COVER PAGE

STATISTICAL ANALYSIS PLAN

Final Version 3.0

February 28, 2019

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A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Design, Multiple-Site Clinical Study to Evaluate the Therapeutic Equivalence of Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) to Ketoconazole Cream 2% (G&W Laboratories Inc.) in the Treatment of Tinea Pedis
Protocol Number: 71875502
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SAP FINAL VERSION APPROVALS

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Revision History

VERSION	DATE	DESCRIPTION OF REVISIONS	REVISED BY
Draft 1.0	October 4, 2018	New Document	Jianhua Liu
Draft 2.0	November 08, 2018	Incorporate client's comments	Jianhua Liu
Final 1.0	December 04, 2018	Finalize SAP	Jianhua Liu
Final 2.0	January 23, 2019	Add missed doses to Listing L16.2.5	Jianhua Liu
Final 2.0	February 05, 2019	Add Dr. Brijesh to the approval page	Jianhua Liu
Final 3.0	February 28, 2019	1) To document that all subjects in the safety need to have at least one dose applied as per new guidance. 2) To remove criteria of had at least one post-baseline evaluation from mITT population definition as per new guidance.	Jianhua Liu

List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
CDISC	Clinical Data Interchange Standards Consortium
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
KOH	Potassium Hydroxide
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
mL	Milliliter
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
TEAE	Treatment Emerget Advers Events
USA	United States of America

TABLE OF CONTENTS

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol 71875502 (Novum Study No. 71875502) Rev. 0 dated 06/13/2018. The SAP provides details on the planned statistical methodology for the analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures.

This SAP describes the study endpoints, derived variables, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP therefore outlines in detail all other aspects pertaining to the planned analyses and presentations for this study.

The following documents were reviewed in preparation of this SAP:

- Final Clinical Study Protocol 71875502 (Novum Study No. 71875502) Rev. 0 dated 06/13/2018
- Casebook for Novum Study No. 71875502

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

2. OBJECTIVES

1. Evaluate the therapeutic equivalence of a generic Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) to the Reference product, Ketoconazole Cream 2% (G&W Laboratories Inc.) in the treatment of tinea pedis.
2. Demonstrate the superiority of the clinical effect of the Test and Reference (active) products over that of the Placebo (vehicle) in the treatment of tinea pedis.
3. Compare the safety of the Test, Reference and Placebo products in the treatment of tinea pedis.

3. OVERALL STUDY DESIGN

This randomized, double-blind, vehicle-controlled, parallel-group, multiple-site study has been designed to evaluate the clinical (therapeutic) effect of a generic Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) compared to the Orange Book Reference Standard (RS) product, Ketoconazole Cream 2% (G&W Laboratories Inc.) in patients with tinea pedis. Additionally, both the Test and Reference (i.e., the RS) treatments will be tested for superiority to a Placebo.

Before any study-specific procedures are performed, all patients will read and sign the IRB-approved informed consent form (ICF).

Approximately 830 eligible patients, 18 years of age and older, will be randomized in a 2:2:1 ratio (Test: Reference: Placebo) to one of the three study products as follows:

- **Test**: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
- **Reference**: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.))
- **Placebo**: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

Patients will complete three clinic visits as follows:

- Visit 1 (Day 1): Screening/Baseline
- Visit 2 (Day 42 ± 4): End of Treatment
- Visit 3 (Day 56 ± 4): Test-of-Cure/End of Study

Patients will be instructed to apply the study product to affected and immediate surrounding areas once daily for a total of 42 ± 4 days starting on the day of enrollment (i.e., Day 1). The last dose should be applied on the day of Visit 2 (Day 42 ± 4). Evaluations will be performed in accordance with the study schematic. Safety assessments will include monitoring of adverse events (AEs), vital signs measurement, and urine pregnancy tests (for females of childbearing potential). Clinical assessments will include the potassium hydroxide (KOH) wet mount, mycological culture, and rating of signs and symptoms. The Investigator should identify the most severe lesion (i.e., target lesion) at baseline. Although the study product should be applied to all infected areas (both feet), only the target lesion will be evaluated for analysis.

Figure 1 Study Schematic

PROCEDURE	VISIT 1 (Day 1) Screening/ Baseline	VISIT 2 (Day 42 ± 4 Days)* End of Treatment	VISIT 3 (Day 56 ± 4 Days) Test-of-Cure/ End of Study
Informed Consent	X		
Medical History and Demographics	X		
Perform Pregnancy Test**	X	X	X
Record Vital Signs	X	X	X
Review and Assessment of Concomitant Medications	X	X	X
Review and Assessment of Adverse Events		X	X
Designate Target Lesion	X		
Assess Local Signs and Symptoms	X	X	X
Collect Sample for KOH Wet Mount	X		X†
Inclusion/Exclusion Criteria Review	X		
Collect Sample for Mycological Culture‡	X		X
Dispense Study Product	X		
Provide Patient Diary	X	X	
Collect/Review Patient Diary		X	X
Collect Study Product		X	X§
Discharge from Study			X

*Dosing regimen is once daily for 42 ± 4 days starting on the day of enrollment (Day 1) through the day of Visit 2 (Day 42 ± 4).
**For females of childbearing potential
†KOH sample will not be collected if baseline culture is negative.
‡Mycological culture sample will not be sent if KOH is negative at baseline or positive at Visit 3. See Appendix B.
§Study product will be collected at Visit 3 if it is not returned at Visit 2.

4. RANDOMIZATION AND BLINDING

All randomized study product will be blinded and packaged in sealed boxes by an independent packaging company. Randomization will be pre-planned according to a computer-generated randomization schedule. The randomization will be generated in blocks, each containing five patients' worth of study product (2 Test, 2 Reference, and 1 Placebo).

The randomization/patient number will be a unique four-digit number. This number will be assigned immediately before dispensing of study product and in ascending sequential order, beginning with the lowest available number at the study site. Each patient kit and each dispensed study tube should include the four-digit patient number on the label.

At the end of the study, after all the clinical data have been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician.

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment.

5. SAMPLE SIZE

For the primary endpoint analysis (proportion of patients in the PP population with a Therapeutic Cure at the test-of-cure visit), sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. The sample size estimations are based on previous studies conducted for ketoconazole cream (Teva Pharmaceuticals; ANDA 75-581). Readers are encouraged to see the protocol reference list for the results of the previous studies used for sample size calculation.

In the PP population, the proportion of patients with a Therapeutic Cure in the Reference group is expected to be 50%. Assuming that the Therapeutic Cure rate for the Test treatment group is an absolute difference of 5% lower than the Reference Responder rate (i.e., $p_T - p_R = -5\%$), a sample size of 172 patients in each active group in the PP population will provide approximately 85% power to demonstrate therapeutic equivalence (i.e., the 90% confidence interval [Yates' continuity-corrected] on the $p_T - p_R$ difference is within a defined equivalence range [-20%, +20%]).

The Therapeutic Cure rates for the Placebo and active treatment groups at the test-of-cure visit are anticipated to be approximately 10% and at least 40% (Test = 40%, Reference = 45%), respectively, in the mITT population. Using a 2:1 (Active: Placebo) randomization scheme, and assuming the conversion rate from mITT to PP will be approximately 80%, 216 patients in each active treatment group (Test and Reference) and 108 patients in the Placebo group of the mITT population will provide at least 99% power to demonstrate superiority of active treatments over Placebo ($p < 0.05$; using two-sided, continuity-corrected *Z*-test and a pooled response rate for the standard error of the difference in proportions).

Under the above assumptions, the overall study power to demonstrate therapeutic equivalence and superiority is estimated to be at least 85% (100% × 0.85 × 0.999), assuming 100% correlation between the two superiority tests.

To allow for approximately 35% of patients who may have negative fungal cultures post-randomization, drop out from the study or are otherwise non-evaluable, approximately 830 patients may be randomized (332 in each active group and 166 in the Placebo group) to yield 540 patients in the mITT population.

More than 50% of the patients should have baseline fungal cultures that test positive for *T .rubrum*. If fewer than 50% of enrolled patients have a positive *T .rubrum* culture or the number of patients with negative fungal cultures is more than anticipated, then additional patients may be enrolled to ensure that at least 430 (172:172:86) patients are eligible in the PP population, of which > 50% have a positive *T. rubrum* culture at baseline.

6. EFFICACY VARIABLES AND EFFICACY ENDPOINTS

Efficacy Variables

The primary and secondary efficacy variables are the outcome of the KOH test (negative or positive), outcome of the mycological culture (negative or positive), and signs and symptoms scores.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the proportion of patients in each treatment group with a Therapeutic Cure of tinea pedis at the test-of-cure visit two weeks after the end of treatment (Day 56 ± 4).

Secondary Efficacy Endpoints:

The secondary efficacy endpoints are:

- The proportion of patients in each treatment group with a Clinical Cure at Day 56 ± 4.
- The proportion of patients in each treatment group with a Mycological Cure at Day 56 ± 4.

Definitions

1. Therapeutic Cure: To be considered a Therapeutic Cure, the patient must have both Clinical and Mycological Cure of tinea pedis.
2. Therapeutic Failure: A patient will be considered a Therapeutic Failure if:

a. the patient is a Clinical or Mycological Failure

b. the patient was considered to have an insufficient therapeutic response

c. the patient used topical drug therapy for irritation or pruritus on the feet between Visit 2 (Day 42 ± 4 days) and Visit 3 (Day 56 ± 4 days)

3. Clinical Cure: To be considered a clinical cure the patient's total severity score must be ≤ 2 with no individual severity score > 1.
4. Clinical Failure: A patient will be considered a Clinical Failure if the patient's total severity score is > 2 or any individual score is > 1.
5. Mycological Cure: To be considered a mycological cure the patient must have a negative KOH test and a negative fungal culture.
6. Mycological Failure: A patient will be considered a Mycological Failure if the patient's KOH test is positive or the patient's fungal culture is positive.

7. STUDY POPULATIONS

Per-Protocol Population

The PP population will include all randomized patients who:

- Met all inclusion and exclusion criteria.
- Made the final study visit within the protocol window of Day 56 ± 4 days (Day 52 to Day 60 inclusive) with no protocol violations that would affect the treatment evaluation.
- Did not have any significant protocol deviations.
- Were compliant with dosing between 75%-125% of the required doses.
- Had a positive baseline KOH and fungal culture for *Trichophyton rubrum, Trichophyton mentagrophyties* or *Epidermophyton floccosum.*

Patients discontinued from the study because of lack of treatment effect after completing at least 14 days of treatment will be included in the PP population as Therapeutic Failures provided they had a positive baseline KOH, positive baseline fungal culture, and did not have any significant protocol deviations. For these patients, there will be no mycological testing at time of discontinuation; therefore, they will be considered Therapeutic Failures in the primary analysis but the Mycological Cure data will be set to missing for the secondary endpoint.

Patients who meet the criteria above, but who also used topical drug therapy for irritation or pruritus on the feet after the treatment phase of the study will be included in the PP population as Therapeutic Failures. If no mycological testing is performed, the patients will be considered Therapeutic Failures in the primary analysis but the Mycological Cure data will be set to missing for the secondary endpoint.

All analyses performed using the PP population will be done on an observed case basis (i.e., no last observation carried forward [LOCF] will be performed).

Modified Intent-to-Treat Population

The mITT population will include randomized patients who:

- Met all inclusion/exclusion criteria.
- Applied at least one dose of assigned product.
- Had a positive baseline KOH and fungal culture for *Trichophyton rubrum, Trichophyton mentagrophyties* or *Epidermophyton floccosum.*

Patients discontinued early for reasons other than lack of treatment effect will be excluded from the PP population and included in the mITT population using LOCF. Patients who qualify for inclusion in the mITT population with missing endpoint data who were not discontinued for lack of treatment effect will also be evaluated using LOCF; that is, if a patient who was not discontinued for lack of treatment effect does not have KOH or mycological culture results at Visit 3, this patient will be evaluated for the primary and secondary endpoints using LOCF from Visit 1. Patients who discontinued because of lack of treatment effect will not have LOCF performed.

Patients who meet the criteria above, but who also used topical drug therapy on the feet for the treatment of irritation or pruritus after the treatment phase of the study will be included in the mITT as Therapeutic Failures. If no mycological testing is performed, these patients will be considered Therapeutic Failures in the primary analysis but the Mycological Cure data will be set to missing for the secondary endpoint. No LOCF will be performed.

Safety Population

The Safety population will include all randomized patients who use at least one dose of product.

8. STATISTICAL ANALYSIS METHODS

If not otherwise specified, statistical significance is defined as $p < 0.05$ and is two-tailed. Data will be summarized with respect to demographic and baseline characteristics and safety

variables.

For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, statistics will include n, mean, standard deviation, median and range.

All statistical analyses will be conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and ADaM (Analysis Dataset Model) and FDA Guidance of Technical Specifications - Comparative Clinical Endpoints Bioequivalence Study Analysis Datasets for Abbreviated New Drug Application (September 2018) .

8.1 Baseline Characteristics

8.1.1 Patient Disposition

The patient disposition information will be summarized by treatment group as well as total. The number of patients randomized will be tabulated by treatment group and total. In addition, completion status and primary reason for withdrawal will be summarized by treatment group and total.

8.1.2 Demographic and Other Baseline Characteristics

Baseline comparability of all treatment groups will be evaluated separately in the PP, mITT and Safety populations.

The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Sex (male/female)
- Ethnicity (Hispanic/non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- Type of infection (interdigital only or interdigital with extension)
- Total baseline signs and symptoms score
- Presence or absence of onychomycosis
- Number of Tinea Pedis infections in the past 12 months

- Primary infective organism

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median and range). Range will have the same decimal places as raw values. Mean, median and standard deviation will have one decimal place more than that of raw values. Categorical variables will be summarized using frequencies and percentage.

Baseline comparability of the treatments will be presented using Cochran-Mantel-Haenszel (CMH) test for the categorical variables, and Analysis of Variance for the continuous variables.

All data will be listed by treatment group and patient.

8.1.3 Medical History

At Visit 1, Patients will also be questioned about personal medical history, including tinea pedis history.

Medical history data will be listed by treatment group and patient.

8.2 Efficacy Analyses

8.2.1 Efficacy Analyses on Primary and Secondary Endpoints

Therapeutic Equivalence

Therapeutic equivalence will be evaluated for the primary endpoint in the per-protocol (PP) population. If the 90% confidence interval (calculated using Yates' continuity correction) on the absolute difference between the proportion of patients with a Therapeutic Cure in the Test and Reference groups (p_T - p_R) is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated.

The same statistical approach will be conducted for analyses of the secondary endpoints in the PP population.

To declare therapeutic equivalence of the Test product to the Reference product, equivalence must be demonstrated for only the primary endpoint in the PP population.

Patients who are missing mycological culture data at the test-of-cure visit will not be included in the analysis for the secondary endpoint of Mycological Cure.

Superiority to Placebo

Superiority of the Test and Reference products against the Placebo product for the primary endpoint will be evaluated in the mITT population using, if necessary, LOCF as described in section 11.3.2 of the protocol.

Patients discontinued early for reasons other than lack of treatment effect will be excluded from the PP population and included in the mITT population using LOCF. Patients who qualify for inclusion in the mITT population with missing endpoint data who were not discontinued for lack of treatment effect will also be evaluated using LOCF; that is, if a patient who was not discontinued for lack of treatment effect does not have KOH or mycological culture results at Visit 3, this patient will be evaluated for the primary and secondary endpoints using LOCF from Visit 1. Patients who discontinued because of lack of treatment will not have LOCF performed.

Patients who meet the criteria above, but who also used topical drug therapy on the feet for the treatment of irritation or pruritus after the treatment phase of the study will be included in the mITT as Therapeutic Failures. If no mycological testing is performed, these patients will be considered Therapeutic Failures in the primary analysis but the Mycological Cure data will be set to missing for the secondary endpoint. No LOCF will be performed.

If the proportions of patients with a Therapeutic Cure in the Test and the Reference product groups are numerically and statistically superior to that of the Placebo ($p < 0.05$; using a two-sided Cochran-Mantel-Haenszel [CMH] test, stratified by clinical site) then superiority of the Test and Reference products over Placebo will be concluded.

The same statistical approach will be conducted for analyses of the secondary endpoints in the mITT population.

To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population.

Treatment-by-Site Interaction and Pooling of Clinical Sites

As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population for equivalence testing. The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$, 2-sided). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the stratification of the sites in the CMH test and in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ($p < 0.05$) for the primary endpoint, then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Therapeutic Cure rates at each site where sample sizes per treatment may be influential in the assessment of the interaction. The treatment-by-site

interaction may also be evaluated for the analyses of the secondary endpoints in the PP population for equivalence testing if the treatment-by-site interaction is found to be significant in the primary analysis.

8.3 Safety Analysis

8.3.1 Adverse Events

All the adverse events (AEs) reported throughout the study will be coded and classified according to the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary (Version 21.0 or higher).

Treatment emergent adverse events (TEAE) are those that have a start date after the study treatment has been administered or the events that were present before administration of study treatment and worsen in severity after administration of study treatment. Treatment emergent adverse events will be summarized and analyzed in a summary table. Pre-treatment adverse events will be presented in the listing.

A summary table of the number and percent of patients with TEAEs by system organ class, preferred term, and treatment will be presented. Each patient will be counted only once within each preferred term.

A frequency summary table of the number of TEAEs by system organ class, preferred term, severity, and treatment will be presented. Severity will be classified as “Mild”, “Moderate”, or “Severe”.

Similarly, a frequency summary table of the number of TEAEs by system organ class, preferred term, and relationship to a study drug, and treatment will be presented. Relationship to a study drug will be classified as “Not Related” or “Related”.

If sufficient data exist, then TEAE frequencies will be compared among the three treatments using Fisher’s exact test; if this test is statistically significant at the 5% significance level, then a pairwise Fisher’s exact test comparing Test and Reference will be conducted.

TEAEs will be listed by treatment group and patient. Pre-treatment adverse events will be listed by patient.

8.3.2 Vital Signs

The patient’s vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at each visit.

Descriptive summaries (number of observations, mean, standard deviation, minimum, median and maximum) will be provided by treatment group and visit.

8.3.3 Local Signs and Symptoms

The Clinical Signs and Symptoms of tinea pedis will be rated by the Investigator as "none", "mild," "moderate" or "severe" using the following standardized rating scale.

0 = None (complete absence of any sign or symptom)

1 = Mild (Slight)

2 = Moderate (Definitely Present)

3 = Severe (Marked, Intense)

The following signs and symptoms will be rated at each visit:

- Signs: Fissuring/cracking, erythema, maceration, and scaling
- Symptoms: Pruritus and burning/stinging

A frequency summary table comparing the signs and symptoms for each treatment group will be presented by visit.

All data will be listed by treatment group and patient.

8.3.4 Concomitant Medications

At Visit 1, patients will be questioned about medication use over the previous six months. At all subsequent visits, patients will be questioned about ongoing or new concomitant medication use.

All prior and concomitant medications taken since screening until the end of the study will be listed by treatment group and patient.

8.4 Multiple Comparisons

No multiple comparison adjustment will be made in this study.

8.5 Methods for Handling Missing Data

For demographic and baseline characteristics, each variable will be analyzed using all available data. Patients with missing data will be excluded only from analyses for which data are not available.

Superiority of the Test and Reference products against the Placebo product for the primary endpoint will be evaluated in the mITT population using LOCF.

Patients discontinued early for reasons other than lack of treatment effect will be excluded from the PP population and included in the mITT population using LOCF. Patients who qualify for inclusion in the mITT population with missing endpoint data who were not discontinued for lack

of treatment effect will also be evaluated using LOCF; that is, if a patient who was not discontinued for lack of treatment effect does not have KOH or mycological culture results at Visit 3, this patient will be evaluated for the primary and secondary endpoints using LOCF from Visit 1. Patients who discontinued because of lack of treatment will not have LOCF performed.

Patients who meet the criteria above, but who also used topical drug therapy on the feet for the treatment of irritation or pruritus after the treatment phase of the study will be included in the mITT as Therapeutic Failures. If no mycological testing is performed, these patients will be considered Therapeutic Failures in the primary analysis but the Mycological Cure data will be set to missing for the secondary endpoint. No LOCF will be performed.

8.6 Interim Analyses

There is no interim analysis planned in this study.

8.7 Changes to the Protocol Defined Statistical Analysis Plan

To conform to recommendations in the recently updated Draft Guidance on Ketoconazole (Revised Feb 2019), the following changes to the statistical analyses described in the protocol will be made.

Wordings in protocol	Changed to
Protocol section 11.3.3 The Safety population will include all patients who are randomized and received study product.	The Safety population will include all randomized patients who use at least one dose of product.
Protocol section 11.3.2 The mITT population will include randomized patients who: • Met all inclusion/exclusion criteria. • Applied at least one dose of assigned product. • Had at least one post-baseline evaluation. • Had a positive baseline KOH and fungal culture for *Trichophyton rubrum, Trichophyton mentagrophyties* or *Epidermophyton floccosum.*	The mITT population will include randomized patients who: • Met all inclusion/exclusion criteria. • Applied at least one dose of assigned product. • Had a positive baseline KOH and fungal culture for *Trichophyton rubrum, Trichophyton mentagrophyties* or *Epidermophyton floccosum.*

9. TABLE, LISTING AND FIGURE SHELLS

The following shells provide a framework for the display of data from this study. These shells may not be reflective of every aspect of this study but are intended to show the general layout of the Tables, Listings and Figures that will be included in the final clinical study report. Tables, Listings and Figures are numbered following the ICH structure. Table headers, variables names and footnotes will be modified as needed following data analyses. All descriptive and inferential statistical analyses will be performed using SAS® statistical software Version 9.4 or higher, unless otherwise noted.

TABLE, LISTING AND FIGURE SHELLS

T14.1.1 Summary of Patient's Disposition

(Randomized Population)

Patients Randomized	Test N = xxx n (%)	Reference N = xxx n (%)	Placebo N = xxx n (%)	Total N = xxx n (%)
Completed Study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Terminated Early	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Adverse event	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lack of efficacy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lost to follow-up	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Negative baseline culture result	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Noncompliance with study drug	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Patient scheduled/came in early for Visit 3				
Pregnancy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Protocol deviation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Significant worsening of condition requiring alternative or supplemental therapy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Withdrawal by subject	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = number of patients randomized in that particular group; n = number of patients with data available for that particular group; total % is based on N

T14.1.2 Summary of Protocol Deviations

(Randomized Population)

Patients Randomized	Test N = xxx n (%)	Reference N = xxx n (%)	Placebo N = xxx n (%)	Total N = xxx n (%)
Total Patients with Protocol Deviations	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Total Deviations	xxx	xxx	xxx	xxx
Lost to follow-up	xxx	xxx	xxx	xxx
Missed visit	xxx	xxx	xxx	xxx
Noncompliance with study product	xxx	xxx	xxx	xxx
Noncompliance with study procedures	xxx	xxx	xxx	xxx
Outside visit window	xxx	xxx	xxx	xxx
Randomized in error	xxx	xxx	xxx	xxx
Restricted medication	xxx	xxx	xxx	xxx
Other	xxx	xxx	xxx	xxx

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = number of patients randomized in that particular group; n = number of patients with data available for that particular group; total % is based on N

T14.1.3.1 Summary of Patients Excluded from Efficacy Analysis (Randomized Population)

	Test N = xxx n (%)	Reference N = xxx n (%)	Placebo N = xxx n (%)	Total N = xxx n (%)
Safety Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Excluded from Safety population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Did not receive study product	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
mITT Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Excluded from mITT population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Inclusion/Exclusion criteria not met	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Did not have at least one post-baseline evaluation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Etc.	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PP Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Excluded from PP population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Significant protocol deviations	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Etc.	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = number of patients randomized in that particular group; n = number of patients with data available for that particular group; total % is based on N

Programming note: exclusion reasons are not duplicated across the populations.

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

T14.1.3.2 Summary of Patients Included in Analysis Population by Study Site

(Randomized population)

Site No.	Name	Total Randomized	Safety				mITT				PP			
			Test	Ref	Placebo	Total	Test	Ref	Placebo	Total	Test	Ref	Placebo	Total
xx	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
xx	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

T14.1.3.3 Study Timelines (Randomized Patients)

	Trial Timelines Date
First Patient First Visit (FPFV)	mm/dd/yyyy
Last Patient Last Visit (LPLV)	mm/dd/yyyy
Trial Duration (Days)	xxx

Note: Trial Duration (Days) = (Date of LPLV - Date of FPFV) + 1

T14.2.1 Summary of Demographic Data (Safety Population)

		Test (N = xxx) n (%)	Reference (N = xxx) n (%)	Placebo (N = xxx) n (%)	P-value
Age (years)	n	xxx	xxx	xxx	x.xxxx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	
	Median	xx.x	xx.x	xx.x	
	Range	xx-xx	xx-xx	xx-xx	
Age Groups	< 18	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	x.xxxx
	18 – 40	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
	41 – 64	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
	65 – 75	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
	> 75	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
Race	American Indian or Alaska Native	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	x.xxxx
	Asian	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
	Black/African American	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
	Native Hawaiian or other Pacific Islander	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
	White	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
	Multiple	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = number of patients in the Safety Population in that particular group; n = number of patients with data available for that particular group; total % is based on N

P-values are from Cochran-Mantel-Haenszel (CMH) test for the categorical variables, and Analysis of Variance for the continuous variables.

T14.2.1 Summary of Demographic Data (Safety Population)

		Test (N = xxx) n (%)	Reference (N = xxx) n (%)	Placebo (N = xxx) n (%)	P-value
Sex	Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	x.xxxx
	Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	
Ethnicity	Hispanic or Latino	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	x.xxxx
	Not Hispanic or Latino	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = number of patients in the Safety Population in that particular group; n = number of patients with data available for that particular group; total % is based on N

P-values are from Cochran-Mantel-Haenszel (CMH) test for the categorical variables, and Analysis of Variance for the continuous variables.

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

T14.2.2 Summary of Baseline Characteristics (Safety Population)

		Test (N = xxx)	Reference (N = xxx)	Placebo (N = xxx)	Overall P-value	P-value Test vs. Reference
Type of infection, n (%)	Interdigital	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	x.xxxx	x.xxxx
	Interdigital with extension	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)		
Onychomycosis, n (%)	Presence	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	x.xxxx	x.xxxx
	Absence	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)		
Primary infective organism, n (%)	xxxxx	xxx (x.x)	xxx (xx.x)	xxx (xx.x)		x.xxxx
	xxxxx	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)		
Total baseline signs and symptom score, n (%)	n	xxx	xxx	xxx	x.xxxx	x.xxxx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x		
	Median	xx.x	xx.x	xx.x		
	Range	xx-xx	xx-xx	xx-xx		
Number of Tinea Pedis infections in the past 12 months, n (%)	n	xxx	xxx	xxx	x.xxxx	x.xxxx
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x		
	Median	xx.x	xx.x	xx.x		
	Range	xx-xx	xx-xx	xx-xx		

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = number of patients in the Safety Population in that particular group; n = number of patients with data available for that particular group; total % is based on N

P-values are from Cochran-Mantel-Haenszel (CMH) test for the categorical variables, and Analysis of Variance for the continuous variables.

Note to programmer: If the overall P-value is statistically significant among the three treatment groups at the 5% alpha level (i.e. $p < 0.05$), then ANOVA or CMH test using only the test and reference groups will be performed to identify any potential statistically significant differences that are clinically relevant between the two active treatment groups.

Similar tables will be created for T14.2.3, T14.2.4, T14.2.5 and T14.2.6

T14.2.3 Summary of Demographic Data
(modified Intent-to-Treat Population)

T14.2.4 Summary of Baseline Characteristics
(modified Intent-to-Treat Population)

T14.2.5 Summary of Demographic Data
(Per-Protocol Population)

T14.2.6 Summary of Baseline Characteristics
(Per-Protocol Population)

T14.2.7.1 Summary of Total Severity Score of Local Signs and Symptoms (modified Intent-to-Treat Population)

Visit	Total Severity Score	Test N = xxx n (%)	Reference N = xxx n (%)	Placebo N = xxx n (%)
1	<=2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
2	<=2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
3/Early termination	<=2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	>2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

Similar table will be created for:

T14.2.7.2 Summary of Total Severity Score of Local Signs and Symptoms (Per-Protocol Population)

T14.2.8.1 Summary of KOH Wet Mount and Mycological Culture (modified Intent-to-Treat Population)

	Visit	Result	Test N = xxx n (%)	Reference N = xxx n (%)	Placebo N = xxx n (%)
KOH Wet Mount	1	Positive	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Negative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	2	Positive	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Negative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	3/Early termination	Positive	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Negative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Mycological Culture	1	Positive	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Negative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	2	Positive	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Negative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	3/Early termination	Positive	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
		Negative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

Similar table will be created for:

T14.2.8.2 Summary of KOH Wet Mount and Mycological Culture (Per-Protocol Population)

T14.2.9 Summary of Analysis Results of Primary Efficacy Endpoint
Proportion of Patients in each Treatment Group with a Therapeutic Cure of Tinea Pedis
at the Test-of-cure Visit (Day 56 ± 4)

Equivalence: Per-Protocol Population

Treatment Group	Number of Patients (N)	Number of Patients with Therapeutic Cure (n)	Proportion of Therapeutic Cure (%)	Difference Between Treatments	
				Difference (%)	90% CI Evaluation
Test	xxx	xxx	xx.x		
Reference	xxx	xxx	xx.x	xx.x	xx.x – xx.x

Superiority: modified Intent-to-Treat Population

Treatment Group	Number of Patients (N)	Number of Patients with Therapeutic Cure (n)	Proportion of Therapeutic Cure (%)	Treatment vs. Placebo	
				Difference (%)	P-value
Placebo	xxx	xxx	xx.x		
Test	xxx	xxx	xx.x	xx.x	x.xxxx
Reference	xxx	xxx	xx.x	xx.x	x.xxxx

The 90% confidence interval for the difference in proportions between test and reference was calculated using Yates' correction.
Superiority of Active treatments over Placebo were tested using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by clinical site, at the 5% significance level using last observation carried forward (LOCF).
Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

T14.2.10 Summary of Analysis Results of Secondary Efficacy Endpoint
Proportion of Patients in each Treatment Group Who are Considered a Clinical Cure at Day 56 ± 4

Equivalence: Per-Protocol Population

Treatment Group	Number of Patients (N)	Number of Patients with Clinical Cure (n)	Proportion of Clinical Cure (%)	Difference Between Treatments	
				Difference (%)	90% CI Evaluation
Test	xxx	xxx	xx.x		
Reference	xxx	xxx	xx.x	xx.x	xx.x – xx.x

Superiority: modified Intent-to-Treat Population

Treatment Group	Number of Patients (N)	Number of Patients with Clinical Cure (n)	Proportion of Clinical Cure (%)	Treatment vs. Placebo	
				Difference (%)	P-value
Placebo	xxx	xxx	xx.x		
Test	xxx	xxx	xx.x	xx.x	x.xxxx
Reference	xxx	xxx	xx.x	xx.x	x.xxxx

The 90% confidence interval for the difference in proportions between test and reference was calculated using Yates' correction.
Superiority of Active treatments over Placebo were tested using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by clinical site, at the 5% significance level using last observation carried forward (LOCF).
Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

T14.2.11 Summary of Analysis Results of Secondary Efficacy Endpoint
Proportion of Patients in each Treatment Group Who are Considered a Mycological Cure at Day 56 ± 4

Equivalence: Per-Protocol Population

Treatment Group	Number of Patients (N)	Number of Patients with Mycological Cure (n)	Proportion of Mycological Cure (%)	Difference Between Treatments	
				Difference (%)	90% CI Evaluation
Test	xxx	xxx	xx.x		
Reference	xxx	xxx	xx.x	xx.x	xx.x – xx.x

Superiority: modified Intent-to-Treat Population

Treatment Group	Number of Patients (N)	Number of Patients with Mycological Cure (n)	Proportion of Mycological Cure (%)	Treatment vs. Placebo	
				Difference (%)	P-value
Placebo	xxx	xxx	xx.x		
Test	xxx	xxx	xx.x	xx.x	x.xxxx
Reference	xxx	xxx	xx.x	xx.x	x.xxxx

The 90% confidence interval for the difference in proportions between test and reference was calculated using Yates' correction.
Superiority of Active treatments over Placebo were tested using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by clinical site, at the 5% significance level using last observation carried forward (LOCF).
Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

T14.3.1 Overall Summary of Adverse Events
(Safety Population)

Description	Test (N = xxx) n (%)	Reference (N = xxx) n (%)	Placebo (N = xxx) n (%)	Total (N = xxx) n (%)
Patients in Safety Analysis population	xxx	xxx	xxx	xxx
Patients with at least one AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Discontinued study product due to above AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
AEs reported	Xxx	xxx	xxx	xxx
Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not Related	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Related	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Death	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Serious AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
MedDRA Version 21.0

T14.3.2 Summary of Frequency of Adverse Events by Body System (Safety Population)

Body System	Preferred Term	Test N = xxx		Reference N = xxx		Placebo N = xxx		Overall Fisher's P-value	Fisher's P-value Test vs. Reference
		Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)		
Patients with at least one AE	Total	xx	xxx (xx.x)	xx	xxx (xx.x)	xx	xxx (xx.x)	0.1234	NA
Ear and labyrinth disorders	Ear pain	xx	xxx (xx.x)	xx	xxx (xx.x)	xx	xxx (xx.x)	0.0425	0.0372
	etc.								

etc.

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = number of patients in safety population in that particular group; n= number of patients with data available for that particular group; total % is based on N
MedDRA Version 21.0

Note to programmer: If the global Fisher's exact test is statistically significant among the three treatment groups at the 5% alpha level (i.e. $p < 0.05$), then Fisher's exact test using only the test and reference groups will be performed to identify any potential statistically significant differences that are clinically relevant between the two active treatment groups.

T14.3.3 Summary of Frequency of Adverse Events by Relationship (Safety Population)

Body System	MedDRA Term	Test # of Events (N = xxx)		Reference # of Events (N = xxx)		Placebo # of Events (N = xxx)	
		Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)
Total AEs	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ear and labyrinth disorders	Ear pain	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Hypoacusis	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = Total number of events in that particular group; Percentage is based on total number of events.
MedDRA Version 21.0

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

T14.3.4 Summary of Frequency of Adverse Events by Severity (Safety Population)

		Test # of Events (N = xxx)			Reference # of Events (N = xxx)			Placebo # of Events (N = xxx)		
Body System	**MedDRA Term**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Total AEs	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ear and labyrinth disorders	Ear pain	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Hypoacusis	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = Total number of events in that particular group; Percentage is based on total number of events.
MedDRA Version 21.0

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX
Created on: ddmmmyy hh:mm

OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Page 1 of N

T14.3.5 Summary of Frequency of Serious Adverse Events (Safety Population)

Body System	Preferred **Term**	**Test # Events**	**Reference # Events**	**Reference # Events**
Injury, poisoning and procedural complications	Alcohol poisoning	xxx	xxx	xxx

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
MedDRA Version 21.0

T14.3.6 Summary of Vital Signs
(Safety Population)

Vital Signs	Visit	Statistic	Test N = xxx	Reference N = xxx	Placebo N = xxx
Systolic Blood Pressure (mmHg)	Visit 1	n	xxx	xxx	xxx
		Mean ± SD	xxx.x ± xx.x	xxx.x ± xx.x	xxx.x ± xx.x
		Median	xxx.x	xxx.x	xxx.x
		Range	xxx.x – xxx.x	xxx.x – xxx.x	xxx.x – xxx.x
	Visit 2				
	Visit 3/Early Termination				
Diastolic Blood Pressure (mmHg)					
Pulse Rate (beats/min)					
Respiration Rate (breaths/min)					
Temperature (F)					

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
N = Total number of events in that particular group; Percentage is based on total number of events.

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.1 Listing of Discontinued Patients

Treatment Group	Patient Screening Number	Patient Randomization Number	Discontinuation Reason	Population
Test	xx-xxx	xxxx	Withdrawal by Patient	Per-Protocol
	xx-xxx	xxxx	Lost to Follow-up	Safety
Reference				
Placebo				

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.2 Listing of Protocol Deviations

Treatment Group	Patient Screening Number	Patient Randomization Number	Event Description	Population	Significant Protocol Deviation
Test	xx-xxx	xxxx	Outside Visit Window (Visit 3)	Safety	No
Reference					
Placebo					

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.3.1 Listing of Patients Excluded from the Per-Protocol Population

Treatment Group	Patient Screening Number	Patient Randomization Number	Exclusion Reason
Test	xx-xxx	xxxx	Significant protocol deviation
Reference			
Placebo			

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.3.2 Listing of Patients Excluded from the modified Intent-to-Treat Population

L16.2.4.1 Listing of Demographic Data

Treatment Group	Patient Screening Number	Patient Randomization Number	Age	Sex	Ethnicity	Race	Birth Control
Test	xx-xxx	xxxx	30	Female	Not Hispanic or Latino	Black or African American	Double Barrier
Reference Placebo							

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.4.2 Listing of Medical History

Treatment Group	Patient Screening Number	Patient Randomization Number	System	Diagnosis or Surgical Procedure	Start Date	End Date	Ongoing	Number of Tinea Pedis infections in the past 12 months
Test	xx-xxx	xxxx	Gynecologic	Menopause	--/--/2012	mm/dd/yyyy		xxx

Reference
Placebo

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

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Created on: ddmmmyy hh:mm Page 1 of N

L16.2.4.3 Listing of Prior and Concomitant Medication

Treatment Group	Patient Screening Number	Patient Randomization Number	Treatment Area	Medication	Dosage/Unit	Frequency*	Route	Start/End Date/ Ongoing	Indication	Prior?
Test	xx-xxx	xxxx	No	Lisinopril	20 MG	QD	PO	--/--/2017/ 08/12/2017	Hypertension	No
Reference										
Placebo										

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
*PRN - As needed; QD – Daily (once per day); Q4H - Every 4 hours; Q8H - Every 8 hours; Q12H - Every 12 hours; BID - Twice per day; TID - 3 times per day; QID - 4 times per day; QOD - Every other day; QS - Every week; QM - Every month; Q3M - Every 3 months

L16.2.5 Listing of Drug Administration

Treatment Group	Patient Screening Number	Patient Randomization Number	Date of First Dose	Date of Last Dose	Total Doses Applied	Missed Doses	Treatment Compliance
Test	xx-xxx	xxxx	mm/dd/yyyy	mm/dd/yyyy	xx	xx	Yes
Reference							
Placebo							

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PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.6.1 Listing of Local Signs and Symptoms

Treatment Group	Patient Screening Number	Patient Randomi-zation Number	Visit	Evaluator	Erythema	Scaling	Pruritus	Fissuring/ Cracking	Maceration	Burning/ stinging	Total Severity Score	Clinical Cure/ Failure
Test	xx-xxx	xxxx	1	xxx	0	0	0	1	0	0	1	
			2	xxx	0	0	0	1	0	0	1	
			3	xxx	0	0	0	1	0	0	1	Cure
Reference												
Placebo												

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PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.6.2 Listing of Mycological Culture and KOH Wet Mount Results

Treatment Group	Patient Screening Number	Patient Randomization Number	Visit	Mycological Culture	KOH Wet Mount	Mycological Cure/Failure	Therapeutic Cure/Failure
Test	xx-xxx	xxxx	1	T. rubrum/E. floccosum	Positive		
			2	T. rubrum/E. floccosum	Negative		
			3	Negative	Negative	Cure	Cure
		xx-xxxx	1	T. rubrum	Positive		
			2	T. rubrum	Negative		
			3	T. rubrum	Negative	Failure	Failure
Reference Placebo							

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PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.7.1 Listing of Treatment Emergent Adverse Events by Treatment

Treatment Group	Patient Screening Number	Patient Randomi-zation Number	Body System / MedDRA Term / AE Term	Treatment Area	Start /End Date/ Ongoing	Severity	Relationship to Study Drug	Outcome	Action Taken/ Other Action Taken	SAE
Test	xx-xxx	xxxx	Nervous system disorders / Headache / Headache	No	mm/dd/yyyy / mm/dd/yyyy	Mild	Related	Recovered	Dose Not Changed/ None	No
Reference Placebo										

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.7.2 Listing of Pre-treatment Adverse Events

Patient Screening Number	Patient Randomi-zation Number	Body System / MedDRA Term / AE Term	Treatment Area	Start /End Date/ Ongoing	Severity	Relationship to Study Drug	Outcome	Action Taken/ Other Action Taken	SAE
xx-xxx	xxxx	Nervous system disorders / Headache / Headache	No	mm/dd/yyyy / mm/dd/yyyy	Mild	Related	Recovered	Dose Not Changed/ None	No

L16.2.8.1 Listing of Pregnancy Test Results

Treatment Group	Patient Screening Number	Patient Randomization Number	Visit 1	Visit 2	Visit 3 / Early Termination
Test	xx-xxx	xxxx	Negative	Negative	Negative
Reference					
Placebo					

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Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N

L16.2.8.2 Listing of Vital Signs

Treatment Group	Patient Screening Number	Patient Randomization Number	Visit	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse Rate (beats/min)	Respiration Rate (breaths/min)	Temperature (F)
Test	xx-xxx	xxxx	Visit 1	120	70	84	18	98.6
			Visit 2	140	100	74	18	97.0
			Visit 3	140	100	74	18	97.0

Reference
Placebo

Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

PROGRAM: L:\DEV\755\71875502\SAS\PGM\XXXX OUTPUT: L:\DEV\755\71875502\SAS\OUT\XXXX
Created on: ddmmmyy hh:mm Page 1 of N