A Phase 2a Multi-Center, Prospective, Randomized Controlled Study to Evaluate the Safety and Efficacy of Topically Applied PEP-TISSEEL in Subjects with Diabetic Foot Ulcers (DFU)

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PROTOCOL SYNOPSIS

Study Synopsis	
Sponsor: Rion Inc.	**Investigational Product: PEP-TISSEEL** PEP™ Drug Product (Biologic)/ Fibrin Sealant (TISSEEL® VH Kit) (Biologic)
Title of Study: A Phase 2a Multi-Center, Prospective, Randomized, Controlled Study to Evaluate the Safety and Efficacy of Topically Applied PEP-TISSEEL in Subjects with Diabetic Foot Ulcers (DFU)	
Indication: Diabetic Foot Ulcer (DFU)	
Number of Study Centers: Up to 15 centers in the United States	
Objectives: • Evaluate the safety of PEP-TISSEEL applied weekly on subjects with DFUs of area 1 cm^2 to 15 cm^2 up to 12 weeks, with long-term monitoring to 3-month safety visit post-randomization • Evaluate the efficacy of PEP-TISSEEL applied weekly on subjects with DFUs of area 1 cm^2 to 15 cm^2 up to 12 weeks, with long-term monitoring to 3-month safety visit post-randomization • To support determination of the appropriate duration of PEP-TISSEEL dose to be employed in future clinical studies	
Number of Subjects: Up to 60	
Methodology: Phase 2a, multi-center, prospective, randomized controlled study <u>Overview</u> The objective of this multi-center, prospective, randomized controlled study is to evaluate the safety and efficacy of PEP-TISSEEL+ Standard of Care (SOC) compared to SOC only treatment in up to 60 subjects (30 subjects PEP-TISSEEL + SOC and 30 subjects SOC only), specifically for the treatment of their non-healing DFU. Treatment for the PEP-TISSEEL+SOC arm is: • PEP-TISSEEL • Mepitel dressing followed by Tegaderm® (Mepilex can be used if subjects are allergic to Tegaderm) • 3M Cavilon® (may be used on the borders prior to placing the Tegaderm or Mepilex) • Padded 3-layer secondary outer layer dressing (Profore (Smith and Nephew (Memphis, TN)); and • Offloaded with an offloading Controlled Ankle Movement (CAM) Boot (Foot Defender (Miami, FL) or Total Contact Cast (TCC)) ○ Use of an alternate offloading device (e.g., Charcot Restraint Orthotic Walker (CROW) boot, custom shoe, etc.) may be approved on a case-by-case basis	

Treatment for the Standard of Care (SOC) only arm is:

- Fibracol
- Mepitel dressing followed by Tegaderm (Mepilex can be used if subjects are allergic to Tegaderm)
- 3M Cavilon (may be used on the borders prior to placing the Tegaderm or Mepilex)
- Padded 3-layer secondary outer layer dressing (Profore (Smith and Nephew (Memphis, TN)) or equivalent); and
- Offloaded with an offloading CAM Boot (Foot Defender (Miami, FL) or TCC)
    - Use of an alternate offloading device (e.g., Charcot Restraint Orthotic Walker (CROW) boot, custom shoe, etc.) may be approved on a case-by-case basis

Enrolled subjects will be randomized in a 1:1 ratio with 30 subjects receiving 2 vials PEP delivered in 10 mL TISSEEL plus SOC and the other 30 subjects receiving SOC only.

Before randomization, subjects must complete a two (2) week run-in period (Screening) in which they will be evaluated for inclusion and exclusion criteria and will receive standard of care treatment with required off-loading CAM Boot (Foot Defender, Miami FL) or TCC. The Investigator will choose and document the appropriate type of off-loading modality based on their clinical judgement and the subject's diabetic foot ulcer off-loading requirements.

Pharmacovigilance

Subject safety will be monitored using all appropriate measures including vital signs, ulcer assessments, and clinical and laboratory assessments.

Criteria for Inclusion:

1. Males and females ≥ 18 years of age
2. Properly obtained written informed consent
3. Documented history of Type I or Type II Diabetes Mellitus, requiring oral and/or insulin replacement therapy
4. The index ulcer is classified as Wagner Grade 1 ulcer and remains Wagner 1 Grade between Screening and Randomization/Baseline visit (Visit 1 through Visit 3)
5. These ulcers are superficial, full-thickness ulcers limited to the dermis, not extending to the subcutaneous tissue
6. Area of index ulcer must be between 1 cm^2 to 15 cm^2 post debridement at screening and baseline
7. The index ulcer must be located anatomically on the foot with ≥ 50% of the wound area below the medial or lateral malleolus
8. Presence of a persistent non-healing DFU for at least 4 weeks from Randomization and not more than 1 year that has failed to respond to SOC at any point during this timeframe
9. Adequate vascular perfusion as evidenced by one of the following:

a. Dorsal transcutaneous oxygen measurement (TCOM/TcPO2) measurement of ≥ 40 mmHg within 90 days of Screening (Visit 1 or 2)
b. Ankle Branchial Index (ABI) between 0.7 and 1.3 within 90 days of Screening (Visit 1 or 2) using the extremity on which the index ulcer is located
c. Arterial Doppler ultrasound evaluating for biphasic or triphasic dorsalis pedis and/or posterior tibial vessels at the level of the ankle or a TBI (Toe Brachial Index) of > 0.6 is acceptable within 90 days of Screening (Visit 1 or 2)

10. The index ulcer has been offloaded with protocol defined offloading device during Screening (Run-In) period through Randomization/Baseline visit.
11. Must meet one of the following criteria:
    a. Female subjects of Non-Child-Bearing Potential defined as:
    i. Postmenopausal for at least 1 year (Subject verbal confirmation acceptable), or surgically sterilized (i.e., hysterectomy or bilateral oophorectomy more than 3 months prior to Screening (Visit 1 or 2)), or
    ii. Bilateral tubal ligation more than 6 months prior to Screening (Visit 1 or 2), or
    iii. Must have a negative serum β-hCG pregnancy test at Visit 1 and not be breastfeeding prior to being administered with the study drug
    b. Male subjects of Non-Childbearing Potential are defined as those vasectomized subjects whose vasectomy was performed 6 months prior to Screening (Visit 1 or 2) or those diagnosed as sterile by a physician
    c. Females and Males of Childbearing Potential who practice an acceptable method of contraception defined as the use of any form of hormonal contraceptive, a barrier method with spermicide, condoms, intrauterine device, or abstinence from sexual intercourse starting at least 60 days prior to Screening and continuing at least 30 days following the last treatment. Female will undergo a negative serum β-hCG pregnancy test at Visit 1 and an additional urine test at Baseline/Randomization (Visit 3 or Day 0) and must not be breastfeeding prior to being administered with the study drug
12. Ability to comply with the study protocol as per investigator discretion

Criteria for Exclusion:

1. Actively undergoing chemotherapy treatment (localized radiation treatment is allowed if it is not on the DFU wound site and in remission based on scans, bloodwork or some other kind of test, such as a breast biopsy or a bone marrow biopsy)
2. Ulceration with exposed tendon, capsule, or bone
3. Suspicion of bone or joint infection by clinical or other criteria as per STONEES criteria below:
    a. STONEES criteria for infection:
        i. size increase,
        ii. temperature elevation,
        iii. os (probe to bone)
        iv. new areas of breakdown

v. exudative
vi. erythema/edema
vii. smell

4. Unable or unwilling to utilize the protocol defined offloading device
5. Subjects who have undergone endovascular or open revascularization of the index limb within the last 30 days from Screening.
6. Index ulcer has decreased in area by ≥ 30% between Screening (Visit 1) and Baseline visits
7. Any subject that is currently on/or requires oral, systemic or topical antibiotics, or is anticipated to require their use during the course of the study
8. Any subject that has vascular compromise requiring surgical intervention or has undergone vascular reconstruction or angioplasty less than 1 month prior to randomization. Any planned surgical procedures during the study participation
9. Serum Creatinine level > 3.0 mg/dL
10. Hemoglobin A1c (HbA1c) >12%
11. Aspartate Aminotransferase (AST, GOT) and/or Alanine Aminotransferase (ALT, GPT) >3x the upper limit of normal
12. Acute active Charcot foot
13. The location of the index ulcer is within 2 cm of any other ulcer
14. Any subject that would be unable to safely monitor the infection status of the index ulcer at home and return for scheduled visits
15. History of immunosuppression or taking immunosuppressive agents including systemic corticosteroids, except stable daily doses of 5 mg/day or less for chronic conditions for up to 5 days
16. Any subject with a life expectancy ≤ 6 months
17. Pregnancy, including a positive pregnancy test at Baseline, or lactation/breastfeeding at anytime
18. Use of investigational drugs or biologics within 28 days prior to screening (Visit 1 or 2)
19. History of a concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the subject or compliance with the protocol
20. Known or suspected active abuse of alcohol, or non-prescription drugs
21. Participation in another interventional clinical study or study in the past 30 days of Screening (Visit 1 or 2) or concurrent participation in another interventional clinical study
22. Subjects who have untreated Hep C
23. Subjects who are HIV positive
24. Subjects on anticoagulation that are not maintained within the International Normalized Ratio (INR) of > 3.0

Drug Product, Dose and Mode of Administration:
PEP™ Drug Product is a lyophilized powder contained within a 10R glass vial. The powder cake weighs approximately 75 mg per vial. This protocol will evaluate 2 vials of PEP Drug Product delivered in

10 mL TISSEEL fibrin sealant (15mg/mL PEP-TISSEEL) for 12 weeks. Debridement should be done prior to the first treatment and as medically appropriately determined on each visit thereafter by the investigator. For subjects randomized to the active arm of this study, all doses will be applied topically at each weekly visit to the DFU. There will be 2 vials of PEP reconstituted in 10 mL TISSEEL that will be administered topically. After PEP-TISSEEL application, each subject will have a Mepitel dressing followed by a Tegaderm dressing (Mepilex can be used if subject is allergic to Tegaderm) then covered with a barrier film Cavilon, and then the wound will be dressed in a padded 3-layer secondary outer dressing; Profore and the subject will be offloaded with a diabetic offloading boot (Foot Defender or TCC. Use of an alternate offloading device (e.g., CROW boot, custom shoe, etc.) may be approved on a case-by-case basis).
Study Duration: 14 months

Criteria for Evaluation – Endpoints:
For each endpoint, data will be compared between treatment groups.

Co-primary Endpoint:

- Evaluate the safety of weekly topical applications of PEP – TISSEEL on subjects with DFUs of area 1 cm^2 to 15 cm^2 DFU up to 12 weeks by counting the DLTs (dose limiting toxicity events); if there are 4 or less DLTs in the cohort the endpoint will be considered as met or positive.
- Evaluate the efficacy of weekly topical applications of PEP – TISSEEL on subjects with DFUs of area 1 cm^2 to 15 cm^2 DFU up to 12 weeks by comparing the proportions of complete wound healing with the SOC group
    - Complete closure (wound healing) is defined as skin re-epithelialization without drainage or dressing requirements confirmed at two (2) consecutive study visits within 17 days

Secondary Endpoint:

- Percentage area reduction (PAR) at 12 weeks.

Tertiary Endpoint

- VAS pain (mean difference between baseline and 12 weeks)
- Semmes-Weinstein score (mean difference between baseline and 12 weeks)
- WOUND-Q (domains: wound characteristics and health-related quality of life; mean difference between baseline and 12 weeks)

Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) will meet monthly to follow the first 10 subjects, which would be deemed the sentinel cohort for safety. The DSMB will make recommendations to the Sponsor in conjunction with the Medical Monitor regarding study pauses, stoppage, or subject removal.

Assessments

Index ulcers will be assessed using digital photography and tracings (inSight® 3D system, eKare; Arlington, VA) should be performed on the index ulcer pre- and post- debridement. Index ulcers will be examined at all study visits, from Screening through end of treatment, including unscheduled wound care visits. The presence of symptoms or signs of infection, such as purulent drainage, erythema, warmth, exudation, odor, pain, fever and leukocytosis will be assessed during each ulcer assessment. The entire eKare platform is HIPAA, GDPR, as well as 21 CFR Part 11 compliant to maximize data integrity with full audit trail. Assessment of skin irritation and/or sensitization will be performed at every visit for the area which surrounds the ulcer up to 3 cm from the edges using a 5-point scale (numerical scoring system of Draize;

Draize JH. Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. The Association of Food and Drug Officials of the United States, Austin,TX: 1959: 46–59.

Statistical Methods

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, standard deviation, minimum, maximum, median, interquartile range, 95% confidence limits for the mean) as detailed in the statistical analysis plan. Categorical variables will be described by counts and percentages. Subject comorbidities and AEs will be defined using MedDRA (current version) (system organ class (SOC); preferred term (PT)). Subject medications at screening and changes during the study will be defined using WHODrug.

Efficacy and safety data will be summarized by treatment group with full analysis defined per the statistical analysis plan.

Sample Size

A sample size of up to 60 subjects randomized in a 1:1 distribution to PEP-TISSEEL:SOC. No formal sample size calculations based on statistical powering were conducted.

Interim Analysis

After complete data are available for 20 subjects for the duration of 12 weeks an interim analysis will be conducted for efficacy and safety (excluding early terminations). The following is an overview of the analysis that will be conducted (the complete list plus tables will be defined in the interim analysis plan (IAP))

- Primary, secondary and tertiary endpoint statistics per treatment group
- Summary statistics for each treatment group (count of TEAEs per group/per patient; summary rates per group; notes of unexpected occurrences during the study; relevant decisions made).
- SAE list for each treatment group: (brief description; resolution; impact on study (e.g., withdrawal, etc.).
- Complete listing of all AEs by subject, system organ class and preferred term(s).
- Classification of all AEs by severity and relatedness