredient but will have all inactive ingredients in the same concentration as used in Galnobax® gel.

Standard of Care

The SoC includes wound cleaning by normal saline, maintenance of moist wound environment and off-loading of the Target Ulcer. In addition, during site visits removal of necrotic, infected and/or nonviable tissue by debridement and management of infection will be done by the Investigator, if required.

6.1.2 DOSING AND ADMINISTRATION

The amount of the IP (Galnobax®) or Vehicle gel to be applied will vary depending upon the area and depth of the Target Ulcer. To calculate the length of gel to apply to the Target Ulcer such that a uniform layer of IP over the wound surface, refer the Target Ulcer area obtained using advance camera in the corresponding visit and use the following formula to calculate the length of gel in centimeters to be applied:

Length of Gel in Centimeters to be applied at each application

= Area of ulcer in cm^2 (using advance camera) X 0.6 centimeter of gel from 15 g tube

For example, if the ulcer area measures 10 cm^2, then a 6-centimeter length of gel should be used from a 15 g tube [10 X 0.6 = 6 cm].

Further, depending on the surface area of Target Ulcer, additional amount of IP may be applied to ensure formation of uniform layer of IP over the wound bed.

How to administer treatment (Instructions to unblinded Investigator and Study Nurse):

a. For group randomized to IP (Galnobax®)/Vehicle + SoC treatment

For morning application:

1. Remove the dressing
2. Rinse the Target Ulcer using saline
3. Squeeze out the required length of the gel from tube on to a sterile wax paper (printed with centimeter scale) provided with the kit
4. Using sterile applicator (provided with the kit) spread the gel over the entire ulcer area to yield a thin continuous layer that covers the wound bed, but no peri-wound skin
5. The Target Ulcer will then be covered by appropriate dressing and the Subject must be advised to leave it in place till next application

For evening application:

1. Remove the dressing
2. Only the peri ulcer area should be cleaned by cotton dipped in saline (do not rinse the Target Ulcer by saline for evening application)
3. Squeeze out the required length of the gel from tube on to a sterile wax paper (printed with centimeter scale) provided with the kit
4. Using sterile applicator (provided with the kit) spread the gel over the entire ulcer area to yield a thin continuous layer that covers the wound bed, but no peri-wound skin

5. The Target Ulcer will then be covered by appropriate dressing and the Subject must be advised to leave it in place till next application

b. For group randomized to SoC treatment

For morning application:

1. If the Target Ulcer is already dressed, remove the dressing
2. Rinse the Target Ulcer using saline
3. The Target Ulcer will then be covered by appropriate dressing and the Subject must be advised to leave it in place till next application.

For evening application:

1. The dressing should be removed
2. Only the peri ulcer area should be cleaned by cotton dipped in saline (do not rinse the Target Ulcer by saline for evening application)
3. The Target Ulcer will then be covered by appropriate dressing and the Subject must be advised to leave it in place till next application

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Sponsor/Contract Research Organization (CRO) will provide IP (Galnobax® as well as Vehicle gel) to the site. The accountability of IP will be maintained as follows:

- The Investigator/co-Investigators or designee would acknowledge receipt of Study IP supplies for each shipment received
- The unblinded Investigator responsible for dispensing the IP to the Study Nurse must maintain a drug accountability log. The IP accountability log records the receipt, dispensing and return of the IP
- At any time the sum of quantity of used and unused IP should match with the quantity of medication supplied. Account must be given of any discrepancies
- The Study monitor and Sponsor should be notified immediately of details of any IP, which is inadvertently damaged or lost
- The used or unused IP tubes will be returned by the Study Nurse to the site. Tubes will be replenished as required with identical kit number
- The quantity of IP utilized for the treatment will be monitored by checking the weight of the tube at the time of issuing it for the treatment and at the time of collecting the used tube
- If all tubes from the kit are consumed, a new kit with identical treatment will be issued

Handling of Investigational Product:

Both used and unused IP tubes would be sent back to Sponsor/their representative for destruction as per standard procedure. Reconciliation between the amount of IP supplied, used and returned to the Sponsor must be performed by the Sites and the CRO. If any discrepancies are found in the reconciliation of IP, it will be resolved. This reconciliation will be logged by each site on the IP reconciliation form, signed and dated.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Formulation and Appearance

The details of formulation are given in *Section 6.1.1*. The IP is a colorless gel at room temperature.

Packaging

The IP will be packaged in to lacquered aluminium tubes in the quantity of 15 g per tube. The tubes will be placed in cartons which has product information and kit number printed on it (Table 4). Each carton will contain one tube. Each kit will contain 4 such cartons and two boxes of sterile gel measurement strips. Sufficient number of such kits will be made available to ensure sufficient supply of IP for the Study.

Table 4 Labelling information of Galnobax®

Galnobax® Topical Gel | Study code: NG-A16	
Kit No.:	
Topical gel contains Vehicle or Esmolol Hydrochloride 14% w/w Preservative: Benzalkonium chloride solution (50%) 0.26% w/w	Net Wt. 15 g
Batch No.: | Mfg. Lic. No.:	
Sponsor: NovaLead Pharma Private Limited, Pune, INDIA Manufacturer:	
Store in cool environment	
Mfg. Date: | Exp. Date:	
FOR CLINICAL TRIAL USE ONLY. NOT TO BE SOLD. **FOR EXTERNAL USE ONLY**	
Caution: Keep out of reach of children. In case of Emergency, contact your study doctor or Local Emergency Services	
Subject No.: To be written by study site	
Investigator's name: To be written by study site Investigator Contact Number: To be written by study site Name of the Institution: To be written by study site	
Visit No.: To be written by study site Date of dispensing: To be written by study site	
Kit No.: Subject No.: To be written by study site Visit No.: To be written by study site Date of dispensing: To be written by study site	

The manufacturer will label the tubes, cartons and kits. In case additional IP is required for any Subject, new kit with same treatment will be issued.

6.2.3 PRODUCT STORAGE AND STABILITY

IP will be stored at 15 to 25˚C at the warehouse and at the investigational sites. Upon dispensing to the Study Nurse, instruction will be given to store in refrigerator as far as possible and if not available, in dry and cool environment.

6.2.4 PREPARATION

The IP will be manufactured under Good Manufacturing Practice (GMP) conditions and following all regulations of CDSCO as well as State FDA.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a double-blind study wherein the Investigator, the Sponsor, the Subject, the CRO and the Study Nurse Coordinator will be kept blinded to the randomization throughout the Study. There will be one unblinded Investigator per site who will administer the treatment during each treatment visit of the Subject as well as dispense the IP to the Study Nurse and the SoC material to the Subject. The Study Nurse who will administer treatment to the Subject (twice daily during Treatment Phase) will be unblinded. However, the unblinded Investigator and Study Nurse will still remain blinded to whether the Study drug applied is Galnobax® or Vehicle gel. The blinding of the Subject will be ensured by the Study Nurse by using shield while treating the Target Ulcer.

In case the Subject is staying far from the site (i.e. 40 km or more from the site) and/or Nurse is unable to visit every week to the site for treatment compliance check, following procedure will be followed for IP transport and compliance check: IP will be issued to the study Nurse at the time of the randomization visit along with study diary in an aluminum box having a lock. One key of this lock will be with the study Nurse and other with the unblinded CRC at the site. At the time of weekly site visit of the Subject, study Nurse will keep used IP tubes and Study diary in this box which will be locked and sent to the site with the Subject. Site unblinded CRC will take aluminum box from the subject and will check IP compliance as well as study diary. The IP will be reissued to the nurse after weighing the tubes and new study diary will also be issued (through which new dose of the subject will be conveyed to the Nurse). These materials will be kept in the aluminum box which will be locked and given to the Subject for handing over it to the study Nurse. This process will continue during all treatment visits.

While the IP compliance will be verified by the unblinded Investigator, the Target Ulcer Closure will be decided and confirmed by the blinded Investigator, thus mitigating any bias.

Unblinding will be done only if necessary for the welfare of the Subject or in the case of emergency suspected to be IP related. If such emergency is clearly not IP-related in the opinion of the Investigator, the Subject management can be done without the need of unblinding. Standard norms and procedures for unblinding will be followed.

6.4 STUDY INTERVENTION COMPLIANCE

Blank Study diary will be dispensed to the Subject from Baseline Visit (V2). The Study Nurse will receive the blank diary from the Subject and record the daily compliance of the following during the Treatment Phase (V2-V14) as applicable:

a. Off-loading
b. Daily applications of the treatment (to confirm the dose application schedule),
c. Missed applications,
d. Excess dose drawing
e. Completion of dressing of the Target Ulcer
f. Any unusual happening

The Study Nurse will not disclose these entries to the Subject and retain the Study diary with her before submitting it to the unblinded Investigator. Collection and review of Study diary will

continue from V3 till V12 or EOT. The un-blinded Investigator will transcribe the information from the Study diary into the CRF. During the Treatment Phase, unblinded Investigator should record the weight of single application of treatment prescribed during every Treatment visit of the Subject and this basis will be used to check weekly compliance of the dose. The dose to be applied will be informed to the Study Nurse by the unblinded Investigator after every weekly Treatment visit. During Follow-Up Phase (V15-V18), Subject diary will be filled and handled by the Subject since there will be no treatment provided during the Follow-up. The Subject will hand over the completed Study Diary to the un-blinded Investigator during Follow-up visits.

The Subjects with treatment compliance of less than 80% or more than 120% of the IP, during the week, will be considered treatment non-compliant for that week. If such non-compliance is observed for more than three weeks, and if the blinded Investigator opines that it may affect the outcome of the Study, then the Subject shall be considered non-compliant for the Study and shall be discontinued from the Study.

6.5 CONCOMITANT THERAPY

Any medication regularly used by the Subject including anti-diabetic medications as prescribed by the physician and approved by the Investigator will be permitted to be used.

If Investigator suspects infection at any wound site of the Subject, oral and/or parenteral antibiotics (except topical) and standard of wound care will be permissible to prevent the wound from leading to osteomyelitis. It will be at the Investigator's discretion to decide if it is necessary to defer the Study treatment to the Subject during the antibiotic treatment to control the wound infection. In case the non-Study ulcer is seen with infection, it will be treated with oral or parenteral antibiotics. The local antimicrobial therapy, if required will be permitted to the non-Study ulcer.

The concomitant medication administered must also be recorded in the CRF with generic name and/or trade name of the medication, dose, start and end dates of treatment.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The subjects that report Osteomyelitis, cellulitis or SAE/AE where study intervention cannot be given, should be discontinued. For all discontinued Subjects, maximum possible and relevant Study information shall be gathered and be described in the source. This information can be gathered at Site visit or telephonically. If the discontinuation happens during the Treatment /Follow up Phase, the last visit prior to discontinuation will be treated as EOT/EOS visit and corresponding CRF will be completed by the Investigator.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the Study at any time. If the withdrawal happens during the Treatment /Follow up Phase, the last visit prior to withdrawal will be treated as EOT/EOS visit and corresponding CRF will be completed by the Investigator.
Subjects who sign the informed consent form (ICF) and are randomized but do not receive the study intervention will not be replaced and will not be part of ITT Population.

Subjects who sign the ICF, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced and yet be part of ITT Population.

Subjects must be discontinued from the Study after randomization if any of the following events occur (Stopping or Discontinuation Rules for Individual Subjects):

1. A Subject withdraws consent
2. Investigator recommends that the Subject should discontinue the participation in the Study
3. Subject misses two consecutive Weekly Visits during Treatment Phase
4. If the Target Ulcer and the adjoining wound merge together and if the Investigator opines that following the Target Ulcer is difficult. A detailed note by the Investigator will be recorded in the e-CRF outlining reasons for such merger in line with the preceding measurement of Target Ulcer
5. If Subject requires hospitalization for more than two consecutive weeks during the Study
6. The Subjects with treatment compliance of less than 80% or more than 120% during the week, will be considered treatment non-compliant for that week. If such non-compliance is observed for more than three weeks, and if the blinded Investigator opines that it may affect the outcome of the Study, then the Subject shall be considered non-compliant for the Study and shall be discontinued from the Study
7. If the blinding of a Subject is compromised
8. Any form of major protocol violation
9. The Target Ulcer increases in size (more than 30%) for two consecutive weeks or requires deep, surgical debridement for more than two occasions during the Treatment Phase to address Target Ulcer deterioration
10. The Target Ulcer becomes infected requiring topical antimicrobial treatment
11. If Subject develops osteomyelitis or cellulitis during the Study on the foot having the Target Ulcer
12. If female Subject becomes pregnant, during the study
13. If Subject misses 6 consecutive dressings

In the event of a Subject withdrawal or discontinuation from the Study, the following information must be recorded in the e-CRF

- Date of withdrawal
- Reason for withdrawal
- Last treatment date

In the event of withdrawal or discontinuation, the Subject will be requested to cooperate for the following:

a. Recording AEs that may occur post withdrawal/discontinuation till End of Study
b. Follow-up on all SAEs or other AEs that may have occurred prior to withdrawal/discontinuation and are considered to be related to the Study IP, until resolved or assessed to be chronic or stable by the Investigator. The details would be documented in the Subject's medical records

7.3 LOST TO FOLLOW-UP

A randomized Subject will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled site visits and is unable to be contacted by the Study site staff. In such situation, following actions will be taken:

- The site will attempt to contact the Subject and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Study Nurses would be doing a Subject's home visit every day during the treatment period for wound dressing. In case Subject remains not reachable, the Investigator site team and Study Nurses will make every effort to regain contact with the Subject (where possible, 3 telephone calls and, if necessary, a certified letter to the Subject's last known mailing address or local equivalent methods) before a Subject is deemed lost to follow-up. These contact attempts should be documented in the Subject's medical record or Study file
- Should the Subject continue to be unreachable, he or she will be considered to have withdrawn from the Study with a primary reason of lost to follow-up
- For Lost to Follow-Up Subject, the last scheduled Study Visit will be treated as EOT/EOS visit and corresponding CRF will be completed by the Investigator

8 STUDY ASSESSMENTS AND PROCEDURES

Screening Visit V1 (Day -10 to Day -7)

The Screening Phase is designed to determine whether Subjects are eligible to proceed to the Treatment Phase of the Study. The activities in this Phase include:

- Obtain written consent from the Subject/LAR
- Investigator or authorized Study staff will explain to the Subject/LAR, the Study procedures and signed informed consent will be obtained

Note: Signed informed consent must be obtained prior to Subject participation in any protocol-related activities that are not part of routine care.

The following assessments and procedures will be performed and results will be recorded:

- Inclusion-exclusion criteria evaluation
- Demographic information of the Subject
- Sample collection for Urine pregnancy test (as necessary)
- Initial evaluation including medical history and foot specific history. The ulcer history will include the location and duration of all the potential Target Ulcers. In addition to disease history [DM (Type 1 or Type 2)], all other medical and social histories, in the opinion of the Investigator, that are relevant to the safety of the Subject or could impact safety or efficacy results for the Subject will be recorded. Recording of all current and prior treatment/therapies used within the 30 days prior to the V1 visit
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Systematic physical examination and body weight
- Laboratory tests (hematology tests, biochemistry, and $HbA1_C$)
- ECG or 2 D echocardiography (2D-ECHO only if ECG is not conclusive)
- Ankle-Brachial Index assessment and corresponding eligibility assessments as per Inclusion Criteria for ABI *(See Attachment 2).*
- Assessment of Study foot by SW 5.07 monofilament test. Peripheral neuropathy will be assessed by using a 10-g Semmes Weinstein 5.07-gauge monofilament to test 4 points on

the foot for touch sensation (Greater toe, 1st, 3rd and 5th metatarsal head) *(See Attachment 3)*

- Assessment of all potential Target Ulcers for osteomyelitis. The osteomyelitis should be ruled out by clinical examination and X-ray findings. If the Investigator is unable to ascertain the condition of osteomyelitis by probing of the Target Ulcer or by digital X-ray then Investigator may use other techniques such as MRI, bone scintigraphy, leukocyte scanning or bone biopsy to rule out the presence of osteomyelitis based on availability of the investigation facility
- Detail Foot Examination to assess vascular, neurological, dermatological and musculoskeletal signs and symptoms of the foot(s) with potential Target Ulcers
- Classification of all the potential Target Ulcers will be completed as per Texas system *(See Attachment 1)*
- Local examination and infection status of all potential Target Ulcers for presence of edema, warmth, erythema, pain, scaling, pus, exudates, cellulitis, callus, maceration or swelling and any signs of infection
- Assessment of all potential Target Ulcers characteristics in terms of wound edge, color, drainage amount and type, peri-wound conditions and color and percent wound bed covered by granulation tissue, fibrin slough, and necrotic tissue
- Target Ulcer measurement
- Subject education on diabetes management. Counseling on diabetes management will be provided as and when required during the Study
- Recording of concomitant medications
- Surgical or Sharp debridement of any of potential Target Ulcers, if required, along with documentation of type of debridement (e.g. callus removal, sharp or surgical), reason for debridement
- Nutritional information (i.e., the importance of diet in controlling glucose levels) will be provided to and reviewed with, each Subject at the Screening Visit (V1). Further counseling to the Subject will be available on request during the course of Study
- Photographs of both the legs from various angles (medial, lateral, dorsal, plantar) would be captured to verify that not more than three ulcers are present at this visit

During the Screening Phase, all the potential Target Ulcer will be treated by as per recommendation of the Investigator keeping in view the exclusion criteria

Baseline Visit V2 (Week 0, Day 0) [Window period 7-10 days from Screening Visit]

The Baseline Visit will take place between 7-10 days after the Screening Visit. Subjects will be re-checked for eligibility criteria and the Target Ulcer will be selected for the Study from all the potential Target Ulcers. Subjects who fail to meet eligibility criteria at Baseline Visit or those Subjects whose Potential Target Ulcers reduces in area by ≥30% during Screening period are considered screen failures and will exit from the Study without further evaluation.

The eligible Subjects will be randomized and their Treatment Phase shall begin at this visit. Following assessments and procedures will be performed during this visit:

- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Measurement of random blood glucose. If abnormality is observed, the Investigator may recommend pre- and post-prandial blood glucose measurement and modify dose or medication for adequate blood sugar control
- Recording of Change in the Medical History

- Surgical or Sharp debridement of any Target Ulcer, if required, along with documentation of type of debridement (e.g. callus removal, sharp or surgical), reason for debridement.
- Photographs of both the legs from various angles (medial, lateral, dorsal, plantar) would be captured to verify that not more than three ulcers are present at this visit
- Target Ulcer measurement
- Assessment of local pain in terms of 11-point (0-10) universal pain scale for the Target Ulcer *(See Attachment 4)*
- Assessment of local edema in terms of 5-point (0-4) edema scale for the Target Ulcer *(See Attachment 4)*
- Assessment of local erythema in terms of 5-point (0-4) erythema scale for the Target Ulcer *(See Attachment 4).*
- Clinical assessment of infection status of non-Study ulcer(s)

- Dispensing of appropriate off-loading footwear. All Subjects with a plantar Target Ulcer will be advised to wear suitable off-loading foot ware (e.g. Darco Ortho-Wedge or Heel-Wedge or any suitable footwear suggested by Investigator). Investigator may use additional or alternative off-loading equipment such felta foam, local plaster, etc. Use of casts is not permitted
- Subject education and training on use of off-loading device.
- Nutritional information (i.e., the importance of diet in controlling glucose levels) will be provided to the subject
- Recording of concomitant medications
- Dispensing of Study treatment by the unblinded Investigator: Unblinded Investigator will issue Study treatment material and communicate to the Study Nurse regarding the quantity of IP to be applied to the Target Ulcer during the week
- Dispensing of Study diary: Study Nurse will collect the study diary from the unblinded investigator. The study nurse will ensure to record in the diaries, the hours each day that the Subject does not wear the off-loading device and the duration of weight-bearing time experienced without the offloading/protective device, if relevant. The Study Nurse will also record twice daily treatment application and dressing changes done in the diary

Treatment Visits V3 to V14 (Week 1 to Week 12, Day 7 to Day 84 [Window period ±3 days for each scheduled visit])

The Subjects assigned to Galnobax® plus SoC, Vehicle plus SoC or only SoC Group will receive the treatment twice daily from Study Nurse for up to 12-weeks or until complete closure of Target Ulcer, whichever is earlier.

All Subjects will visit the Study site once every week as given in Study calendar. Assessment will be done at various Treatment visits as follows:

- Urine pregnancy test will be performed (as applicable) after every 4 weeks till V14 or EOT, whichever is earlier
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Systematic physical examination and body weight after every 4 weeks till V14 or EOT, whichever is earlier
- Laboratory tests (hematology tests and biochemistry) after every 4 weeks till V14 or EOT, whichever is earlier
- $HbA1_C$ test at V14 or EOT, whichever is earlier

- Measurement of random blood glucose. If abnormality is observed, the Investigator may recommend pre- and post-prandial blood glucose measurement and modify dose or medication for adequate blood sugar control
- ECG or 2 D echocardiography (2D-ECHO only if ECG is not conclusive) after every 4 weeks till V14 or EOT, whichever is earlier
- X-ray of the foot under the Study will be taken at the Investigator's discretion for ruling out osteomyelitis. Other methods such as bone scan, leukocyte scan or MRI as needed may be used by the Investigator, for confirming the osteomyelitis depending on the Target Ulcer status
- Detail Foot Examination to assess vascular, neurological, dermatological and musculoskeletal signs and symptoms of the foot(s) with Target Ulcer after every 4 weeks till V14 or EOT, whichever is earlier
- Grading and staging of Target Ulcer as per Texas system of wound classification *(See Attachment 1)*
- Local examination and infection status of Target Ulcer for presence of edema, warmth, erythema, pain, scaling, pus, exudates, cellulitis, callus, maceration or swelling and any signs of infection
- Assessment of Target Ulcer characteristics in terms of wound edge, color, drainage amount and type, peri-wound conditions and color and percent wound bed covered by granulation tissue, fibrin slough, and necrotic tissue
- Surgical or Sharp debridement of Target Ulcer, if required along with documentation of type of debridement (e.g. callus removal, sharp or surgical), reason for debridement
- Target Ulcer measurement
- Assessment of local pain in terms of 11-point (0-10) universal pain scale for the Target Ulcer *(See Attachment 4)*
- Assessment of local edema in terms of 5-point (0-4) edema scale for the Target Ulcer *(See Attachment 4)*
- Assessment of local erythema in terms of 5-point (0-4) erythema scale for the Target Ulcer *(See Attachment 4)*
- Clinical assessment of infection status of non-Study ulcer(s)
- Subject education on diabetes management and off-loading as and when required
- Recording of concomitant medications
- AE recording
- Nutritional information (i.e., the importance of diet in controlling glucose levels) will be provided to and reviewed. Further counseling to the Subject will be available on request during the course of Study
- Study Diary review will be done by unblinded Investigator for treatment compliance check and use of offloading device at each visit of the Study Nurse to the investigator Site

Follow-up Visit Week 14 to Week 24 (FU1 to FU4) [V15/Day 98 to V18/Day 168 (Window period ±3/±5 days)]

The Subjects whose Target Ulcer is closed (first observation of Target Ulcer Closure) or the Subject who completes the 12-weeks of Treatment Phase, whichever is earlier, will immediately enter the Follow-Up (FU) Phase of 12-weeks. All Subjects who enter the Follow-Up Phase are required to attend the Follow-up visit FU1-two weeks after EOT; FU2-four weeks after EOT, FU3-eight weeks after EOT and FU4-twelve weeks after EOT, regardless of whether the Target Ulcer is open/closed/re-opened.

For the Subjects whose Target Ulcer has closed within the 12-week Treatment Phase, the 12-week Follow-Up Phase is divided in to 4-week Closure Confirmation period and 8-week Observation period. The Closure Confirmation period will be of total four weeks with two visits two weeks apart for confirming initial closure of the Target Ulcer. The Observation period will be of total eight weeks with two visits, four weeks apart for assessing quality of healing, progress of ulcer closure and AEs, if observed.

For the Subjects whose Target Ulcer has not closed within 12-week Treatment Phase, the 12-week Follow-Up Phase will be considered as 12-week Observation period.

Subjects who have entered the Follow-Up Phase will be subjected to SoC treatment as deemed necessary by the Investigator. Unless recommended by the Investigator otherwise, SoC during the Follow-Up Phase will be self-administered by the Subject.

The Subject whose Target Ulcer has closed within 12-week Treatment Phase and has entered the Follow-Up Phase will continue to use protective covering or bandage (if advised by the Investigator) on the Target Ulcer until confirmation of the Target Ulcer closure. If the Target Ulcer remains closed during Closure Confirmation period, then the Target Ulcer will be confirmed to be closed. The time to Target Ulcer closure will be the time from the Baseline Visit when Target Ulcer was first observed closed for which Target Ulcer Closure was confirmed.

During this follow-up phase, if the Target Ulcer reopens during the Closure Confirmation period which lies within 84 ± 3 days from Baseline visit, the Subject would be given the treatment to complete 12-week of Treatment Phase. For example, if the Target Ulcer closes before 8 weeks of treatment and reopens within 4 weeks of Closure Confirmation period, the Subject will restart the treatment and continue only till 12-weeks (84±3 days) of treatment from Baseline visit. On completion of that period, Subject will enter the Follow-Up Phase.

During this follow-up phase, if the Target Ulcer reopens after confirmation of the Target Ulcer closure, the Subject will still be continued with the Follow-up assessment period and further evaluations would be as per Follow-up visit scheduled.

During this 12-week Follow-Up phase (84 ± 5 days from EOT), the closed Target Ulcer will be monitored to distinguish actual healing from transient wound coverage and for AEs, if any.

All Subjects will undergo following assessments during FU1 to FU4 visits

- Sample collection for Urine pregnancy test (as necessary) at FU2
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Systematic physical examination and body weight at EOS or FU4, whichever is earlier
- Laboratory tests (hematology tests, biochemistry, and HbA1c) at EOS or FU4, whichever is earlier
- Measurement of random blood glucose. If abnormality is observed, the Investigator may recommend pre- and post-prandial blood glucose measurement and modify dose or medication for adequate blood sugar control
- ECG or 2 D echocardiography (2D-ECHO only if ECG is not conclusive) at FU1
- Subject Diary review will be done by blinded Investigator for all subjects in follow up Phase
- Offloading, dressing compliance
- Detail Foot Examination to assess vascular, neurological, dermatological and musculoskeletal signs and symptoms of the foot(s) with Target Ulcer at EOS or FU4, whichever is earlier
- Classification of Target Ulcer will be completed, if ulcer remains open *(See Attachment 1)*

- Local examination and infection status of Target Ulcer for presence of edema, warmth, erythema, pain, scaling, pus, exudates, cellulitis, callus, maceration or swelling and any signs of infection, if ulcer remains open
- Assessment of Target Ulcer characteristics in terms of wound edge, color, drainage amount and type, peri-wound conditions and color and percent wound bed covered by granulation tissue, fibrin slough, and necrotic tissue, if ulcer remains open
- Target Ulcer measurement (if the Target Ulcer still persists). Ulcer will be photographed at each Follow-Up visit, even if it is closed
- Subject education on diabetes management and off-loading as and when required
- Recording of concomitant medications
- AE recording
- Surgical or Sharp debridement of the Target Ulcer, if required, along with documentation of type of debridement (e.g. callus removal, sharp or surgical), reason for debridement
- Nutritional information (i.e., the importance of diet in controlling glucose levels) will be provided to and reviewed. Further counseling to the Subject will be available on request during the course of Study
- Assessment of local pain in terms of 11-point (0-10) universal pain scale for the Target Ulcer *(See Attachment 4)*
- Assessment of local edema in terms of 5-point (0-4) edema scale for the Target Ulcer *(See Attachment 4)*
- Assessment of local erythema in terms of 5-point (0-4) erythema scale for the Target Ulcer *(See Attachment 4)*
- Clinical assessment of infection status of non-Study ulcer(s)
- Dispensing wound dressing material to the Subject as and when required

Note: Subject will be reminded to perform dressing changes if the Target Ulcer persists or as recommended by the Investigator. Subject will be reminded to follow off-loading of Target Ulcer irrespective of whether it has closed or not

Unscheduled Visits

Any visit to site by the Subject other than a regularly scheduled Study visit will be regarded as an unscheduled visit. Assessments at such unscheduled visits will be as follows:

- If the unscheduled visit is for recording of the Target Ulcer Closure, then the Investigator should complete all assessment as per EOT and proceed to Follow-Up Phase immediately.
- If the unscheduled visit is due to reopening of the Target Ulcer during Closure Confirmation period, then the Investigator should assess:
  - If the Subject is still within the 12-weeks from Baseline Visit V2, the Investigator should restart the treatment till the EOT Phase or re-closure of Target Ulcer, whichever is earlier
  - If the Subject is beyond 12-weeks of Treatment Phase, the Investigator should continue Follow-Up procedures
- If the unscheduled visit is for any other purpose, the Investigator should complete the assessments that are relevant to Phase of the Study for the Subject and complete corresponding CRF

8.1 ASSESSMENTS AND PROCEDURES IN THE STUDY

The assessments and procedures in the Study are as follows:

Ankle-Brachial Index (ABI): Measurement of the ABI will be performed in a clinician's office using a blood pressure (BP) cuff and handheld Doppler device with a vascular probe (*See Attachment 2*). Systolic BP will be determined in both arms and both ankles. ABI will be assessed at Screening Visit V1.

Random blood glucose measurement: Random blood glucose measurement will be done at Baseline Visit V2 and all Treatment and Follow-up Visits (V3 to V18). If abnormality is observed, the Investigator may recommend pre- and post-prandial blood glucose measurement and modify medication for adequate blood sugar control. This test will be performed locally.

Assessment of study foot: Study foot will be assessed at Screening Visit V1 by Semmes Weinstein (SW) 5.07 monofilament test. Peripheral neuropathy will be assessed by using a 10 g SW 5.07-gauge monofilament to test 4 points on the foot for touch sensation (Greater toe, 1st, 3rd and 5th metatarsal head) (*See Attachment 3*).

Detail foot examination: Detail foot examination to assess vascular, neurological, dermatological and musculoskeletal signs and symptoms of the foot under Study will be done at Screening Visit V1, Baseline Visit V2, every 4 weeks thereafter during treatment visits (i.e. at V6, V10, and V14 or EOT) and during follow-up at V18 or EOS/FU4, whichever is earlier.

Local examination and infection status of Target Ulcer for presence of edema, warmth, erythema, pain, scaling, pus, exudates, cellulitis, callus, maceration or swelling and any signs of infection will be done at all Visits (V1 to V18).

Target Ulcer classification and its measurement: Classification of all the potential Target Ulcers and its measurement will be completed as per Texas system at the screening visit (V1). The classification and measurement will be done for selected Target Ulcer at Baseline Visit (V2) as well as in all Treatment and Follow-up Visits (V3 to V18) (*See Attachment 1*). The measurement of the Target Ulcer area will be done using advance camera. The parameters captured will be area, volume, mean depth and maximal depth. It should however be noted that volume and depth measurements may be inaccurate to the extent of the advance camera's technical limitations. In the event of inability to measure wound size by advance camera, the Target Ulcer area measurement will be done with the help of wound tracing in conjunction with planimetry software. In such situation, only Target Ulcer area will be measured.

Target Ulcer characteristics: Assessment of Target Ulcer characteristics in terms of wound edge, color, drainage amount and type, peri-wound conditions and color and percent wound bed covered by granulation tissue, fibrin slough, and necrotic tissue will be done at all Visits (V1 to V18).

Wound Care: Wound care to be taken during the Study will be explained to the Subject by the Investigator at the time of Screening and periodically. This will include following:

1. A moist wound environment as suitable for the condition of wound (moist bandage should not be used in case wound is oozing and highly moist)
2. Non-adherence of dressing to the wound
3. Allowance for removal of dressing from the wound without pain or trauma
4. Role of the dressing to absorb the excess wound exudates
5. Allowance for gaseous exchange through the protective dressing
6. Prevent permeance to microorganisms

Debridement of Target Ulcer: Debridement of the Target Ulcer, if required along with documentation of type of debridement (e.g. callus removal, sharp or surgical), reason for debridement will be recorded at Screening Visit V1 and all treatment and Follow-up visits V2 to V18 (as and when necessary).

The Target Ulcer will be surgically debrided, if required as per procedure given below.

1. Perform sharp debridement to remove all necrotic soft tissue, hyperkeratotic wound margins, bacterial burden, cellular debris, sinus tracts, fistulae, undermined borders, and callus to produce viable wound margins and a clean ulcer site.
2. Use sterile saline to remove any debris at the ulcer site. Irrigate the ulcer with saline and gently wipe debris from the ulcer with sterile gauze.
3. Use sterile gauze moist by sterile saline to keep the ulcer environment moist. The moist gauze may not be used for oozing or highly moist wound.

Debridement of tissue will be done till all dead necrotic tissues are removed from Target Ulcer to expose healthy tissue which enhances wound healing.

Target Ulcer dressing: Use a dressing that will maintain a moist wound-healing environment (if found appropriate for the condition of wound), manage wound exudates, and protect the peri-ulcer skin. Cut sterile sponge in the approximate size and shape of the ulcer, moisten the sponge with saline, and place it over the ulcer. Place sterile gauze on top of sponge. Then wrap the dressing with a non-adherent bandage to secure the wound dressing.

The Target Ulcer will be dressed in one of the protocol-specified dressings (Aquacel®, TenderWet® or sterile gauze dipped in sterile normal saline or sterile Lactated Ringers solution). After the Target Ulcer has been designated, protocol-specified dressings should be used only on the Target Ulcer. All other ulcers will be treated as per Investigator discretion and per Standard Care.

Systematic physical examination and vital sign: Physical examination will be assessed at Screening Visit V1, V6, V10, V14 or EOT and V18 or EOS. However, vital signs (blood pressure, pulse rate, respiratory rate, and temperature) will be assessed at all visits (V1 to V18).

Laboratory tests: Hematology tests (WBC, RBC, Hematocrit, Hemoglobin, MCV, MCH, MCHC, RDW, Platelet Count, Mean Platelet Volume) and Biochemistry tests [Glucose, Calcium, Albumin, Total Protein, Sodium, Potassium, CO_2, Chloride, Blood Urea Nitrogen (BUN), eGFR, Alkaline phosphatase (ALP), Alanine transaminase (ALT), aspartate aminotransferase (AST), Bilirubin] will be done at Screening Visit V1, V6, V10, V14 or EOT and V18 or EOS. HbA1c will be performed at Screening Visit V1, V14 or EOT and V18 or EOS/FU4, whichever is earlier. Random blood glucose will be measured by the glucometer, provided by the sponsor, at Baseline Visit V2 and all Treatment and Follow-up visits (V3 to V18).

Approximately 5 mL blood will be collected from each Subject at visits where laboratory assays are to be performed. These visits are Screening visit V1, V6, V10, V14 or EOT visit whichever is earlier and V18 or EOS/FU4 whichever is earlier. The laboratory assessments are haematology, biochemistry and HbA1c. Thus, total volume of blood that will be withdrawn per Subject during the Study will be approximately 25 mL.

Any additional/unscheduled investigation(s) can be done at the Investigator's discretion as needed. These investigations may also be done at local laboratory, if required.

Urine pregnancy test will be done locally in women of child bearing potential at Screening Visit V1, V6, V10, V14 or EOT whichever is earlier, and V16/FU2 at Follow-Up.

ECG and X-ray: ECG will be done at Screening Visit V1, and every 4 weeks after Baseline during Treatment visit V6, V10, and V14 or EOT and V15/FU1 at follow-up. X-ray of the foot under Study will be performed at the Screening Visit and further at the Investigator's discretion to rule out osteomyelitis.

Recording and Assessment of adverse events: if there is any clinically significant abnormality or signs or symptom detected in the Subject or reported by the Subject after the application of treatment, it will be recorded as an adverse event. The AE assessment will be done from Baseline Visit V2 to V18 or EOS/FU4, whichever is earlier.

Assessment of local pain: Local pain at the Target Ulcer site will be measured in terms of 11-point universal pain scale as mentioned in *Attachment 4*.

Assessment of local edema: Local edema at the Target Ulcer site will be measured in terms of 5-point edema scale as mentioned in *Attachment 4*.
Assessment of local erythema: Local erythema at the Target Ulcer site will be measured in terms of 5-point erythema scale as mentioned in *Attachment 4*.
The local pain, edema and erythema will be recorded at all the visits from Baseline Visit V2 to V18 or EOS/FU4, whichever is earlier.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention (Galnobax® plus SoC or only SoC or Vehicle plus SoC) in humans, whether or not considered intervention-related.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

The intensity of all AEs occurring during the course of the Study will be graded according to NCI-CTCAE, version 4.0. as provided in Table 5:

Table 5 Assessment of Intensity

Grade	Description of Intensity Grading
1	Mild
2	Moderate
3	Severe
4	Life-threatening or disabling
5	Death

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

Every effort would be made by the Investigator to explain each AE and assess its causal relationship, if any, to application of the IP.

Causality of all AEs would be assessed by the Investigator depending upon various factors like the temporal relationship of the AE to Study IP application, whether AE follows a known pattern of response to IP, any other cause to which the AE can be attributed or intensity of AE changes.

Relationship of AEs to Study treatment will be classified as follows:

1. Unrelated – The event is definitely not associated with the Study drug. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication explain the reported AE.
2. Unlikely – The temporal association, Subject history and/or circumstances are such that the Study drug is not likely to have had an association with the observed event. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication, appear to explain the reported AE.
3. Possibly – The event follows a reasonable temporal sequence from Study drug but could have been produced by the Subject's clinical state or other therapies administered to the Subject.
4. Probably – The event follows a reasonable temporal sequence from the Study drug, abates upon discontinuation of the Study drug or control, and cannot be reasonably explained by known characteristics of the Subject's clinical state.
5. Definitely – The event follows a reasonable temporal sequence from the Study drug, abates upon discontinuation or cannot be explained by known characteristics of the Subject's clinical state.

8.2.3.3 EXPECTEDNESS

Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information available for the study intervention. The treatment is being given topically in this Study, therefore the AEs that are expected at and around the Target Ulcer location are: hypersensitivity, irritation, inflammation of ulcer. Since the Target Ulcer is an open wound, possibility of infection at the wound site cannot be ruled out. The infection at Target or non-Target Ulcer will be reported as AE.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of Study personnel during Study visits or Study Nurse during visits to Subject and interviews of a Study Subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate electronic case report form (eCRF). Information to be collected includes duration (start and end dates), severity/intensity, relationship to IP, specific therapy, results and consequences and seriousness. All AEs occurring while on Study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened or before application of first dose will be considered as baseline and not reported as an AE. However, if the Study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained till the last day of Study participation. At each Study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. An AE can reach one of the following outcomes:

a. Complete recovery (AE/ SAE end date will be captured).
b. Recovered with sequelae. (AE/ SAE end date will be captured and the sequelae will be specified).
c. Ongoing
d. Death
e. Unknown: The outcome of the event may be captured as unknown only in the exceptional cases when the Subject is lost to follow-up (AE end date will be left blank).

8.2.5 ADVERSE EVENT REPORTING

AEs will be assessed during each visit by doing clinical examination, review of the laboratory investigations and by directly questioning the Subject/LAR/impartial witness. The increase of Target Ulcer size or its worsening will be considered as adverse event. The change from Baseline in laboratory values, vital signs and ECG/EKG parameters outside accepted or normal range will be reported as adverse event irrespective of Investigator's opinion on clinical significance of such abnormality.

As far as possible each AE should be described to include:

- Duration (start and end dates)
- Severity/Intensity
- Relationship to IP or Specific therapy
- Results and Consequences
- Seriousness

Those AEs that are already documented in the CRFs, at a previous assessment and designated as 'ongoing' would be reviewed at subsequent visits, as necessary. If these have resolved, the documentation in the CRF would be completed.

8.2.6 HANDLING OF UNRESOLVED ADVERSE EVENTS

- If any AE is present when a Subject completes the Study or if a Subject is prematurely withdrawn from the Study, an attempt will be made to follow the Subject up for 12-weeks. Amongst the AEs ongoing on the last Study visit as per the Study protocol, all the AEs have to be recorded in the AE form
- The Investigator assesses the status of the AEs
- The AEs recorded at the time of exit are to be followed until,
  - The AEs are considered to become stable as per the Investigator's discretion, or
  - The AEs are no longer considered to be medically significant by the Investigator, or
  - The database of the Study is declared to be locked
- The sponsor reserves the right to ask further information on any AE/SAE, which may be considered of interest

8.2.7 EVENT NOT TO REPORTED AS AE

Progression of underlying disease (at Investigator's discretion) / Study indication/lack of efficacy of the IP would NOT be reported as an AE/SAE.

8.2.8 SERIOUS ADVERSE EVENT REPORTING

- Any SAE occurring during the course of the Study would be treated by established standards of care to protect the life and health of the Subject
- Any SAE, irrespective of causality, must be immediately notified to the safety team at the CRO and the Sponsor. It must be followed up within 24 hours on the Study specific SAE reporting form with as much detailed information regarding the event that is available
- Investigators would not wait to receive additional information to fully document the event, before notifying SAE to the CRO.
- The SAE reporting form should detail all relevant aspects of the AEs in question. Where applicable, information from relevant hospital case records and autopsy reports would be obtained and provided, in a blinded fashion, to the CRO.
- All SAEs would be reported within 24 hours of Investigator's knowledge of the event to the CRO. and to the respective EC and Regulatory authorities (CDSCO) by the Investigator as soon as possible as per applicable regulations. The Investigator site and the sponsor would have to copy all SAE related communications on safety@jssresearch.com while communicating with the CRO and *galnobax@novaleadpharma.com* for communicating with the Sponsor. The SAE forms should be shared via E-mail as scanned attachments
- The event must also be recorded on the CRF AE page
- The follow up SAE form also should be filled and sent to the CRO, the Sponsor, CDSCO and EC within 24 hours of updated information on SAE
- Communicate filled CIOMS-I MedWatch form within 14 calendar days to CDSCO

The CRO does not prefer Fax as the mode of communication for SAEs. However, if a site would insist on using fax then the site should have to send an email stating the information that the fax has been sent. In the event of any technical issue wherein the site would not be able to send the

Email, then a phone call should be made to the concerned medical monitor to inform that SAE form sent via fax.

Fax: + 91-11-1296613510

All the events will be monitored by the Investigator until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

8.2.9 REPORTING EVENTS TO PARTICIPANTS

Not-applicable

8.2.10 EVENTS OF SPECIAL INTEREST

Not-applicable

8.2.11 REPORTING OF PREGNANCY

In event of a pregnancy during the Study, the same is required to be reported to the CRO safety team immediately via telephone and in the form of Pregnancy Report Form (PRF) within 24 hours from the knowledge of the Investigator about the pregnancy. The Subject would be discontinued from the Study and the End of Study visit procedure would be completed.

A Pregnancy Outcome form (POF) will then be sent to the site from the CRO/the Sponsor, which should be filed and a copy of which will be faxed back to the CRO/the Sponsor safety team within 24 hours from the knowledge of the pregnancy reaching its outcome

Pregnancy during a clinical trial itself is not regarded as an AE/ SAE unless pregnancy falls in the following types:

- Ectopic pregnancy
- Molar pregnancy
- The concerned pregnancy results in one of the following outcomes:
- Miscarriage/late spontaneous abortion
- Stillbirth
- Congenital Malformation/Anomaly
- Neonatal death (within 28 days from birth)
- Infant death (after 28 days from birth but assessed as related to the IP by the Investigator)

In case for any pregnancy reported during a clinical trial, results in one of the above outcomes, the Investigator is required to fill the AE form and the corresponding SAE form and report to the CRO/the Sponsor safety team within same timelines as mentioned above.

8.2.12 EXPEDITED SAFETY REPORTING

Any serious AE, which is unexpected and at least possibly related to the IP calls for expedited reporting to the regulatory authorities and the ECs as per CDSCO requirements.

As the CRO acts on behalf of the Sponsor, the regulatory reporting time clock starts when any member of the CRO safety team qualifies a SAE as an expedited SAE, in consultation with the Sponsor.

8.2.13 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Not-applicable

8.2.14 UNANTICIPATED PROBLEM REPORTING

Not-applicable

8.2.15 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not-applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s):
Proportion of Subjects achieving Target Ulcer closure within 12-week Treatment Phase, as assessed by blinded Investigator.

Secondary Efficacy Endpoint(s):

- Time to Target Ulcer Closure during the 12-week Treatment Phase, as assessed by the blinded Investigator
- Proportion of Subjects achieving Target Ulcer Closure till End of study, as assessed by the blinded Investigator

9.2 SAMPLE SIZE DETERMINATION

This Study will have FAS Population (Efficacy Evaluable Population) of minimum of 240 Subjects (minimum of 120 each in Group 1 and Group 2). To ensure this and assuming 20% drop out rate, the population of two groups would be up to 300 Subjects. For safety analysis of Vehicle of Galnobax®, maximum of 50 Subjects will be recruited in Vehicle plus SoC group. Thus, overall population of maximum of 350 Subjects will be recruited in the Study.

Sample Size Determination and Rationale:

The sample size calculation has two components. One is based on statistical power and the other is based on clinical judgment.

The sample size calculation is based on the primary endpoint for the Study that is proportion of Subjects achieving complete closure of Target Ulcer within 12-week Treatment Phase, as determined by blinded Investigator's assessment.

The sample size is obtained based on the assumption that there will be a clinically meaningful difference of 21%, (i.e., 39% of SoC vs 60% of Galnobax®-treated achieved complete closure of Target Ulcer, odds ratio of 0.65). This assumption is based on the following:

a. Literature reports from various DFU trials showed that average percent wounds closed using SoC treatment is 24% globally.[5] [27] However, percent wounds closed using SoC treatment in recently completed DFU trial in India is reported to be 37.8%.[28] In view of this, it is assumed that 39% wounds may close in the SoC group.

b. In Phase 1/2 study of Galnobax®, 60% wounds closed within 12-week of Galnobax® treatment. Furthermore, 67% wounds were closed in Galnobax® arm for wounds with wound age > 6 weeks. In view of this, the inclusion criterion is revised to include Subjects with wounds of at least 6 weeks (which was 4 weeks in Phase 1/2 study) and it is assumed that 60% wounds may close in the Galnobax® treatment group.

To meet the Type I error rate of 0.05 (95% confidence interval), 2-sided analysis and 90% power, 120 Efficacy Evaluable Subjects in Group 1 and Group 2 will be required for making the FAS Population in the Study as 240. To accommodate the potential drop outs rate of 20%, a total of 300 Subjects will be randomized in these Groups to ensure more than 90% power for the primary endpoint analysis (i.e., proportion of Subjects achieving Target Ulcer Closure within 12-week Treatment Phase).

The safety evaluation of Vehicle of Galnobax® will be done by recruiting population of 50 Subjects in the Vehicle plus SoC group. As there is not hypothesis testing or statistical comparison proposed for this arm, this population might not be statistically significant, but would enough to give reasonable estimate of safety for Vehicle of Galnobax®.

9.2.1 RANDOMIZATION AND STRATIFICATION OF STUDY POPULATION:

Prior to randomization, Subjects will be stratified by location of Target Ulcer (planter or non-planter), and the Target Ulcer size (<5 cm^2 or ≥5 cm^2). The randomization will be done at the ratio of 3:3:1 in one of the following groups, using an IWRS:

- Galnobax® 14% plus SoC or
- SoC or
- Vehicle plus SoC

9.3 POPULATIONS FOR ANALYSES

For this Study, analysis will be done on ITT Population (Safety Evaluable Population), FAS Population (Efficacy Evaluable Population) and PP Population.

The ITT Population i.e. Safety Evaluable Population will include all those Subjects who are randomized and received at least one dose of the study treatment.

The FAS Population (Efficacy Evaluable Population) will include all randomized Subjects who has had at least six weekly assessments for Target Ulcer Closure or has Target Ulcer closed earlier than six weeks.

The PP Population will include all randomized Subjects who have completed the Study without any major protocol deviation.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing the detailed methods for analyses outlined below. Any deviation from the planned analyses will be described and justified in the final integrated clinical Study report.

A maximum of 350 Subjects will be competitively recruited at 40 sites from the DFU Subject population as described in *section 4.1*

The number and percentage of all the DFU Subjects entering and completing the clinical Study will be provided across treatment groups. The summarization of primary reason of discontinuation will also be provided across treatment groups.

For this Study, analysis will be done on ITT Population (Safety Evaluable Population), FAS Population (Efficacy Evaluable Population) and PP Population.

The continuous data will be summarized by treatment Group using descriptive statistics (number of Subjects [n], Mean, Standard Deviation [SD], Median, Minimum and Maximum [Range]). Categorical data will be summarized by treatment group using frequency count (n) and percentages (%).

The primary and secondary efficacy analysis will be performed on all Subjects in FAS Population (Efficacy Evaluable Population) and PP Population comparing Group 1 (Galnobax® plus SoC) and Group 2 (SoC) only. All the statistical analysis will be performed using SAS® version 9.4 or later.

The Safety analysis will be performed on all Subjects in ITT Population (Safety Evaluable Population).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary efficacy analysis will be performed on all Subjects in FAS Population (Efficacy Evaluable Population) and PP Population comparing Group 1 (Galnobax® plus SoC) and Group 2 (SoC only) only.

Proportion of Subjects achieving Target Ulcer closure within 12 week Treatment Phase (EOT) = [Number of Subjects having Target Ulcer closed by treatment at or before week 12 (84 ± 3 days)]/ [Total Number of Subjects in the Population].

The logistic regression analysis will be used for the primary efficacy analysis for the proportion of Subjects achieving Target Ulcer closure within 12-week Treatment Phase, considering Target Ulcer closed (Yes/No) as dependent variable and treatment group, ulcer type (plantar or non-plantar), and site as independent factors and baseline ulcer size as continuous covariate.

9.4.3 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINT(S)

The secondary efficacy analysis will be performed on all Subjects in FAS Population (Efficacy Evaluable Population) and PP Population comparing Group 1 (Galnobax® plus SoC) and Group 2 (SoC only) only and are defined as:

- Time to Target Ulcer Closure in days = (Date of Target Ulcer Closure by Week 12 of treatment or earlier – Date of first dose of Study treatment) + 1
- Proportion of Subjects achieving Target Ulcer Closure till End of Study = [Number of Subjects having Target Ulcer Closure at by week 24 or earlier /Total number of Subjects in the Population].

For analysis of secondary endpoint of time to Target Ulcer closure during the 12-week Treatment Phase, Cox proportional hazards model with treatment group, ulcer type (plantar or non-plantar) and site as independent factors and baseline ulcer size as continuous covariate will be used to compare between the treatment groups. In addition, Kaplan-Meier analysis will also be used to depict the median time (days) to Target Ulcer closure for the two treatment groups.

The other categorical secondary endpoints comparing proportion of Target Ulcer using different criteria will be analyzed using chi-square/fishers exact test as well as the same method described for primary efficacy analysis with the same model of logistic regression.

9.4.4 SAFETY ANALYSES

Safety will be analyzed for all Subjects in ITT Population in the three groups. No formal statistical analysis will be performed.

To investigate the safety of Galnobax® vehicle for establishing non-deleterious effects of Vehicle on wound healing, number and percentage of events as well as number and percentage of Subjects with events related to local wound assessment (local pain, edema, erythema) of Target Ulcer in Vehicle plus SoC group will be tabulated and reported.

9.4.4.1 TREATMENT EMERGENT ADVERSE EVENT

Treatment emergent adverse events (TEAE) are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment. The TEAEs, which is defined as all AEs on or after the application of first dose of IP will be summarized according to the numbers and percentages of TEAEs as well as numbers and percentages of Subjects with one or more occurrences of TEAEs during the Study. Number of Subjects with TEAEs and number of events of TEAEs will be tabulated by preferred term (PT) and system organ class (SOCL). If a Subject had more than one TEAE, event will be counted only once in SOCL and once for each PT.

Summaries of TEAEs by severity grade, relationship to Study medication, leading to death, SAEs of study, IP related TEAEs will be provided.

Also, summarization for SAE, SAEs by severity, SAEs by relationship to Study IP will be provided separately.

Listing will be provided for all Subjects who have at least one adverse event.

AEs will be coded using the MedDRA, version 20.0 or later.

9.4.4.2 CLINICAL LABORATORY TEST

The clinical laboratory tests will be summarized descriptively for each of the continuous parameter at Subject's visits when tests are carried out for the changes from the baseline parameter. Shift tables in terms of counts and percentages will be presented at each relevant visit versus baseline for categorical laboratory parameters.

Individual data listings of laboratory results will be presented for each Subject. Clinically significant laboratory test abnormalities that are considered AEs by the Investigator will be presented in the AE listings.

9.4.4.3 PHYSICAL EXAMINATION AND VITAL SIGNS

The vital sign parameters will be summarized descriptively for each of the continuous parameters at each visit and for change from baseline.

The frequency counts and percentages of Normal, Abnormal NCS, and Abnormal CS will be provided for each body system of the physical examination.

Subject wise data listing will be provided for all vital sign parameters and physical examination.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The demographic and baseline characteristics will be summarized and listed for all Subjects in ITT Population.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 20.0. The count and percentage of Subjects will be summarized according to the coded terms of system organ class and preferred term across all the treatment groups.

The prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD)-September, 2016 or later. The count and percentage of Subjects will be summarized according to the coded terms of system organ class and preferred term across all the treatment groups.

Other baseline parameters like ECG and X-Ray will be listed as appropriate.

9.4.6 PLANNED INTERIM ANALYSES

No interim analysis is planned for this Study.

9.4.7 METHODS USED FOR MISSING DATA

Missing data points will be dealt with using appropriate statistical techniques, depending on the nature of the data and will elaborately explained in statistical analysis plan (SAP).

9.4.8 HANDLING OF OUTLIER DATA

The outlier data will be dealt with using appropriate statistical techniques, depending upon the nature and type of data and will elaborately explained in statistical analysis plan (SAP).

9.4.9 HANDLING OF TREATMENT FAILURE

Subjects with need for more than two surgical debridement procedures during Treatment Phase will be considered as treatment failure for the Subject.

9.4.10 STATISTICAL ANALYSIS OF DATA

The CRO will perform the statistical evaluation using appropriate statistical tests. Statistical analysis will be performed using SAS® system Version 9.4 software (SAS Institute Inc., NC, and USA) or later.

9.4.11 SUB-GROUP ANALYSES

The subgroup analysis for ulcer type (plantar and non-plantar) and ulcer size (<5 cm^2 vs. ≥ 5 cm^2) will also be performed for the primary efficacy endpoint i.e. proportion of Subject achieving Target Ulcer Closure within 12-week Treatment Phase by considering ulcer type (plantar and non-plantar) and ulcer size (<5 cm^2 vs. ≥ 5 cm^2) as the subgroup strata.

9.4.12 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Listing of individual Subject data per visit (wherever applicable) for all key variable will be presented.

9.4.13 EXPLORATORY ANALYSES

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

The method of explanation to the Subject/legally accepted representative (LAR)/impartial witness and obtaining their consent would comply with the ICH GCP Guidelines, with GCP for Clinical Research in India, 2001; Indian Council of Medical Research's (ICMR) Ethical Guidelines for Biomedical Research on Human Participants, 2006 and Schedule Y, Amended 2005 under Drugs and Cosmetics Act and Rules there under, and the ethical principles in the amended Declaration of Helsinki version 2013.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the Study intervention, Study procedures, and risks are given to the potential participant and written documentation of informed consent is required from the Subject/LAR prior to starting intervention/administering Study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Prior to any Study-related Screening procedures being performed on the Subject, written informed consent will be obtained from each Subject before enrolling in the Study. The site should first obtain consent from the Subject/LAR on video recording of consent process. The Investigator or his/her representative will explain the nature of the Study to the Subject and the LAR (including the impartial witness if required) and answer all questions regarding this Study. This consent process will be video recorded by the site and stored carefully for any regulatory audit. The information and consent form will be reviewed, signed and dated by the Subject/LAR. In case the Subject or the LAR is illiterate, the impartial witness will attend the informed consent process and sign and date the ICF.

10.1.1.3 ETHICAL CONSIDERATION

The Study will be conducted according to the approved protocol (and amendments, if applicable), GCP standards (Good Clinical Practice Guidelines for Clinical Trials in India, FDA Title 21 part 312 and International Conference on Harmonization guidelines) and all applicable Government regulations.

The protocol will be submitted for review to EC of each site and their suggestions on Subject safety will be reviewed and adopted. Upon approval of protocol by EC, site will be initiated and Subjects will be randomized.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The Sponsor reserves right to terminate the Study at any time. The Principal Investigator (PI) and the Sponsor, if appropriate can mutually decide premature termination of the Study. The regulatory authorities or ECs may also recommend the Study termination before completion.

In the event of an early termination of the Study,

1. Investigators will cease the use of the IP immediately.

2. All outstanding electronic case report forms (eCRFs) will be completed and returned to the CRO/the Sponsor together with completed IP inventory, records and remaining Study material.
3. The CRO/the Sponsor will inform regulatory authorities reasons for such termination
4. Investigators will inform to respective ECs
5. The reason for termination will also be communicated to the Subjects in the trial.

Stopping or Discontinuation Rules for a Study Site:

The Study may be halted at any Study site if,

1. A Study site and/or its participating personnel are non-compliant with respect to
   - following the defined clinical Study protocol
   - reporting any adverse or unforeseen event to the EC/Regulatory in the minimum mandatory time or reporting AEs/Subject non-compliance to the CRO/the Sponsor
   - non-cooperation of the Investigator and/or Site with the CRO/the Sponsor
   - timely providing SoC to the Subjects
   - negligence to Subject's health and protocol by the Investigator/unblinded Investigator/site personnel involved in the Study
2. There is a significant decrease in the number of compliant Subjects anytime during the ongoing Study
3. If the Study Site / members of the site compromise(s) on the dignity or integrity of a Subject recruited into the Study
4. The EC recommends stop of Study based on occurrence of serious and unforeseen AEs

Stopping or Discontinuation Rules for a Full Study:

The Sponsor reserves right to discontinue the Study at any time.

10.1.3 CONFIDENTIALITY AND PRIVACY

The CRO and the Sponsor will affirm and uphold the principle of the Subject's right to protection against the invasion of privacy. Throughout this Study and any subsequent data analyses, all data reported to the Sponsor will be identified only by protocol number, Subject number and Subject initials.

The records of the Subject's medical history, physical examination, laboratory results and any other information or data generated during the Study will be made available to the Sponsor or its designee (auditors, monitors), the EC. It will also be made available to drug regulatory bodies in India and possibly other countries, formulary committees of hospitals, at the opinion of the Sponsor. A pre-condition for entry into this Study will be Subject's agreement to release the documentation and data for any lawful purpose. In such cases, the Subject's name will be removed from all documentation to ensure anonymity.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Sponsor's designee JSS India Medical Research Pvt. Ltd. will be responsible.

Study Management	Dr. Jayashri Krishnan
Project Manager	Dr. Sowmya. K.S

Study Monitoring	JSS Monitors
Medical Monitor	Dr. Gursimran Kaur
Regulatory	Mr. Harish Chander
Data Management	Dr. Neha Pant
Statistics	Mr. Santosh Kumar
Medical Writing	Ms. Meenakshi Chaudhary

10.1.5 CLINICAL MONITORING

10.1.5.1 SITE INITIATION

Upon obtaining EC approval for a site, a "Site Initiation Visit" will be held before the first Subject is enrolled. The Subjects cannot be recruited at the site until occurrence of such visit and its documentation. During this visit, requirements of GCP, protocol procedures, and all logistic issues will be discussed at length. The availability of IP and supplies at the site will be ensured and documented. The training of Investigator, site staff and Study Nurse will be documented.

The CRO team will also determine the adequacy and readiness of the clinical Study facility to start enrolment. The team will discuss the responsibilities of the blinded and unblinded Investigators and Study Nurse as well as other personnel involved with the Study with regard to protocol adherence.

10.1.5.2 STUDY MONITORING AND SOURCE DATA VERIFICATION

After the Study is initiated, Study monitor(s) from the CRO will contact the Investigator to obtain information on the performance of the Study. These contacts will be scheduled at regular intervals and be either in person or telephonic.

Subsequent to start of recruitment, the first "Monitoring Visit" would occur as soon as possible after recruitment of the first Subject. The monitoring visits will take place at regular intervals during the entire Study (once a month or once in two months depending on recruitment rate of the site).

The Investigator and site staff are obliged to set aside adequate time and place for the monitoring visits. All Study related site records where original entries are made will be reviewed to make sure that all Study related compliances are met.

In addition to the monitoring visits, the sites may be audited or inspected. The audit may be carried out by the Quality Assurance Department of the CRO and/or independent entity authorized by the Sponsor. In addition, regulatory authorities may inspect the Study. The Investigator undertakes to expeditiously inform the CRO of an inspection by a regulatory authority.

10.1.5.3 CRF COMPLETION

All Subject data (including Subject information, laboratory values, efficacy parameters etc.) will be collected in the source document during each visit of the Subject to the Site. This source data will be transcribed to electronic case report form (eCRF) by the site staff within 2-3 days from the visit. The entered data will be validated by running logic checks and manual reviews. For any discrepancies identified in study database, queries will be generated in the e-CRF for resolution. Site staff will be responsible for resolving all queries in the database. The queries raised in the e-CRF will be first investigated by site from source data and Subject records. Then, appropriate corrections will be done to the e-CRF by the Investigator or their authorized designee. When the data has been entered, verified, and validated, the database will be locked for analysis.

Medical Reviewers will review the CRF as well as data discrepancies generated by electronic edit check programs. Any discrepancies noted in the data will be queried to the Investigator for appropriate resolution. The AEs will be coded using MedDRA, version 20.0 and the concomitant Medications will be coded using World Health Organization drug dictionary (WHO-DD) (Version 1st March 2017 or later).

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

In accordance with applicable regulations, ICH-GCP guidelines, The Sponsor or its designee's monitors will contact the Site prior to the start of the Study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

The Sponsor and or its designee will monitor the Study for the protocol compliance verifying the following, but not limited to:

- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP guidelines, and all applicable regulatory requirements
- Data are authentic, accurate, and complete

The Site Investigator agrees to allow the monitor direct access to all relevant documents for the purpose of verification of available data.

To ensure compliance with ICH-GCP guidelines and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit following intimation and appointment. Regulatory agencies may also conduct a regulatory inspection of this Study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Site Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the Site under the supervision of the Site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the Study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

10.1.7.2 STUDY RECORDS RETENTION

All documentation pertaining to the Study will be kept by the Sponsor for the lifetime of the product. The final report pertaining to this Study will be kept by the CRO for a further five years.

The Study monitor will provide each Investigator with a Site Master File, which would be used to file the IB, protocol, IP accountability records, correspondence with the EC and national regulatory authority, the CRO, the Sponsor and other Study-related documents.

As required by ICH GCP guidelines, the Investigator would keep essential documents for his/her Site until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

In addition, the Investigator would make provision for the Subject's medical records to be kept for the same period of time.

No data would be destroyed without the agreement of the Sponsor. The Sponsor will inform the Investigator in writing of the need for record retention and will notify the Investigator in writing when the trial related records are no longer needed.

Subjects' medical records and other original data will be archived in accordance with the local regulations and ICH GCP guidelines.

10.1.8 PROTOCOL DEVIATIONS

During the conduct of the Study, if any deviation(s) is noticed from the norm mentioned in the Protocol, this will be documented as protocol deviation(s).

The severity of the protocol deviation will be graded as minor if the deviation is not altering the integrity of the Study plan or its safety and efficacy outcome. The deviation is said to be major or is designated as violation, if it is altering the integrity of the Study plan or its safety and efficacy outcome in the opinion of the Investigator.

Examples of the major deviations or violations of the Protocol shall include:

- Recruitment of a Subject in conflict with the inclusion and exclusion criteria
- If Subject misses two consecutive Treatment visits or maximum of four Treatment visits
- If Subject misses 6 consecutive wound dressings, anytime during the Treatment Phase
- If Subject misses both of the Closure Verification Visit as well as Closure Confirmation visit
- Use of a non-permitted concurrent treatment
- Failure to obtain informed consent prior to initiation of Study related procedures

Examples of minor deviations of the Protocol shall include:

- Visits that occurred outside the time frame permitted in the protocol
- Subjects have not met with Study drug compliance (80% - 120%) for a week during Treatment Phase

- Laboratory tests not performed as per timelines specified in the protocol

Protocol Waivers

There are no protocol waivers proposed for this Study.

10.1.9 PUBLICATION AND DATA SHARING POLICY

A Clinical Study Report, per the ICH Guideline for Structure and Content of Clinical Study Reports, will be prepared by the CRO in close collaboration with the Sponsor upon full completion of the Study. This Clinical Study Report, as well as any discovery and improvement related to IP, shall be the property of the Sponsor. The report will include, but not be limited to, a description of the study objectives, methodology (including any deviations from protocols), results, and conclusions regarding attainment of study objectives (from the standpoint of safety). All significant AEs will be described, with the Investigator's assessments as to whether related to Study drug administration.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the Sponsor for the purposes of performing the Study, will be published or passed on to any third party without the prior written consent of the Sponsor.

Any Investigator involved with this Study is obligated to provide the Sponsor with complete test results and all data derived from the Study. The Investigators agree to keep all unpublished information and results concerning this Study 'Strictly Confidential'. Unpublished information must not be published or disclosed without Sponsor's prior written approval

10.1.10CONFLICT OF INTEREST POLICY

Any Investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee of the Site with a Committee-sanctioned conflict management plan that has been reviewed and approved by the Study Sponsor prior to participation in this study.

10.2 ADDITIONAL CONSIDERATIONS

10.2.1 POSSIBLE DRUG INTERACTIONS AND PROHIBITED MEDICATIONS

Apart from SoC and Study treatment described above, no other topical treatment (such as creams, gels, ointments, liquids, sprays, patches, etc.) at the Target Ulcer site is permitted during the Study. The drugs that may affect the healing of ulcer for e.g., corticosteroids, immune-suppressants (e.g. except inhalers for respiratory disorders) and colchicines will not be permitted to be used during the Treatment Phase of the Study. Any medication from alternative medicinal therapy for wound healing (e.g. negative pressure or hyperbaric oxygen) will not be permitted during the period of Study.

Contraindicated drugs: Esmolol hydrochloride is contraindicated in Subjects using inotropic agents and/or vasopressors to maintain systemic blood pressure. It is also contraindicated in Subjects with sinus bradycardia, second and third degree AV block, right ventricular failure secondary to pulmonary hypertension, overt cardiac failure or cardiogenic shock.

Concurrent use of Verapamil with Esmolol hydrochloride: The use of i.v. verapamil with a beta-blocker may cause severe depression of ventricular function. Accordingly, Subjects with atrial fibrillation or atrial flutter who have received Esmolol hydrochloride should only be administered verapamil if the benefits outweigh the risk in the opinion of the Investigator.

Drugs having interactions with esmolol like other beta-blockers (e.g., propranolol, metoprolol), beta agonists (e.g. Formoterol, Clenbuterol, Salbutamol), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine), digoxin, morphine, NSAIDs (e.g., ibuprofen), arbutamine, dopamine, succinylcholine, epinephrine/norepinephrine, other blood pressure medicine (e.g. clonidine), blood thinners (e.g., warfarin) should be administered with due risk/benefit consideration by the Investigator. Investigators should look for alternatives (if it is ethically acceptable that the Subject can be put on alternative treatment) to above drugs when Galnobax® treatment is underway. Investigator can contact the CRO's Study monitor for any clarification on this, if necessary.

10.3 ABBREVIATIONS

Table 6 List of Abbreviations

ABI	Ankle-Brachial Index
AE	Adverse Events
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMWT	Advanced Moist Wound Therapy
AST	Aspartate Transaminase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDSCO	Central Drugs Standard Control Organization
CRO	Contract Research Organization
CTMP	Clinical Trial Management Plan
DFU	Diabetic Foot Ulcer
DGHS	Directorate General Of Health Services
DM	Diabetes Mellitus
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerulus Filtration Rate
EKG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow Up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBOT	Hyperbaric Oxygen Therapy
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICMR	Indian Council of Medical Research
IDF	International Diabetes Federation
IND	Investigational New Drug Application
IP	Investigational Product
ITT	Intention-to-Treat
IWRS	Interactive Web-Based Randomization System
LAR	Legally Authorized Representative
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MP	Monitoring Plan
NCS	Nerve Conduction Study
NCT	National Clinical Trial

NO	Nitric Oxide
NPWT	Negative Pressure Wound Therapy
NYHA	New York Heart Association
PI	Principal Investigator
PK	Pharmacokinetic
POF	Pregnancy Outcome Form
PP	Per Protocol
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cell
RDW	Red cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOA	Schedule of Activities
SoC	Standard of Care
SOCL	System Organ Class
SPP	Skin Perfusion Pressure
SW	Semmes-Weinstein
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Events
WBC	White Blood Cell

10.4 PROTOCOL AMENDMENT HISTORY

Not applicable

11 APPENDICES

ATTACHMENT 1

TEXAS CLASSIFICATION FOR DIABETIC FOOT DISEASE

Grade-0	Pre-or post ulcerative site that has healed
Grade -1	Superficial wound not involving tendon, capsule, or bone
Grade -2	Wound penetrating to tendon or capsule
Grade -3	Wound penetrates to bone or joint
Stage A	No infection or ischemia
Stage B	Infection present
Stage C	Ischemia present
Stage D	Infection and ischemia present

ATTACHMENT 2

ANKLE-BRACHIAL INDEX (ABI)

STEP-BY-STEP INSTRUCTIONS ON HOW TO PERFORM AND INTERPRET THE ABI

What is the ABI?

The ankle-brachial index (ABI) is a simple, noninvasive tool used to screen for peripheral arterial disease (PAD), a vascular condition affecting more than 8 million adult Americans and associated with significant morbidity and mortality.[1] Despite its prevalence and cardiovascular risk implications, only 25% of PAD Subjects are undergoing treatment.[1] As only about 10% of Subjects with PAD present with classic claudication—40% of Subjects are asymptomatic—clinicians need to have a high level of suspicion for this disease in their adult Subject population.[2] According to AHA/ACC guidelines, an ABI should be conducted on Subjects presenting with risk factors for PAD so that therapeutic interventions known to diminish their increased risk of myocardial infarction (MI), stroke, and death may be offered.[2] (Level of Evidence: B)

How to perform the ABI?

Measurement of the ABI can be easily performed in a clinician's office using a blood pressure (BP) cuff and handheld Doppler device with a vascular probe. Systolic BP is determined in both arms and both ankles. An ABI measurement can usually be performed in less than 10 minutes.

Tools Needed for Measuring ABI

- Sphygmomanometer with appropriately sized cuff(s) for both arm and ankle
- Handheld Doppler device with vascular probe
- Conductivity gel compatible with the Doppler device

Step 1: Measure the brachial systolic pressure in both arms [3, 4]:

- Allow Subject to rest for 5-10 minutes in the supine position.
- Place the BP cuff on Subject's upper arm with the lower edge approximately 1 inch above the antecubital fossa.
- Palpate for the brachial pulse and apply conductivity gel over the brachial artery. Place the tip of the probe into the gel at a 45-60-degree angle until clear arterial pulse sounds are heard.
- Inflate the cuff to the point that pulse sounds disappear, then go 20 mm Hg above that point. Slowly deflate at a rate of 2 mm Hg per sec and record the point where arterial pulse sounds resume. This is the brachial systolic pressure.
- Repeat this procedure in the other arm.
- The higher of the two brachial systolic pressure readings will be used to calculate the ABI.
- There should be a difference of less than 10 mm Hg between each brachial BP.

Step 2: Measure the posterior tibial and dorsalis pedis systolic pressures in both legs:

- Place the BP cuff on the Subject's leg approximately 2 inches above the ankle's medial malleolus.
- Locate the posterior tibial (PT) pulse, apply gel, and position the Doppler probe. Measure the systolic pressure following the same procedure described for the brachial artery.
- On the same leg, locate the dorsalis pedis (DP) pulse and measure systolic pressure.

- Repeat measurement of both the PT and DP systolic pressures on the other leg.
- Select the higher of the two ankle readings for each leg (PT or DP). These numbers will serve as the ankle systolic pressures in the ABI calculation.
- If either the PT or DP ankle pulse is absent, use the measurable reading to calculate the ABI.

Step 3: To calculate the ABI, divide each ankle systolic pressure by the brachial systolic pressure.

- Divide the higher of the two systolic pressures for each leg by the higher of the two arm pressures to get the right and left ABI.

For example, consider the table given below. The ABI for this Subject is calculated by using 130 (the higher of the two brachial pressures) as the denominator and 95 and 130 as the numerators for the right and left legs, respectively. The ABI for the right leg is 0.73 and for the left leg is 1.0.

ABI results

Systolic Pressure	Right	Left
Brachial	130	129
Posterior Tibial	95	120
Dorsalis Pedis	90	130
ABI = Ankle systolic/brachial systolic		
	95/130	130/130
ABI	0.73	1.0

How to interpret the ABI?

An abnormal ABI may be an independent predictor of mortality, as it reflects the burden of atherosclerosis. [5, 6] Most will agree that a normal ABI is >0.9. An ABI <0.9 suggests significant narrowing of one or more blood vessels in the leg. The majority of Subjects with claudication have ABIs ranging from 0.3 to 0.9. Rest pain or severe occlusive disease typically occurs with an ABI <0.5. ABIs <0.2 are associated with ischemic or gangrenous extremities. Conditions such as DM or end stage-renal disease can give falsely elevated ABIs (1.3-1.5). The ABI test approaches 95% accuracy in detecting PAD. [7] However, a normal ABI value does not absolutely rule out the possibility of PAD. Some Subjects with normal or near-normal ABI results may have symptoms suggesting PAD. If the resting ABI is normal, an exercise ABI should be conducted.

ABI Ranges

Normal: 1.0 - 1.1
Borderline: 0.91 - 0.99
Abnormal: <0.9 or >1.3

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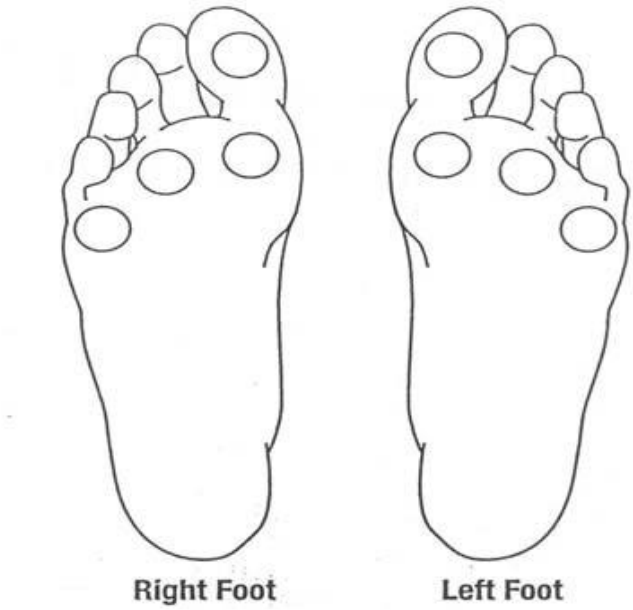
ATTACHMENT 3

SUGGESTED TECHNIQUE FOR USING THE 10-G MONOFILAMENT

1. Obtain two or more reusable monofilaments or a packet of disposable monofilaments (MFs) from one of the sites listed under "Resources For 10-g Monofilaments."
    - Use the 10-g MF < 100 applications/day, then "rest" it for 24h – thus the need for at least 2 MFs.
    - The accuracy of 10-g MFs obtained as samples from pharmaceutical companies is unknown.
2. Check the 10-g MF for defects. Replace if bowed, kinked, or twisted.
3. Compress the 10-g MF twice before use each day.
4. Place the Subject in the supine position for ease of testing.
5. Tell the Subject that you are testing for loss of protective sensation that increases the risk for foot ulcer and amputation.
6. Demonstrate buckling of the 10-g MF on the Subject's forearm or hand.
7. Have the Subject close their eyes.
8. Test four sites (See diagram) on each foot in random sequence. Avoid scars, calluses, and ulcers.
a. Test the plantar surface of each great toe.
b. Test the plantar surfaces of the 1st, 3rd, and 5th metatarsal heads of each foot.



If callus, scar, or ulcer is present, test at adjacent sites on the plantar surface of the foot.
9. Hold the 10-g MF perpendicular to the test site, and then bow it to a C-shape for one second.
    Do not allow the 10-g MF to slide along the skin.
    The Subject should sense the 10-g MF by the time that it bows.
10. Grade the Subject's response by using the approach suggested by the International Consensus Group on the Diabetic Foot:
    - Bow the 10-g MF at a designated site, and ask the Subject, "Do you feel it touch you – yes or no?"

- Repeat testing twice at each site and randomly include a “sham” application in which the 10-g MF is not applied. There will be a total of three applications at each site, one of which does not touch the skin.
- Protective sensation is considered to be present if the Subject correctly answers two or more of the three applications, one of which was a sham.
- If the Subject correctly answers only one or none of the three applications, return and retest that site.
- The Subject is considered to have insensate feet if they fail on retesting at just one or more sites on either foot.

11. Caveats:

- The feet may be falsely insensate when cold or edematous.
- Heel testing does not discriminate ulcer formers.
- Subjects who have normal protective sensation should be retested annually.

Technically, Subjects who have insensate feet need not be retested. Some clinicians believe that repeated testing of the individual with insensate feet may be a useful educational and motivational tool.

ATTACHMENT 4

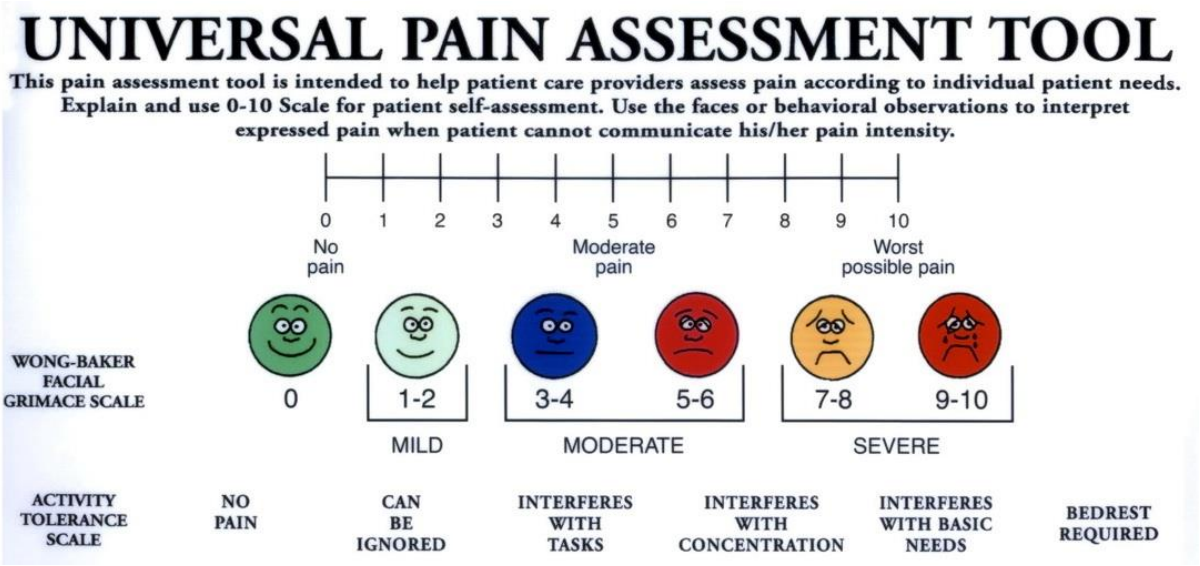
SCALES FOR PAIN, EDEMA AND ERYTHEMA

Local assessment of pain, edema and erythema by respective scales will be done as follows:

PAIN SCALE

Local pain at the Target Ulcer site will be measured in terms of 11 point universal pain scale with scale of

- 0: No pain
- 1-3: Mild pain (Able to adapt to pain)
- 4-6: Moderate pain (Interferes with many activities)
- 7-10: Severe pain (Subject disable or unable to function independently)



EDEMA SCALE

Local edema at the Target Ulcer site will be measured in terms of 5 point edema scale as:

- 0: No edema
- 1: Very slight edema (barely perceptible)
- 2: Well defined edema (edges of area well defined raising)
- 3: Moderate edema (raised approx. 1 mm)
- 4: Severe edema (raised more than 1 mm and beyond exposed area)

ERYTHEMA SCALE

Local erythema at the Target Ulcer site will be measured in terms of 5 point erythema scale as:

- 0: No erythema
- 1: Very slight erythema (barely perceptible)
- 2: Well defined erythema
- 3: Moderate to severe erythema
- 4: Severe erythema (Beet redness to slight eschar formation)

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