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

02-24-2021

STATISTICAL ANALYSIS PLAN

PRG-NY-19-002: Mupirocin Cream USP, 2%

[redacted]

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

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[redacted]

[redacted]

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List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel Test
ITT	Intent-to-Treat (Population)
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat (Population)
PD	Protocol Deviation
PP	Per-Protocol (Population)
PV	Protocol Violation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S. aureus	*Staphylococcus aureus*
SIRS	Skin Infection Rating Scale
S. pyogenes	*Streptococcus pyogenes*
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
WHO Drug	World Health Organization Drug Dictionary

Statistical Analysis Plan

1 Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of Clinical Study Protocol PRG-NY-19-002 [redacted]

In the event the protocol is further amended and that amendment has no impact on the statistical analysis methodology, this SAP will not require an amendment.

This SAP has been developed and finalized prior to database lock of the clinical database for Protocol PRG-NY-19-002.

2 Study Objectives

To compare the safety and efficacy profiles of Perrigo UK FINCO's 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.

3 Study Design and Sample Size

3.1 Study Design

For the purpose of exploring the above objectives, the study will be conducted as a double-blind, randomized, parallel-group, vehicle-controlled, multicenter trial.

Each subject will be randomly assigned to one of the following treatment groups [redacted]:

(1) Test: Mupirocin Cream USP, 2%, Perrigo [redacted]

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

(3) Vehicle of test product, Perrigo [redacted]

Subjects will be admitted into the study only after written informed consent has been obtained and all of the inclusion and none of the 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. 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 after the final database is locked. An independent third party will generate and hold the randomization code throughout the study. Randomized 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 come to the study site for clinical evaluations Visit 1/Day 1 (Baseline), Visit 2/During Treatment (Day 3), Visit 3/End of Treatment (Day 11 and Visit 4/Follow-up (Day 18).

3.2 Sample Size

Approximately subjects will be enrolled to obtain at least modified intent-to-treat (mITT) subjects and to complete per-protocol (PP) subjects

4 Analysis Populations

The analysis populations are defined as follows:

(1) Intent-to-treat (ITT) (safety) population: any subject that was randomized, received and used study medication;

(2) Modified Intent-to-treat (mITT) population: 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;

(3) Per Protocol (PP) population; any subject who (a) met all inclusion/exclusion criteria (including a positive baseline bacteriological culture); (b) was randomized, received and used study medication; (c) met the protocol criteria for compliance (d) completed Visit 4 evaluations within the designated window (Day 17 OR was discontinued from the study due to treatment failure, and (e) Without 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.

5 Planned Analyses

5.1 Methodological Considerations

Tables will have columns corresponding to or be stratified by the treatment groups.

All data will be listed by treatment group, subject and visit/time point where appropriate. The total number of subjects under the stated population (N) will be displayed in the header of summary tables. Efficacy data will be tabulated by site and if obviously inconsistent discrepancies will be observed with the results across all sites, then these differences will be explored and addressed in the final study report.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. The statistic "Missing" will also be presented as the number of missing entries/subjects, if any at that visit/timepoint, and presented as a summary statistic only when non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

Categorical variables will be summarized by frequency (n) and percentage (%). Percentage will be obtained as (n/N)*100. Unless otherwise stated, all percentages will be expressed to one decimal place.

Study days will be calculated as follows:

- For events or findings on or after the date of the first study treatment:
  - Study Day = Date of the event or finding – Date of the first treatment + 1

- For events or findings prior to the date of the first study treatment:
  - Study Day = Date of the event or finding – Date of the first treatment

- All dates will be displayed in DDMMMYYYY format.

Two-sided hypothesis testing will be conducted for all the tests. 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.

All statistical analysis will be conducted using SAS® version 9.4 or higher (SAS® Institute, Cary, North Carolina).

[redacted]

5.3 Demographics and Baseline Characteristics

Baseline variables (e.g., sex, age, ethnic origin) will be summarized descriptively by treatment group. Any significant baseline differences will be reviewed for their potential impact on the efficacy findings.

Continuous variable at baseline will be examined by two-way analysis of variance (ANOVA) with treatment and site as fixed effects when normal error and homogeneous variance assumptions are satisfied, or by non-parametric rank-based ANOVA when they are not, to compare treatment group differences. The summary tables will include the mean, standard deviation, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages and be examined by Cochran-Mantel-Haenszel test and stratified by site.

5.4 Subject Disposition

The numbers of subjects enrolled, treated, discontinued from treatment (by reason) will be presented by treatment group.

A summary of subject disposition will be provided for all subjects. Descriptive summaries of subject disposition, reason for discontinuation, and analyses population will be provided by treatment group. The data will also be presented in subject data listings.

[redacted]

[redacted]

[redacted]

A summary of protocol deviations by treatment will be prepared. The protocol deviations data with the verbatim description and the reason for deviation will also be presented in a by-subject data listing.

5.6 Study Drug Exposure and Compliance

Duration of Treatment and Medication Compliance

Number of applications, days of exposure (i.e. duration of treatment), and compliance rate will be summarized by treatment group using descriptive statistics. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.7 Efficacy Variables and Analyses

5.7.1 Primary Endpoint

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).

Equivalent Efficacy

The compound hypothesis to be tested for clinical equivalence between test and reference is:

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 are the proportions of subjects with clinical cure at Visit 4/Follow-up for the test and reference products, respectively. The test product will be considered to be therapeutically equivalent to the reference product if the 90% CI on the difference in their proportions of subjects with clinical cure, calculated by Wald's method with Yates' continuity correction, is contained within the limits -0.20 to +0.20. Rejection of the null hypothesis supports the conclusion of therapeutic equivalence between the test and reference products for the primary efficacy variable.

The result of the analysis in the PP population will be considered definitive and that in the mITT population as supportive.

Analysis for therapeutic equivalence (i.e. 90% confidence interval) will be performed based on the following SAS code (SAS Institute v.9.4) e.g. trt=1 for Test and trt=2 for Reference:

```
proc freq data=XX;
  where trt in (1,2);
  tables trt* cure /alpha=0.10 riskdiff (CORRECT CL=(WALD));
run;
```

Superiority

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

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 Visit 4/Follow-up for the test, reference and Vehicle products, respectively. The tests will be conducted independently for the test product vs. vehicle and the reference product vs. vehicle using two-sided, $\alpha = 0.05$,

continuity-corrected Z-tests. Superiority will be established if the proportion of subjects with clinical cure in the active treatment group is greater than and statistically different ($p< 0.05$) from that in the Vehicle. Rejection of the null hypothesis supports the conclusion of superiority of the test and reference products over the Vehicle product for the primary efficacy variable.

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

Analysis for superiority (continuity-corrected p-value for treatment comparison) will be performed based on the following SAS code (SAS Institute v.9.4) e.g. trt=2 for Reference vs. trt=3 for Vehicle:

```
proc freq data=XX ;
where trt in (2,3);
table trt * cure /chisq ;
run;
```

5.7.2 Secondary Endpoints

Secondary efficacy endpoints are:

- the proportion of subjects with clinical cure at Visit 3/End of Treatment;
- the proportion of subjects with 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;
- the proportion of subjects with bacteriological cure at Visit 4/Follow-up.

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

5.8 Safety Variables and Analyses

All safety data will be listed and tabulated. The analysis will be performed on the safety/ITT population. Safety parameters include adverse events, vital signs and concomitant medications.

<u>Adverse Events</u>
Adverse events (AEs) will be coded in MedDRA, version 22.0. Treatment-Emergent Adverse Event (TEAE) is defined as any AE occurs on or after application of the first dose of study drug. Number and percent of subjects reporting TEAEs will be tabulated by treatment group. Summary of TEAEs will be presented by body system and preferred term for the ITT population, and further by severity and relationship to study medication. Most common TEAEs will include those reported by 5% or more subjects for any treatment group will be summarized by preferred term. In the summaries of incidence rates (frequencies and percentages), severity and relationship to study drug, subjects who report more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship, accordingly. The difference between Test and Reference treatments with regard to severity and

frequency of their dermatological adverse events will be statistically evaluated using Chi-Square or Fisher's exact test to compare the proportions of subjects of the two active treatment groups who report any TEAE.

Treatment-Emergent Serious Adverse Events (TESAEs) will be discussed within the clinical study report. TEAEs, TESAEs and TEAEs that led to treatment interruption temporarily or treatment discontinued permanently will be presented in data listings.

Concomitant Medications and Vitals Signs
Concomitant medications will be coded using the WHO Drug Dictionary, version March 2019, and will be presented in data listings. All vital signs data will be displayed in listings.

6 Appendices

6.1 Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Adverse Events
Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first dose
- the day and month are missing and the start year is the same or greater than the year of the first dose date
- the start date is completely missing

Concomitant Medications
Handling of partial dates is only considered for the stop date. A medication with a partial stop date is considered concomitant if:

- only the day is missing and the stop month/year is the same or after the month/year of the first dose
- the day and month are missing and the stop year is the same or greater than the year of the first dose date
- the stop date is completely missing or the medication is ongoing

6.2 Summary of Assessments

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

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