A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Limited Partnership's Mupirocin Cream USP, 2% to Glenmark Pharmaceuticals Mupirocin Cream USP, 2% and to Compare Both Active Treatments to a Vehicle Control in the Treatment of Secondarily Infected Traumatic Skin Lesions

Protocol No.: PRG-NY-19-002

NCT04155203

02-25-2019

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Limited Partnership's Mupirocin Cream USP, 2% to Glenmark Pharmaceuticals Mupirocin Cream USP, 2% and to Compare Both Active Treatments to a Vehicle Control in the Treatment of Secondarily Infected Traumatic Skin Lesions

Protocol No.: PRG-NY-19-002

[redacted]

Confidential

The confidential information provided in this document is for use by parties directly involved in this investigation. By accepting this document, you agree that the information contained herein will not be disclosed to any person not directly involved in this investigation without written authorization from Perrigo UK FINCO Limited Partnership.

[redacted]

PROTOCOL SIGNATURE PAGE
PROTOCOL NUMBER: PRG-NY-19-002

PROTOCOL TITLE: A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Limited Partnership's Mupirocin Cream USP, 2% to Glenmark Pharmaceuticals Mupirocin Cream USP, 2% and to Compare Both Active Treatments to a Vehicle Control in the Treatment of Secondarily Infected Traumatic Skin Lesions

Signatures of representatives below indicate this is the agreed upon final version of the protocol:

Perrigo:

[redacted]

[redacted]

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[redacted]

[redacted]

STUDY SYNOPSIS

Title:	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Limited Partnership's Mupirocin Cream USP, 2% to Glenmark Pharmaceuticals Mupirocin Cream USP, 2% and to Compare Both Active Treatments to a Vehicle Control in the Treatment of Secondarily Infected Traumatic Skin Lesions
Study Period:	17 days
Study Medication:	1. Mupirocin Cream USP, 2%, Perrigo UK FINCO Limited Partnership, [redacted] 2. Mupirocin Cream USP, 2%, manufactured by Glenmark Pharmaceuticals 3. Vehicle of test product, Perrigo UK FINCO Limited Partnership, [redacted]
Study Objectives:	To compare the safety and efficacy profiles of Perrigo UK FINCO Limited Partnership's Mupirocin Cream USP, 2% to Glenmark Pharmaceuticals Mupirocin Cream USP, 2%, and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of subjects with secondarily infected traumatic skin lesions.
Study Design:	Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be admitted into the study only after written informed consent/assent (as applicable) has been obtained and after all inclusion/exclusion criteria have been met. Male and female subjects 18 months or older, with a secondarily infected traumatic skin lesion such as a laceration, sutured wound, or abrasion will be eligible for enrollment.
Study Population:	Approximately [redacted] subjects [redacted] who meet the inclusion/exclusion criteria, will be enrolled to obtain approximately [redacted] modified-Intent-To-Treat (mITT) and [redacted] per-protocol (PP) subjects.
Dosing:	Subjects will be randomized [redacted] to the test product, reference product, or vehicle treatment group, and will apply [redacted] the study medication to the secondarily infected target lesion 3 times daily for 10 days.
Study Visits:	Clinical Evaluations will be performed at: 1. Visit 1/Day 1 (Baseline) 2. Visit 2/Day 3 [redacted] (During treatment) 3. Visit 3/Day 10 [redacted] (End of treatment) 4. Visit 4/Day 17 [redacted] (Follow-up/Early Termination) Safety will be assessed by monitoring adverse events at each visit.
Evaluations:	To evaluate the clinical response, the Skin Infection Rating Scale (SIRS) will be used by investigators to rate the signs of exudate/pus, crusting, erythema/inflammation, tissue warmth and tissue edema, and by subjects to rate the symptoms of itching and pain. Bacteriological response will also be assessed.

[redacted]

Endpoints:	The primary efficacy endpoint is the proportion of subjects in each treatment group with clinical cure, defined as a SIRS score of zero "0" or absent for all signs and symptoms at Visit 4/Day 17 follow-up visit (7 days after the end of treatment). Secondary efficacy endpoints are the proportion of subjects with clinical cure at Visit 3/Day 10 (End of Treatment), bacteriological cure (defined as elimination of *S. aureus* and *S. pyogenes* or response was such that no culture material was available and therefore evidence of pathogen eradication) at Visit 3/Day 10 (End of Treatment), and bacteriological cure at Visit 4/Day 17 (Follow-up).
Safety:	The incidence of all adverse events reported during the study will be summarized by treatment group. Test and reference product will be compared for safety by analyzing nature, severity and frequency of treatment emergent adverse events.

[redacted]

ABBREVIATIONS

AE	Adverse Event
CI	Confidence interval
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
ICH	International Council for Harmonization
IRB	Institutional Review Board
ITT	Intent- to-treat (population)
IUD	Intra-Uterine Device
LAR	Legally authorized representative
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat (population)
OTC	Over the counter
PP	Per-protocol (population)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S. aureus	*Staphylococcus aureus*
SIRS	Skin Infection Rating Scale
S. pyogenes	*Streptococcus pyogenes*
WHO	World Health Organization

[redacted]

1. BACKGROUND

[redacted]

[redacted].

2. STUDY OBJECTIVES

To compare the safety and efficacy profiles of Perrigo UK FINCO Limited Partnership's Mupirocin Cream USP, 2% to Glenmark Pharmaceuticals Mupirocin Cream USP, 2%, and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of subjects with secondarily infected traumatic skin lesions.

2.1 Endpoints

The primary efficacy endpoint is the proportion of subjects in each treatment group with clinical cure, defined as a Skin Infection Rating Scale (SIRS) score of zero "0" or absent for all signs and symptoms at Visit 4/Day 17 follow-up visit (7 days after the end of treatment).

Secondary efficacy endpoints are the proportion of subjects with clinical cure at Visit 3/Day 10 (End of Treatment), bacteriological cure (defined as elimination of *S. aureus* and *S. pyogenes* or response was such that no culture material was available and therefore evidence of pathogen eradication) at Visit 3/Day 10 (End of Treatment), and bacteriological cure at Visit 4/Day 17 (Follow-up).

2.2 Safety

Safety of the test and reference products will be compared by evaluating the nature, severity and frequency of their adverse event profiles. All adverse events that occur during the study will be recorded whether or not they are considered to be related to the study medication. Descriptions of reactions or complaints will include the approximate date of onset, the date the adverse event ended, the severity of the adverse event, and the outcome. Comparisons between the treatment groups will be made by tabulating the frequency of subjects with one or more adverse events (classified into MedDRA terms) during the study. Pearson's Chi-Square test or Fisher's Exact test, whichever is most appropriate, will be used to compare the proportion of subjects in each treatment group with any adverse event. [redacted].

[redacted]

3. STUDY DESIGN

3.1 Type/Design of Study

Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be assigned [redacted] to test product, reference product, or vehicle, respectively. Subjects will apply [redacted] the assigned study medication topically to cover the entire secondarily infected target lesion 3 times per day for 10 consecutive days.

Subjects will be males and females, 18 months or older, with a secondarily infected traumatic skin lesion such as a laceration, sutured wound, or abrasion. Visits to the study site are scheduled at Day 1 (screening/baseline), Day 3 (during treatment), Day 10 (end of treatment), and Day 17 (follow-up).

At Visit 1/Screening/Baseline informed consent will be obtained. The subject's medical history will be recorded along with concomitant medications. A urine pregnancy test will be performed for women of childbearing potential. A brief physical examination will be performed. The diagnosis of a secondarily infected traumatic skin lesion will be confirmed. The dimensions of the secondarily infected target lesion will be measured, location will be documented, and the Subject's Skin Infection Rating Scale (SIRS) total score of the secondarily infected target lesion will be evaluated and recorded. A specimen for culture will be prepared from exudates collected from the secondarily infected target lesion and a slide will be prepared for Wright stain/Gram stain. Subjects who meet inclusion/exclusion criteria will be dispensed study medication and the site staff will instruct the subject on medication application and completion of subject diary. The first application of study medication will be made at the site under supervision of site staff.

Subjects will return to the office for Visit 2/During Treatment (Day 3 [redacted]), Visit 3/End of Treatment (Day 10 [redacted]) and Visit 4/Follow-up (Day 17 [redacted]). During each visit, SIRS total score of the secondarily infected target lesion will be completed, the subject's concomitant medications will be reviewed, and any adverse events will be recorded. Subjects will return at each appropriate visit with study medication and their Subject Diary. [redacted] At Visit 3/End of Treatment [redacted] all study medication will be collected. At Visit 3/End of Treatment [redacted] and Visit 4/Follow-up [redacted], bacteriological samples for culture will be obtained.

If it is necessary to see a subject other than at a scheduled visit date, the Unscheduled Visit procedures will be followed (Sections 5.11 and 5.12). If the investigator decides to discontinue a subject at any time during the study, a standard of care treatment may be advised at the Investigator's discretion, and an Early Termination Visit may be performed for this purpose. If the investigator discontinues a subject due to a negative baseline culture, the procedures for the Negative Baseline Culture Discontinuation Visit (Sections 5.11 and 5.12) should be performed.

Early Observation of Subjects: At Visit 2/Day 3 [redacted] or at any time the Investigator determines that the infection has become systemic, is not responding to treatment, is not improving, or that the study treatment is not sufficient to treat the infected lesion, he or she should discontinue the subject from the study and prescribe appropriate approved treatment (e.g. Mupirocin Cream USP, 2% or oral therapy) or refer the subject to another physician. This treatment may be topical or

[redacted]

systemic in nature and use of such therapy will be documented in the source documents and electronic case report form (eCRF).

3.2 Study Population

Male and female subjects, 18 months or older with a secondarily infected traumatic skin lesion such as a laceration, sutured wound, or abrasion will be eligible for enrollment.

4. SELECTION OF STUDY SUBJECTS

4.1 Inclusion Criteria

Subjects **must** meet all of the following criteria:

1. Subjects 18 years or older must sign an Institutional Review Board (IRB)-approved written informed consent. Subjects under the age of 18 years must have a parent or legally authorized representative provide IRB approved written informed consent. [redacted]
2. Subjects must be healthy males or nonpregnant females aged 18 months or older.
3. Subjects must have a secondarily infected traumatic skin lesion such as a laceration, sutured wound, or abrasion. [redacted]
4. Subjects must have a positive baseline culture for *S. aureus* and/or *S. pyogenes* from a sample taken from the secondarily infected traumatic skin lesion.
5. Subjects must have a positive Gram stain or Wright stain for confirmation of white blood cells in the pus/exudate from the secondarily infected traumatic skin lesion.
6. Subjects must have a Skin Infection Rating Scale (SIRS) total score for the secondarily infected traumatic skin lesion of at least 8 at baseline (see Section 5.8 for the scale).
7. Subjects must be willing and able to understand and comply with the requirements of the study, apply the medication as instructed, and be able to complete the study.
8. Subjects must be in general good health and free from any clinically significant disease, other than secondarily infected traumatic skin lesion(s), that might interfere with the study evaluations.
9. [redacted]

[redacted]

[redacted]

4.2 Exclusion Criteria

Subjects may **not** be selected if any of the following criteria exist:

1. Subjects who are pregnant, breastfeeding, or planning a pregnancy within the period of their study participation.
2. Presence of any dermatological disorder that may interfere with evaluation of the subject's secondarily infected traumatic skin lesion(s), [redacted]
3. Presence of bacterial skin infection that, because of depth or severity, could not be appropriately treated with a topical antibiotic (e.g., severe cellulitis, abscess, ulcer, furunculosis).
4. Presence of secondarily infected bite (animal, human, or insect) or puncture wound.
5. Presence of systemic signs or symptoms of infection (fever defined as an oral temperature greater than 101°F or 38.3°C).
6. Requirement for surgical intervention for treatment of the infection prior to study entry.
   Presence of cutaneous herpes simplex infections.
7. Use of any topical corticosteroid, topical antibiotic, or topical antifungal, on the secondarily infected target lesion, within 48 hours prior to Visit 1/Day 1 (Baseline).
8. Use of any systemic antibiotic or systemic corticosteroid within 7 days of Visit 1/Day 1 (Baseline).
9. Primary or secondary immunodeficiency.
10. Diagnosed Diabetes Mellitus (controlled or uncontrolled).
11. Any uncontrolled, chronic or serious disease or medical condition that would prevent participation in a clinical trial, or, in judgment of the investigator, would put the subject at undue risk or might confound the study assessments (such as planned hospitalizations during the study).
12. History of hypersensitivity or allergy to mupirocin and/or any ingredient in the study medication.
13. Subject consumes excessive alcohol, abuses drugs, or has a condition that could compromise the subject's ability to comply with study requirements.

[redacted]

14. [redacted]
15. [redacted].
16. [redacted].
17. [redacted].
18. Subjects who, in the opinion of the investigator, are unlikely to be able to follow the restrictions of the protocol and complete the study.

4.3 Prohibited Medications

The following medications/procedures are prohibited during this study:

[redacted]

4.4 Precautions

The following precautions are to be taken during this study:

1. Subjects should use study medication externally only and avoid contact with the eyes, nose, mouth, or vagina or mucosal surfaces.
2. [redacted].
3. [redacted].
4. [redacted].
5. [redacted]

5. PROCEDURES

5.1 Subject Screening and Enrollment

The study personnel will review the IRB-approved informed consent form and assent form, if applicable, with each subject and give the subject an opportunity to have all questions answered before proceeding.

Subjects 18 years or older must sign an Institutional Review Board (IRB)-approved written informed consent. Subjects under the age of 18 years must have a parent or legally authorized representative provide IRB approved written informed consent. In addition, an assent form for minors must be

[redacted]

signed by subjects under the legal age of consent and over 6 years of age. [redacted]

[redacted]

5.2 Assignment of Subject Number

Once the subject has consented and met inclusion/ exclusion criteria, the subject will be assigned a subject number. Each subject will be dispensed their respective medication. The subject number will correspond to a computer-generated randomization schedule assigning the number to one of the three study treatment groups and will be taken from the study medication kit dispensed to the subject at each site.

5.3 Demographics/Medical History

A demographic profile and complete medical history will be recorded prior to starting study medication. The medical history will include a complete review of all current diseases and their respective treatments.

5.4 Concomitant Medications

Concomitant medications and any medications taken [redacted] prior to signing informed consent/assent will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on either a regular or "prn" basis, including vitamins, aspirin, and acetaminophen, should be recorded on this page prior to starting the study medication. A record of medication taken by the subject during the study is to be obtained at each study visit.

5.5 Physical Examination

The investigator, sub-investigator, or appropriately delegated and qualified designee will perform a brief physical examination prior to the subject starting study medication. [redacted]

5.6 Urine Pregnancy Test

A urine pregnancy test will be conducted on women of child-bearing potential at Visit 1/Day 1 (before the subject applies the first dose of the study medication at the site) and Visit 4/Day 17 [redacted]. An investigator may repeat the pregnancy test anytime during the study visit if there is any suspicion or possibility that the subject may be pregnant. [redacted]

[redacted]

[redacted]

5.7 Dermatological Examination and Target Lesion Diagnosis

The investigator or sub-investigator will examine the subject to establish the clinical diagnosis of secondarily infected traumatic skin lesion. The nature and location of the secondarily infected traumatic target skin lesion, such as a laceration, sutured wound, or abrasion, will be recorded on the source document [redacted] and electronic case report form (eCRF). The dimensions of the wound will be measured and recorded. [redacted] To be eligible for the study, a laceration or sutured wound should not exceed 10 cm in length with surrounding erythema not more than 2 cm from the edge of the lesion. An abrasion should not exceed 100 cm^2 in total area with surrounding erythema not more than 2 cm from the edge of the abrasion.

5.8 Skin Infection Rating and Clinical Response

[redacted]

At Visit 1/Day 1 (Baseline), the investigator should complete the SIRS before the subject applies the first dose of the study medication at the site.

[redacted]

The investigator or sub-investigator will assess clinical signs of the secondarily infected target lesion at each visit using the SIRS scoring scale shown below for each of the following signs: exudate/pus, crusting, erythema/inflammation, tissue warmth, and edema. Symptoms (itching and pain) will be

[redacted]

assessed by discussion with the subject at each visit and will be reported as the severity experienced at the time of the study visit.

[redacted].

Clinical cure is defined as a SIRS score of zero "0" or "absent" for all signs and symptoms.

Skin Infection Rating Scale (SIRS):

Sign/Symptom	Score	Definition
Exudate/pus	0 =Absent 1 = Mild 2 = Moderate 3 = Severe	No evidence of exudate or pus Small amount of fluid/pus coming from the skin lesion(s) Exudate/pus infected area is moderate Extensive area of skin lesion is infected and there is draining exudate
Crusting	0 =Absent 1 = Mild 2 = Moderate 3 = Severe	No evidence of crusting A few areas have some evidence of crusting lesions Crusting is present throughout the infected area Thick crusting appears over the entire infected area
Erythema/ inflammation	0 =Absent 1 = Mild 2 = Moderate 3 = Severe	Skin tone and color are normal; no signs of erythema or inflammation Skin is pink with minimal signs of inflammation Skin is red with definite signs of inflammation Skin is red and severe inflammation is present
Tissue edema	0 =Absent 1 = Mild 2 = Moderate 3 = Severe	No evidence of tissue edema Tissue has mild edema Tissue has moderate edema Tissue has severe edema
Tissue warmth	0 =Absent 1 = Mild 2 = Moderate 3 = Severe	No evidence of tissue warmth Tissue has mild warmth Tissue has moderate warmth Tissue has severe warmth
Itching	0 =Absent 1 = Mild 2 = Moderate 3 = Severe	No itching Some evidence of scratching or rubbing the area is evident and subject reports minor discomfort Evidence of scratching and subject reports bothersome itching Evidence of extensive scratching and subject reports itching interferes with daily activities or sleep
Pain	0 =Absent 1 = Mild 2 = Moderate 3 = Severe	No pain Slight pain; not bothersome; no analgesics being taken Definite pain; subject reports bothersome pain, without loss of sleep, mild analgesic may be taken Intense pain that interferes with daily activities or sleep; medication required to control pain

[redacted]

5.9 Bacteriology Specimen Collection and Bacteriological Response

A wound exudate sample for culture and sensitivity testing will be taken with a swab from the secondarily infected target lesion and sent to a designated laboratory for culture. A positive culture (*S. aureus* or *S. pyogenes*) is required for study [redacted]. Subjects with negative baseline cultures are to be discontinued as soon as possible after negative results are received by the clinical research site. [redacted]

Bacteriological cure is defined as elimination of *S. aureus* and *S. Pyogenes* [redacted].

5.10 Study Medication Use, Subject Instructions and Diary

Study personnel will ensure that the subjects can identify the treatment area and know where to apply the study medication. Subjects will be instructed on the correct use of study medication at the study site during Visit 1/ Day 1. [redacted].

Subjects will be instructed to apply [redacted] study medication 3 times per day for 10 consecutive days according to the Subject Instructions [redacted] The Subject Instructions and the Subject Diary will be reviewed with each subject at each visit.

Subjects will be given a Subject Diary card to record study medication applications [redacted] to be used during the study period.

The Subject Diary card will be dispensed to each enrolled subject at Visit 1/Day 1. The subject will be instructed to complete the Subject Diary by recording each application or missed application of study medication. At Visit 2/Day 3 [redacted], study personnel will review the Subject Diary. At Visit 3/Day 10 [redacted], study personnel will collect and review the completed Subject Diary.

5.11 Visit Specific Procedures

The following sections outline the procedures required at each visit.

Visit 1/ Day 1 - Baseline

Prospective subjects will visit the study center and be examined by the study physician who will perform the procedures below at this visit.

[redacted]

The following procedures must be completed and documented on the source document before a subject is randomized on the study:

- [redacted])

Visit 2/Day 3 [redacted] – During Treatment

- [redacted]

Early Observation of Subjects: At this visit, the Investigator will determine if the infection has become systemic, is not responding to treatment, is not improving, or that the study treatment is not sufficient to treat the infected lesion, and if any of these conditions are confirmed, the subject should be discontinued from the study and be prescribed an appropriate approved treatment (e.g. Mupirocin Cream USP, 2% or oral therapy) or refer the subject to another physician. This treatment may be topical or systemic in nature and use of such therapy will be documented in the source documents and electronic case report form (eCRF).

Visit 3/Day 10 [redacted] – End of Treatment

- [redacted]

- [redacted]

Visit 4/Day 17 [redacted] - Follow-up/Early Termination

- [redacted]

[redacted]

Unscheduled Visit

An unscheduled visit is allowed at any time if in the investigator's opinion it is warranted. If the investigator assesses the subject's condition and determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as a treatment failure, Early Termination Visit procedures conducted, and a standard of care treatment may be advised at the investigator's discretion. [redacted]

[redacted]

- [redacted]

[redacted]

5.12 Summary of Assessments

The schedule of visits and procedures to be conducted at each visit are summarized in the Schedule of Study Procedures.

[redacted]

Schedule of Study Procedures

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]					
[redacted]	[redacted]					
[redacted]	[redacted]					
[redacted]	[redacted]					
[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]					
[redacted]	[redacted]					
[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]					
[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

5.13 Screen Failures

Screen failures will not be entered in the database or included in any data analyses. A screen failure is a subject who received information about the study, including signing an informed consent/assent, and possibly underwent some study-related procedures but was not enrolled, dispensed study medication, nor applied the investigational product.

5.14 Protocol Deviations/Violations

This study will be conducted as described in this protocol except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator or a responsible, appropriately trained and credentialed professional(s) designated by the investigator. In the event of a significant deviation from the protocol due to an emergency, accident or mistake, the investigator or designee must contact Perrigo / [redacted] contacts in Section 15 (Appendix A) of this protocol at the earliest possible time.

[redacted]

[redacted]

5.15 Subject/Treatment Compliance

Study personnel will ensure that subjects can identify the secondarily infected target lesion they will be treating and know where to apply the study medication. Subjects will be instructed on the correct use of study medication at the study site during Visit 1/Day 1. Subjects will apply the first application at the study site under the supervision of site staff. Subjects will be instructed to apply [redacted] study medication three (3) times per day for ten (10) consecutive days according to the Subject Instructions [redacted]

[redacted]

5.16 Discontinuation/Withdrawal of Study Subjects

Subjects may be removed from the study for any of the following reasons:

- Negative baseline culture.
- The subject withdraws his or her consent for any reason.
- The subject's condition has worsened to the degree that the investigator feels it is unsafe for the subject to continue in the study or requires an alternative therapy for the treatment of their secondarily infected traumatic skin lesion.
- The subject's medication code is unblinded.
- The subject did not meet or no longer meets the entry criteria.
- An adverse event, including intercurrent illness, occurs for which the subject desires to discontinue treatment or the investigator determines that it is in the subject's best interest to be discontinued.
- A concomitant therapy is reported or required that may interfere with the results of the study.
- The subject is lost to follow-up. The investigator will document efforts to attempt to reach the subject twice by telephone and will send a certified follow-up letter before considering that subject lost to follow-up. All attempts must be thoroughly recorded.
- The subject becomes pregnant during the course of the trial.
- A lack of treatment response, [redacted]
- Investigator discretion (e.g., non-compliant with study protocol requirements).

After a subject has been discontinued, he/she will not be allowed to re-enroll in the study at any facility.

The reasons for a subject being discontinued will be documented in the eCRFs and the enrollment log.

If a subject is discontinued from the study for any reason, the Visit 4/Day 17 (End of Study Visit/Early Termination Visit) procedures should be completed and any outstanding data and study medication should be collected. Data, in addition to the reason for discontinuation and the date of removal, will be recorded on the Source Document and End of Study eCRF.

If a subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event, and its clinical course must be fully documented. For such a subject, the investigator must strive to follow the subject until the adverse event has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up.

[redacted].

[redacted]

6. MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by Perrigo will consist of:

Test Product: Mupirocin Cream USP, 2%,
Perrigo [redacted]

Reference Product: Mupirocin Cream USP, 2% (manufactured by Glenmark Pharmaceuticals)

Vehicle: Vehicle of test product
Perrigo [redacted]

6.2 Medication Management

Labeling, Packaging and Distribution

The study medication assigned to each subject number will be determined by a computer-generated randomization schedule. Study medication is labeled and packaged, according to the randomization code, so that neither the subject nor the investigator can identify the treatment.

[redacted]

[redacted]

The tear-off portion of each kit label contains the identity of the medication in the tube. The investigator will not remove the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency and preferably with prior authorization from Perrigo or designee, whenever possible. If the occluded portion of the label is removed, each involved subject(s) will be discontinued from the study and the reason will be noted on the source documents and eCRFs.

[redacted]

The tear-off portion has an adhesive backing to affix to the study medication dispensing log that will be maintained at the investigator site. **THE LOG AND TEAR-OFF LABELS WILL BE STORED SECURELY AT THE STUDY SITE AS RECORD OF THE SUBJECT'S INTENDED TREATMENT. THE STUDY LABEL FORMS AND THE ATTACHED ORIGINAL LABELS SHOULD NOT BE REMOVED FROM THE SITE UNTIL PERRIGO HAS NOTIFIED THE SITES, IN WRITING.**

[redacted]

Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select one block of study medication [redacted] to be maintained as retain samples. The investigator will maintain one randomly selected block of study medication from each shipment of study medication received. As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel (stored between 20° to 25°C (68° to 77°F).; even after the study has concluded. Each reserve sample shall be retained for a period of at least five (5) years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least five (5) years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained or was used." The investigator will store the retain sample study medication until such time as written notification is received from Perrigo that the samples are no longer required.

Storage and Test Article Accountability

Study articles used to conduct this study will be maintained under adequate security by the investigator or designee. Each investigator site will ensure that the temperature of study medication is monitored and recorded throughout the study. The study medication should be stored between 20° to 25°C (68° to 77°F) and should not be frozen, as recommended in the labeling for Mupirocin Cream USP, 2%. The medication should be kept away from children unless the subject is a child. The investigator will not supply study medication to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

The clinic personnel at each investigator site will keep a running inventory of study medication dispensed that will include subject numbers assigned and the date each tube of study medication is dispensed and returned. A study medication accountability form will be provided to the investigator to document all medications received, dispensed by and used by each subject. At the conclusion of the study all unused, partially used, and empty tubes must be inventoried by the monitor and returned to Perrigo, or designee, for destruction, with the exception of retention samples which shall remain at the investigator site.

[redacted]

Randomization
Randomization will be performed according to a computer-generated randomization scheme where the treatment group designation has been assigned to the subject number. The treatment designation will remain blinded until the final database is closed. An independent third party will hold the randomization code throughout the study. The randomization scheme will be a block randomization, with each block of [redacted] assigned to Test: Reference: Vehicle [redacted].

Procedure for Breaking the Blind
The investigator, staff at the study site, study monitors, and data analysis/management personnel are blinded to the subject assignment. In the event of an emergency, the specific subject treatment may be identified by removing the overlay of the blinded label for each subject at each investigator site, which is attached to the study medication log; however, every effort should be made to maintain the blind. **The investigator must not scratch off the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency situation only and should seek prior authorization by Perrigo or designee when possible.** The reason for breaking the blind must be clearly documented in the source documentation and eCRF and the subject must be discontinued from the study. Perrigo must be notified immediately upon all unblinding situations.

7. ADVERSE REACTIONS

The potential adverse reactions of generic Mupirocin Cream USP, 2%, are anticipated to be similar to those observed with Mupirocin Cream USP, 2%.

The adverse reactions reported by at least 1% of 339 subjects in connection with the use of Mupirocin Cream USP, 2% in clinical trials were headache (1.7%), rash (1.1%), and nausea (1.1%). Adverse reactions that occurred in less than 1% of subjects were abdominal pain, burning at application site, cellulitis, dermatitis, dizziness, pruritus, secondary wound infection, and ulcerative stomatitis.

Systemic allergic reactions, including anaphylaxis, urticaria, angioedema, and generalized rash, have been identified during postmarketing use of Mupirocin Cream USP, 2%. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents and may range in severity from the mild diarrhea to fatal colitis.

7.1 Departure from the Protocol for Individual Subjects

When an emergency occurs requiring a departure from the protocol for a subject, departure will be only for that subject. In such circumstances, the investigator or other physician in attendance will contact the Medical Monitor or Perrigo by telephone and follow-up with a written description as soon as possible. The overseeing IRB should also be notified.

7.2 Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this

treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A serious adverse event (SAE) is an adverse event that results in any of the following outcomes:

- Death
- Life-threatening event (e.g., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires in-subject hospitalization or prolongs hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Other adverse events that may be considered serious based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Immediately Reportable Adverse Events (IRAE): Any serious AE or any AE that necessitates discontinuation of study medication, including pregnancy.

Unexpected Adverse Event: An unexpected event is any adverse drug experience, the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the study medication, the Investigator's Brochure, or as described in the clinical protocol and consent materials.

Intensity of Adverse Events: The maximum intensity of an AE during a day should be recorded on the eCRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates for the changes in severity.

Mild - AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.

Moderate - AEs typically introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe - AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Causal Relationship to Study Medication: The following criteria should be used in assessing the apparent causal relationship of an AE to study medication.

Definitely - The AE:

- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge)

[redacted]

- is confirmed by reappearance of the reaction on repeat exposure

Probably - The AE:
- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge)
- cannot be reasonably explained by the known characteristics of the subject's state.

Possible - The AE:
- follows a reasonable temporal sequence from study medication administration
- but that could readily be produced by a number of other factors.

Unlikely - The AE:
- follows a reasonable temporal sequence from study medication administration.
- could have been produced by either the subject's clinical state or by study medication administration.

Not related - The AE:
- does not have a reasonable temporal association with the administration of study medication
- has some other obvious explanation for the event.

7.3 Eliciting and Reporting of Adverse Events

The investigator will periodically assess subjects for the occurrence of adverse events. [redacted] All adverse events (as defined in Section 7.2), either observed by the investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported and documented in the source document and the study reporting forms. When reporting an adverse event, the investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study medication or procedure. Serious or unexpected adverse events must be reported to [redacted] ***within 24 hours*** of when the investigator first learns of the occurrence of the event.

Adverse events will be documented in the source document and recorded in a timely manner on the eCRFs. Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted.

Adverse event reporting begins from the signing of informed consent/assent. Adverse events should be followed until resolved or 30 days after the final study treatment. In any case, serious adverse events that are not resolved or considered to be chronic within 30 days of the final study treatment must be followed by the investigator until they become resolved or are considered to be chronic (stabilized for at least 30 days). All events that are ongoing at this time will be recorded as ongoing on the eCRF.

[redacted]

Expedited Reporting Responsibilities of the Study Center

For any serious or unexpected adverse event, [redacted] must be notified ***within 24 hours*** of when the investigator first learns of the occurrence of the event. Expedited reporting requirements for serious adverse events are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to Perrigo. The adverse event term on the AE eCRF and the SAE report should agree exactly. Special attention should be given to recording hospitalizations and concomitant medications.

Subjects with unresolved adverse event(s) or serious adverse event(s) should be followed by the investigator until the events are resolved, events determined to be chronic, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to the sponsor up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs within 30 days after the last assessment and is determined by the investigator to be reasonably associated with the use of the study medication, should be reported to the sponsor within 24 hours of when the investigator first learns of the occurrence of the event.

When reporting an SAE the investigator (or the Study Coordinator) will promptly report any serious adverse event or pregnancy by telephone to [redacted] immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier to [redacted] within 24 hours of knowledge of the event by the site. In many cases, only preliminary information will be available. Appropriate follow-up information should be sought (hospital discharge summaries, operative reports, etc.) and a follow-up SAE report form submitted. A designation of causality from the study medication should always be included with a follow-up report. Assess and report the causality of the event.

Submitting an Expedited Safety Report to the IRB

Once [redacted] receives all supporting documentation for the reported event, the Medical Monitor, in conjunction with Perrigo, will determine if the safety report is eligible for expedited review. [redacted] will log the initial event and will notify the sponsor that an event has been reported within 1 business day after initial receipt. [redacted] will complete the review of the event. This form, as well as other supporting documentation, will be forwarded to [redacted] Medical Monitor for review. [redacted] will finalize the report and distribute it to the sponsor within 1 day (one) after initial receipt. When expedited safety reporting to regulatory authorities is indeed required, the investigator should review and update any newly available materials at once. Follow-up queries may be sent to the study center to further clarify the event.

Each expedited safety report will routinely include a brief cover memorandum, the completed report, and any additional pertinent information recommended by [redacted], Perrigo, or the study Medical Monitor. Once the report is assembled, the Principal Investigator must submit the expedited safety report to the IRB within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available.

[redacted]

When a Principal Investigator receives an expedited safety report from [redacted] or the sponsor detailing adverse events occurring at other study centers under this protocol, it must be promptly submitted to the study center's IRB. The Principal Investigator must retain a copy of such reports as submitted to his/her IRB in the site's study Regulatory Binder.

7.4 SAE & AEs Requiring Discontinuation of Study Drug, including Pregnancies

ANY SAE THAT OCCURS AFTER A SUBJECT HAS ENTERED THE STUDY, WHETHER OR NOT RELATED TO STUDY MEDICATION, MUST BE REPORTED TO [redacted] IMMEDIATELY (WITHIN 24 HOURS) VIA TELEPHONE OR FACSIMILE. IF INITIALLY REPORTED VIA TELEPHONE, THIS MUST BE FOLLOWED-UP BY A FACSIMILE OF THE WRITTEN SAE REPORT WITHIN 24 HOURS OF THE CALL TO [redacted].

Non-serious events that require discontinuation of study medication (including laboratory abnormalities) should be reported to [redacted] immediately and within 1 working day.

Subjects who discontinue due to experiencing adverse events should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

A subject who experiences a severe adverse event related to study drug will be discontinued from the study.

The notification about any serious adverse event should be directed to:

[redacted]

[redacted] will report the SAE to the Sponsor:

SPONSOR

[redacted]

[redacted]

[redacted]

7.5 Pregnancy

At the time the Principal Investigator or site personnel becomes aware that a study participant became pregnant during study participation, the Principal Investigator or designee will report the pregnancy immediately by phone and/or by faxing a completed Pregnancy Report to [redacted] within 1 business day of being notified of the pregnancy report.

The report will include the following elements:

- Participant (mother's) coded study identifier;
- Date of participant's last menstrual period;
- Total accumulated dose of study treatment administered to date;
- Date of study medication administration.

The investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the Principal Investigator or designee must forward a follow-up Pregnancy Report with any relevant information on the present condition of the fetus to the [redacted], including:

- Mother's coded study identifier(s);
- Gestational age at delivery, miscarriage or abortion;
- Birth weight, gender, length and head circumference, if available;
- Apgar scores recorded after birth, if available;
- Any abnormalities.

If the outcome of the pregnancy **meets the criteria for immediate classification of an SAE** (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by faxing a completed SAE report form to [redacted] within 1 working day of being notified of the pregnancy report.

If the trial is completed before the outcome of the pregnancy is known, [redacted] will assume the responsibility for following up on the pregnancy. [redacted] will contact the investigator or Study coordinator on or around the potential expected date of delivery to follow-up on the outcome of pregnancy and will also check on the status of the infant 8 weeks post-delivery. Upon awareness of the pregnancy outcome and known status of the infant following 8 weeks of delivery, the investigator will complete the applicable pregnancy report forms and fax to [redacted] within 1 day of being notified.

[redacted]

7.6 Post Study Adverse Events

Non-serious Adverse Events
Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted. These adverse events must be followed by the investigator until the events are resolved, events determined to be chronic or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health or the investigator does not expect any further improvement or worsening of the adverse event.

Serious Adverse Events
Serious adverse events that are identified on the last assessment visit (or the early termination visit) must be recorded on the AE eCRF page and reported to Perrigo according to the procedures outlined above. Subjects with unresolved previously reported serious adverse events, or any new serious adverse events identified on the last assessment visit, should be followed by the investigator until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to Perrigo up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs after the last assessment and is determined by the investigator to be reasonably associated with the use of the study drug, should be reported to Perrigo.

8. STATISTICAL ANALYSIS

The sections that follow highlight sample size determination and the planned analyses for this study. A statistical analysis plan (SAP) that describes the statistical methods, models, hypotheses, and subject populations to be analyzed will be prepared separately from this protocol. The SAP will be completed and approved before locking the database and unblinding the study and will serve as a companion to the protocol and the *de facto* documentation of the proposed statistical evaluation. The SAP will be completed and finalized prior to breaking the blind.

8.1 Statistical Methods

Analysis Populations
The following populations are defined for the purpose of analyses:

- Intent-to-Treat (ITT) (safety population): Any subject who was randomized, received and used study medication.

- Modified Intent-to-Treat (mITT): Any subject who met the inclusion/exclusion criteria (including a positive baseline bacteriological culture), was randomized, received and used the study medication, and returned for at least one post-baseline efficacy assessment.

- Per Protocol (PP): Any subject who:
  - met inclusion/exclusion criteria (including a positive baseline bacteriological culture),

[redacted]

- was randomized, received and used study medication,
- met the protocol criteria for compliance [redacted]
- completed Visit 4/Day 17 evaluations within the designated window [redacted] OR was discontinued from the study due to treatment failure, and
- had no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

[redacted]

Only subjects with a baseline bacteriological culture from the target lesion that is positive for *S. aureus* and/or *S. pyogenes* will be included in the PP and mITT populations for the efficacy analysis. Subjects with a negative baseline culture will be excluded from the PP and mITT populations but included in the ITT population.

Planned Analysis

The safety analysis will be performed for the ITT subjects. The efficacy analysis will be conducted on both the PP and the mITT populations. Two-sided hypothesis testing will be conducted. Resulting p-values less than 0.05 will be considered statistically significant. No adjustments of p-values for multiple comparisons will be made. No interim analyses are planned. SAS software will be used for all data analyses and tabulations.

The treatment response will be summarized by treatment group.

[redacted]

Sample Size Considerations

[redacted]

[redacted]

[redacted]

[redacted]

Efficacy Measures and Analysis

Clinical Endpoints

The primary efficacy endpoint is the proportion of subjects in each treatment group with clinical cure, defined as a SIRS score of 0 for all signs and symptoms at Visit 4/Follow-up (7 days after the end of treatment). Secondary efficacy endpoints are the proportion of subjects with clinical cure at Visit 3/End of Treatment, bacteriological cure (defined as elimination of *S. aureus* and *S. pyogenes* or response was such that no culture material was available and therefore evidence of pathogen eradication) at Visit 3/End of Treatment, and bacteriological cure at Visit 4/Follow-up.

Equivalent efficacy

The clinical equivalence of the test and reference treatments will be based on the proportions of subjects with clinical cure at Visit 4/Day 17 (Follow-up, 7 days after end of treatment).

The hypothesis tested for clinical equivalence between test and reference will be:

H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$ versus

H_A: $-0.20 \leq p_T - p_R \leq 0.20$.

Where p_T and p_R were the proportions of subjects with clinical cure at Visit 4/Day 17 for the Test and Reference products, respectively. The Test product would be considered to be clinically equivalent to the Reference product if the 90% confidence interval (CI) of the difference between their proportions of subjects with clinical cure, calculated by the Wald's method with Yates' continuity correction, is contained within the limits -20.0% to +20.0%. Rejection of the null hypothesis would support the conclusion of therapeutic equivalence between the Test and Reference products for the primary efficacy variable.

Analysis in the PP population will be considered definitive and those in the mITT population will be considered supportive.

Superiority

The test of superiority of each active treatment over vehicle will be based on the proportions of subjects in each treatment group with clinical cure at the Visit 4/Day 17 [redacted]

[redacted]

The hypotheses tested for superiority of the test and reference products over Vehicle will be:

H_0: $p_T \leq p_V$ versus H_A: $p_T > p_V$

H_0: $p_R \leq p_V$ versus H_A: $p_R > p_V$

Where p_T, p_R, and p_V are the proportions of subjects with clinical cure at the Visit 4/Day 17 for the Test, Reference, and Vehicle products, respectively. The tests will be conducted independently for the Test product and the Reference product using two-sided, $\alpha = 0.05$, continuity-corrected Z-tests. Superiority would be established if the proportion of subjects with clinical cure at the Visit 4/Day17 in the active treatment group is significantly greater ($p < 0.05$) than that in the Vehicle group. Rejection of the null hypothesis would support the conclusion of superiority of the Test and Reference products over the Vehicle for the primary efficacy variable.

Superiority analyses in the mITT population will be considered definitive and those in the PP population will be
considered supportive.

The same tests/methods, including the missing data imputation methods, as for the primary analyses will be conducted for the secondary analyses.

Safety and Adverse Events Analysis

The frequency and percent of subjects with adverse events will be summarized by MedDRA system organ class and preferred term and by severity and relationship to study drug for all three treatment groups. [redacted]. The comparable safety of the Test and Reference treatments will be evaluated by statistical comparison of the proportion of subjects who reported any adverse events. Safety comparisons will be performed on the ITT (safety) population.

8.2 Comparability of Subjects at Baseline

Descriptive statistics will be presented, by treatment group, for subject baseline characteristics. The significance of any obvious treatment group differences will be discussed in the clinical study report.

9. CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES

It will be made clear to the subject that, for the purposes of the study, they are consenting only for topical application of medication or vehicle. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent/assent. However, informed consent/assent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The study must be approved in writing by an appropriate IRB as defined by FDA regulations. A copy of the Letter of Approval from the IRB, which also contains specific identification of the documents approved, must be received by Perrigo, prior to study commencement.

[redacted]

Periodic status reports must be submitted to the IRB at least annually as required by the site's IRB, as well as notification of completion of the study and a final report within three months of study completion or termination.

The investigator(s) has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent/assent form, which shall be approved by the same IRB responsible for approval of this protocol. Each informed consent/assent form shall include the elements required by FDA regulations in 21 CFR Part 50. The investigator agrees to obtain approval from Perrigo of any written informed consent/assent form used in the study, preferably prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the IRB-approved written informed consent/assent form shall be signed by the subject (or their parent/legally authorized representative) and the person obtaining consent/assent (investigator or designee). The subject shall be given a copy of the signed informed consent/assent form and the investigator shall keep the original on file.

If the subject fails to meet the inclusion/exclusion criteria at the conclusion of the screening phase, the subject will be withdrawn from screening. If the subject is re-screened for study participation, a new informed consent/assent form must be signed.

9.1 Subject Confidentiality

All participants are concerned for the individual subject's privacy and, therefore, all subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to Perrigo, it is required that the investigator permit the study monitor, any Perrigo authorized representative, and/or FDA representative to review that portion of the subject's medical record that is directly related to the study. This shall include all study-relevant documentation including subject medical histories to verify eligibility, laboratory test result reports to verify transcription accuracy, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study, and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the subject must be informed that his/her medical chart may be reviewed by Perrigo or their authorized representative, or a representative of the FDA. If access to the medical record requires a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

To preserve the subject's confidentiality, the data collected will be available only to the investigators of the study, their support staff, Perrigo or their authorized representative and possibly the FDA.

[redacted]

All reports and communications relating to the subject in the study will identify each subject only by the subject's initials and by the subject number. The investigator agrees to furnish Perrigo with complete subject identification, if necessary, on a confidential follow-up form that will be used for the purpose of a long-term follow-up, if needed. This will be treated with strict adherence to professional standards of confidentiality and will be filed at Perrigo under adequate security and restricted accessibility.

10. CONDUCT OF STUDY

The investigational site is to maintain complete documentation of all events and the times at which they occur.

10.1 Completion of Study

The investigational site will complete the study and complete all documentation required, in satisfactory compliance with the protocol, within 2.5 months of enrollment of the last subject and extending beyond as needed to complete necessary data queries.

It is agreed that, for reasonable cause, either the investigator or Perrigo may terminate this study before completion provided written notice is submitted at a reasonable time in advance of intended termination. Any extension of this study must be mutually agreed upon in writing by both the investigator and Perrigo.

10.2 Protocol Amendments

The investigator will not make any changes to this protocol without prior written consent from Perrigo and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed between [redacted] and Perrigo. If agreement is reached regarding the need for an amendment, the amendment will be written by Perrigo or [redacted]. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for "administrative amendments," investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB notified within five days. Perrigo will submit protocol amendments to the FDA or other regulatory agencies.

When, in the judgment of the reviewing IRB, the investigators and/or Perrigo, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before expecting continued participation.

11. RECORDS MANAGEMENT

11.1 Data Collection

Database set-up will be performed by [redacted] in collaboration with the Electronic Data Capture (EDC) vendor, using an appropriate fully validated, 21 CFR Part 11 compliant EDC system. eCRFs will be provided to each site via a secured web link. All applicable study data collected on each subject will be recorded by approved site personnel into the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Approved staff at [redacted] will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual data queries to correct missing data or discrepancies found against the source within the EDC system.

Data validation will consist of automated and manual edit checks that are created directly into EDC. Automated edit checks will be executed on all data points defined and documented by the study team and data management. Study metrics will be reported from the EDC system.

After all data have been verified by approved staff at [redacted], an investigator or sub-investigator (listed on Form FDA 1572) is required to review and approve all eCRFs prior to database lock and breaking of the blind.

[redacted]

[redacted]

During each subject's visit to the clinic, a designee participating in the study will record progress notes to document all significant observations. At a minimum, these notes will contain:

a) Documentation of the informed consent process;
b) The date of the visit and the corresponding Visit or Week in the study schedule;
c) General subject status remarks, including any significant medical findings. The severity, frequency, and duration of any adverse events and the investigator's assessment of relationship to study medication must also be recorded.
d) Any changes in concomitant medications or dosages;
e) A general reference to the procedures completed; and
f) The signature (or initials) and date of all clinicians who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Any changes to information in the study progress notes and other source documents will be entered in **black or blue ink**, **initialed,** and **dated** by the authorized person making the correction/addition. Changes will be made by striking a single line through erroneous data, and clearly entering the

[redacted]

correct data (e.g., ~~wrong data~~ right data). Entries may not be erased or masked with white-out fluid. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

For transmission to Perrigo, information from the study progress notes and other source documents will be promptly entered into the database. The database also contains a complete audit trail to capture all regulatory components of data corrections (e.g. initial entry, new value, initials and date of the change).

11.2 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes and screening logs. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons. The original signed informed consent form for each participating subject shall be filed with records kept by the investigators and a copy given to the subject.

11.3 File Management at the Study Site

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the International Council for Harmonization (ICH) Guideline for Good Clinical Practices (GCP).

11.4 Records Retention at the Study Site

FDA regulations 21 CFR§312.57 require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

a) A period of at least two years following the date on which a New Drug Application is approved by the FDA;
b) A period of two years after Perrigo notifies the investigator that no further application is to be filed with the FDA.

The investigator must not dispose of any records relevant to this study without either (1) written permission from Perrigo or (2) providing an opportunity for Perrigo to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Perrigo and the FDA.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

Perrigo has ethical, legal, and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. All medical records (source documents) of the subjects participating in this study must be presented for review and verification of eCRFs.

[redacted]

12.2 Auditing

Perrigo (or representative) may conduct audits at the study center(s). Audits will include, but are not limited to, drug supply, presence of required documents, the informed consent process, and comparison of electronic case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact Perrigo or [redacted] immediately if notified of such an audit, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

13. ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the United States Food and Drug Administration (FDA) regulations, any other countries regulations, and ICH GCP Guidelines.

14. USE OF INFORMATION AND PUBLICATION

All information supplied by Perrigo in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (e.g., the clinical protocol, eCRFs), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by Perrigo in its business. Any data, inventions, or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of Perrigo, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of Perrigo, and shall not be used except in the performance of the study. As such, confidential study-related information should not be included on the curriculum vitae of any participating investigator or study staff.

The information developed during the course of this clinical study is also considered confidential, and will be used by Perrigo in connection with the development of the drug. The information may be disclosed as deemed necessary by Perrigo to allow the use of the information derived from this clinical study, the investigator is obliged to provide Perrigo with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of Perrigo. [redacted]

[redacted]

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-19-002

PROTOCOL TITLE:

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Limited Partnership's Mupirocin Cream USP, 2% to Glenmark Pharmaceuticals Mupirocin Cream USP, 2% and to Compare Both Active Treatments to a Vehicle Control in the Treatment of Secondarily Infected Traumatic Skin Lesions

I have carefully read the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by Perrigo to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

_____

Principal Investigator's Printed Name

_____

Principal Investigator's Signature

_____

Date

[redacted]

15. APPENDICES

15.1 Appendix A: Study Personnel Contacts

[redacted]

[redacted]

15.2 Appendix B: Instructions for the Subject

Check Visit Dispensed: Visit 1: ☐ Visit 2: ☐ Unscheduled visit: ☐ Date: _____

SUBJECT INITIALS: _____ SUBJECT NUMBER: _____ SITE NUMBER: _____

- [redacted]

I am scheduled to return at:

_____on _____ During Treatment (Study Day 2-5)
(Time) (Date)

_____on _____ End of Treatment (Study Day 10-12)
(Time) (Date)

Stop applying study medication on _____

_____on _____ Follow-up (Study Day 13-21)
(Time) (Date)

[redacted]

ALL APPOINTMENTS ARE IMPORTANT! IF YOU NEED TO CHANGE YOUR APPOINTMENT, PLEASE CALL YOUR STUDY DOCTOR'S OFFICE

15.3 [redacted]

[redacted]

[redacted]

16. REFERENCES

1. Mupirocin Cream USP, 2% Cream [package insert]. Glenmark Pharmaceuticals; 7/2017.
2. OGD Draft Guidance on Mupirocin Calcium (Cream/Topical). Recommended June 2010; Revised Oct 2011.

[redacted]