Statistical Analysis Plan	
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A RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, THREE-ARM, PLACEBO-CONTROLLED, MULTI-SITE THERAPEUTIC EQUIVALENCE STUDY WITH CLINICAL END-POINTS COMPARING TEST PRODUCT "OXYMETAZOLINE HYDROCHLORIDE CREAM, 1%" TO REFERENCE PRODUCT "RHOFADE™ CREAM, 1%" IN THE TREATMENT OF MODERATE TO SEVERE PERSISTENT FACIAL ERYTHEMA OF ROSACEA

Study Statistician [redacted] Date

Sponsor Representative [redacted] Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomic-therapeutic-chemical
BMI	Body Mass Index
CEA	Clinical Erythema Assessment
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic Case Report Form
EoT	End of Treatment
FDA	Food and Drug Administration
HEENT	Head, eyes, ears, nose, throat
ICF	Informed Consent Form
IWRS	Interactive Web Response System
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
NDA	New Drug Application
PP	Per Protocol
PT	Preferred Term
RLD	Reference Listed Drug
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SSA	Subject Self-Assessment
TEAE	Treatment-Emergent Adverse Event
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol "A Randomized, Double-blind, Parallel-group, Three-arm, Placebo-controlled, Multi-Site Therapeutic Equivalence Study with Clinical End-points Comparing Test Product “Oxymetazoline hydrochloride Cream, 1%” to Reference Product “RHOFADE™ Cream, 1%” in the Treatment of Moderate to Severe Persistent Facial Erythema of Rosacea", version 3.0, dated January 29, 2020.

This therapeutic equivalence study with clinical endpoint is designed to determine the therapeutic equivalence of Oxymetazoline hydrochloride Cream, 1% (manufactured by Actavis Laboratories, Salt Lake City, UT) with the reference listed drug (RLD) RHOFADE™ (Oxymetazoline hydrochloride Cream, 1%) marketed by Allergan, in healthy males and non-pregnant females diagnosed with moderate to severe persistent facial erythema of rosacea.

This document will give a description of the planned methods of the analysis.

2. OBJECTIVES

The primary objectives of this study are:

- To establish the therapeutic equivalence between Test Product (Oxymetazoline hydrochloride Cream, 1%, manufactured by Actavis Laboratories, Salt Lake City, UT) and Reference Product (RHOFADE™ Cream, 1%, Allergan) on Day 29, in subjects with moderate to severe persistent facial erythema of rosacea.
- To demonstrate superiority of the efficacy of the two active treatments over the placebo control.

The secondary (safety) objective of this study is:

- To monitor adverse events (AEs) and assess the safety and tolerability of Test Product and Reference Product in subjects with moderate to severe persistent facial erythema of rosacea.

3. STUDY OVERVIEW

3.1 Study Design

This is a multi-center, randomized, double-blind, parallel-group, three-arm, placebo-controlled, therapeutic equivalence study with clinical endpoints. The study will compare the efficacy and safety of test product "Oxymetazoline hydrochloride Cream, 1%" (manufactured by Actavis Laboratories, Salt Lake City, UT) with that of an approved topical formulation RHOFADE™ (Oxymetazoline hydrochloride Cream, 1%) marketed by Allergan, in healthy males and non-pregnant females diagnosed with moderate to severe persistent facial erythema of rosacea. Both the test and the reference formulations will also be compared to a placebo (vehicle) formulation to test for superiority.

Subjects with a confirmed diagnosis of moderate to severe persistent facial erythema of rosacea will be randomized to either Test Group (Oxymetazoline hydrochloride Cream, 1%); Reference Group (RHOFADE™, Oxymetazoline hydrochloride Cream, 1%); or Placebo Group (Vehicle Cream).

The study subjects will receive treatment for approximately 29 days from the Baseline visit to the End of Treatment (EoT) visit. There will be 4 study visits, 3 to the study site and 1 telephone follow-up:

- Screening
- Baseline (Day 1)
- Telephone Follow-up (Day 14)
- End of Treatment (Day 29)

At screening a written Informed Consent Form (ICF) has to be signed by the subject and the eligibility criteria of the subject will be evaluated by clinical assessments. . Subjects should sign ICF prior to start of any study procedures, complete washout, and return to the clinic to conduct the remainder of the screening procedures.

Study subject numbers will be assigned to study subjects sequentially in the order in which study subjects are enrolled into the study.

After the screening visit, each qualified subject will return to the clinic on Day 1 for confirmation of eligibility. Eligible subjects will be assigned to one of the three study treatment groups as per the computer-generated randomization schedule, and the assigned study medication will be dispensed by the study site staff. Since this is a double-blind study, neither the study team at the site nor the subjects will know the treatment the subject is assigned.

The subject will be instructed to apply a pea-size amount of the study treatment to cover the entire face (forehead, chin, nose, and each cheek [avoiding the eyes and lips]), once daily preferably, at the same time each day, up to and including the day before scheduled Visit 4 (Day 29±2). [redacted]. On Day 1 visit and Day 29±2 visit, the subject will apply the assigned medication at the clinic under the supervision of an Independent Dispenser (unblinded to the treatment the subject is receiving). [redacted]). From Day 2 up to and including the day before scheduled Visit 4 (Day 29[redacted]), the subject will be asked to self-apply the assigned medication once daily and complete the subject diary, handed over by the study site staff at Baseline visit. The subject will note the date and time of application of the study medication, any AE experienced, and any concomitant medication taken or changes from the existing ones, in the subject diary from Visit 2 (Day 1) to Visit 4 (Day 29[redacted]). A phone call will be made around Day 14 to follow up for any change in concomitant medications, and check on compliance of study medication usage.

3.2 Sample Size

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted].

3.3 Randomization and Unblinding Procedures

Subjects will be randomly assigned in a treatment allocation ratio of 1:1:1 to receive the Test product or the Reference Product or the Placebo control, respectively. The randomization schedule for this study will be generated by a third-party vendor such that a non-study-assigned independent expert will allocate the subjects to one of the three treatment arms using a computer-generated automated process, [redacted]. A copy of the randomization scheme

(respective to that site) will be retained at the study site following the completion of the study and should be available to regulatory authority inspectors at the time of site inspection to allow for verification of the treatment identity of each subject.

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the treatment assigned to the subject. Only the Independent Dispenser will have access to the study medication, but their primary responsibilities will be limited to dispensing, collecting and observing and supervising the administration of the study medication by the subject on clinical visits. They will not participate in any activities.

In case of an emergency, if the details of the study drug are required for management of an emergency as per the opinion of Investigator, the Investigator can unblind the product that is received by the subject during the study.

At the conclusion of the study, after the database has been locked, each site will be sent the study randomization scheme (respective to their site) that should be retained with the study documents in the event of an FDA inspection along with evidence of when the randomization scheme was provided.

4. STUDY ENDPOINTS/OUTCOMES

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with treatment success at all time-points 3, 6, 9, and 12 hours post application on Day 29. Treatment success is defined as having CEA score at least 2 grades lower than the baseline (Day 1 pre-dose) value.

Safety Endpoints

Safety endpoints include incidence of AEs.

5. HYPOTHESES TESTING

Hypothesis of Equivalence

A two-sided, continuity-corrected 90% confidence intervals on the Test-vs-Reference difference for the proportion of subjects with treatment success at all timepoints (3, 6, 9 and 12 hours post-application on Day 29) will be constructed. Therapeutic equivalence will be

established if the 90% confidence interval for the difference is contained within the interval [-0.20, +0.20] for the PP population.

Hypothesis of Superiority

The null hypotheses to be tested are that there is no difference in the proportions of subjects with treatment success at all time-points (3, 6, 9 and 12 hours post-application on Day 29). The evaluation of superiority will be conducted separately for the Test treatment versus the Placebo treatment and for the Reference treatment versus the Placebo treatment. The analysis will be conducted using two-sided, $\alpha = 0.05$, exact CMH test stratified by study site.

Superiority will be established if the success proportion for each active treatment is greater than, and statistically different from, that of the Placebo for the mITT population.

6. ANALYSIS SUBSETS

6.1 Safety Population

The safety population includes all randomized subjects who applied at least 1 dose of study medication in the study, as recorded in the subject diary.

The safety population will be the primary population for the safety analysis.

6.2 Modified Intent to Treat Population (mITT Population)

The mITT population includes all randomized subjects who met all the inclusion and none of the exclusion criteria, have a CEA measurement at baseline (i.e. pre-dose on Day 1), applied at least one dose of study treatment, and have at least one post-baseline measurement for CEA or discontinue due to lack of treatment effect after completing 2 days of treatment.

This population will be used for analyses of superiority.

6.3 Per Protocol Population (PP Population)

The PP population includes all subjects in the mITT population who have no major protocol deviations/violations that would affect the treatment evaluation.

See section 7.5 for more details on protocol deviations and how they affect exclusion from the PP population.

The PP population will be used for analyses of therapeutic equivalence.

7. STATISTICAL METHODS OF ANALYSIS

7.1 General Principles

[redacted]

In general, all data will be listed by treatment group, subject and visit/time-point where appropriate. The summary tables will also be stratified by, or have columns corresponding to, treatment groups.

All subjects will be identified by their unique subject numbers. Data from the screen failures will not be included in tables, listings, or figures.

The total number of subjects in the study group (N) under the stated population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation (SD), minimum, median, and maximum. 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. The standard deviation will be presented to two more decimal places than the original data. The number of missing observations will be presented only if non-zero.

In summary tables of categorical variables, counts, and percentages will be used. The count [n] indicates the actual number of subjects in a particular category, which should always be less than or equal to the total number of subjects in the respective study group with known (non-missing) category [M]. Percentage will be obtained by: % = n/M*100. Unless otherwise specified, all percentages will be expressed to one decimal place.

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated. No adjustment will be made for multiplicity.

Unless otherwise specified below, baseline for an assessment will be defined as the last available assessment obtained prior to the first application of the study drug.

[redacted]

In by-visit summaries only scheduled visits/time-points will be presented. Unscheduled assessments will not be included in by-visits summaries, however, will be shown in listings and may be used in selecting the baseline, if applicable.

Relative days will be calculated relative to the date of the first dose of the study medication. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days).

For assessment on or after the day of the first dose of the study drug:

Relative Day = Date of Assessment – Date of First Dose of Study Drug+1.

For assessment before the day of the first dose of the study drug:

Relative Day = Date of Assessment – Date of First Dose of Study Drug.

All dates will be displayed in DDMMMYYYY format.

7.2 Subject Disposition

The number of subjects screened in the study, randomized to treatment, included in the Safety, PP, mITT populations, prematurely discontinued from the study (along with the reasons for discontinuation) will be calculated. The percentages will be based on the number of subjects randomized to each treatment group. Percentages for discontinuation reasons will be based on the sub-population of subjects who discontinued from the study.

Number and percentage of subjects enrolled by site will be tabulated for all enrolled subjects, Safety, mITT, and PP populations.

7.3 Demographic and Baseline Characteristics

Demographic characteristics will include:

- age;

- gender;
- race;
- ethnicity;

Baseline characteristics include:

- Height, weight and BMI;
- Time since rosacea diagnosis (years).
- Baseline CEA score;
- Baseline SSA score;

Descriptive statistics will be presented for age (years), height, weight, BMI and time since diagnosis (years). Frequency counts and percentages will be presented for race, ethnicity, and baseline CEA and SSA score. Height will be reported in centimeters and weight in kilograms.

Age will be derived from Informed Consent Signed Date and Date of Birth as the number of whole years between those two dates.

Demographic and baseline/randomization characteristics will be evaluated for comparability across treatment groups in the following manner. Continuous variables (age, height, weight, BMI, time since diagnosis) will be analyzed with an ANOVA with factors of treatment and investigational site. Overall p-value for the global null hypothesis of all groups being equal will be displayed. Categorical variables (gender, ethnicity, race, CEA and SSA scores) will be analyzed with a Cochran-Mantel-Haenszel, stratified by investigational site. For gender, ethnicity, race, CMH general association statistic will be used. For CEA and SSA scores, "mean scores differ" statistic will be used.

All parameters reported during screening or baseline phase (including informed consent information, inclusion/exclusion criteria, randomization information, method of contraception, etc.) will be presented in by-subject listings.

7.4 Medical History

Medical history terms will be coded using MedDRA version 22.0.

Medical and surgical history other than rosacea history will be summarized by MedDRA system organ class, preferred term and treatment group. One subject will be counted only

once under each applicable system organ class and preferred term. System organ classes and preferred terms will be presented alphabetically.

7.5 Protocol Deviations

[redacted]

Specific deviations and their severities are defined in the separate Protocol Deviations List document.

Protocol deviations will be summarized by deviation type and treatment group. This analysis will be performed for all randomized subjects.

7.6 Efficacy Analyses

7.6.1 Site Pooling

To eliminate potential effect of random fluctuations at a small site on the primary endpoint small sites will be pooled. [redacted]

- [redacted]
- [redacted]

[redacted]

Pooled sites will be used in all the efficacy analyses.

7.6.2 Derivation of the Primary Endpoint

A subject is defined as achieving treatment success at a time-point if the CEA score is at least 2 grades lower than the baseline value of the score. In this case baseline is defined as the pre-dose assessment on Day 1. To achieve the primary endpoint, the subject needs to have treatment success at all 4 post-application timepoints (3, 6, 9 and 12 hours) on Day 29.

The CEA score at all post-application time-points on Day 29 as well as the pre-treatment assessment on Day 1 are required to determine the primary endpoint. [redacted]

7.6.3 Analyses of Primary Endpoints

Proportion of subjects achieving the primary endpoint will be presented by treatment.

Also, proportions of subjects with treatment success will be presented by visit (Day 1 or Day 29), time-points and treatment.

7.6.3.1 Analysis of Therapeutic Equivalence of Test and Reference Treatments

Two-sided, continuity-corrected, 90% confidence intervals on the Test-vs-Reference difference for the proportion of subjects with treatment success at all timepoints on Day 29 will be constructed. Therapeutic equivalence will be established if the 90% confidence interval for the difference is contained within the interval [-0.20, +0.20] for the PP population.

7.6.3.2 Analysis of Superiority to Placebo Control

The evaluation of superiority will be conducted separately for the Test treatment versus the Placebo treatment and for the Reference treatment versus the Placebo treatment, comparing the proportions of subjects with treatment success at all time-points on Day 29. The analysis will be conducted using two-sided exact CMH test stratified by site.

Superiority will be established if the success proportion for each active treatment is greater than, and statistically significantly different from ($p < 0.05$ for the exact CMH test) that of the

Placebo for the mITT population. Analysis of superiority will be performed on the mITT population.

7.7 Safety Analyses

7.7.1 Adverse Events

Adverse Events will be coded using the MedDRA Version 22.0 AE coding system for purposes of summarization.

Only Treatment Emergent Events (TEAEs) will be used for the summary analysis. An AE will be considered as treatment-emergent if the time of onset is after the time of the first study drug administration or if it increased in severity during the study period. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the study drug start date. If the start date is partially missing, then month and year (when available) will be used to determine if the event occurred prior to or post dosing.

Pre-treatment AEs will be listed only.

A TEAE is defined as treatment-related if it is recorded as related to the study medication on the eCRF. In case the relatedness was not assessed, the most conservative result (related) will be chosen for the analysis.

An overall summary will include, by treatment group and overall, the number of TEAEs and the number and percentage of subjects reporting at least 1 TEAE in the following categories:

- Any TEAE
- Treatment-related TEAE
- Serious TEAE
- TEAE leading to discontinuation of the study medication
- TEAE leading to death.

The following TEAE frequency tables will be prepared summarizing the overall number of TEAEs, the number and percentage of subjects reporting at least one TEAE by MedDRA SOC and PT:

- All TEAEs,
- Serious TEAEs

- AEs leading to discontinuation of the study drug
- TEAEs by Severity
- TEAEs by Relationship to Study Drug.

A subject experiencing the same AE (the same preferred term) multiple times will only be counted once for that preferred term. Similarly, if a subject experiences multiple AEs within the same system organ class, that subject will be counted only once in that system organ class. AEs summaries will be presented in alphabetical order of SOC and preferred terms. When summarizing AEs by severity, only the most severe occurrence within the preferred term or system organ class will be used. Similarly, when summarizing AEs by relationship to study drug, only the most related occurrence within the preferred term or system organ class will be selected for displays in summary tables.

Additionally, TEAEs will be summarized by the preferred terms in the descending order of frequency in the total treatment group. In this table a p-value from Fisher's exact test comparing event rates between the Test and the Reference treatment groups will be provided for those preferred terms that have frequency > 1% in either Test or Reference group.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim, preferred term, system organ class, start date, stop date, intensity, outcome, action taken, and causal relationship to the study drug.

7.7.2 Application Site Reactions

At Baseline Visit (Day 1) and End of Treatment visit (Day 29) subjects will be evaluated for signs and symptoms of application site reactions, [redacted]

Number and percentage of subjects with each severity will be presented by visit, sign/symptom and treatment.

7.7.3 Vital Signs

Vital signs, including blood pressure, heart rate and body temperature will be recorded at screening; at pre-dose and 12 hours post-dose on Day 1; and at pre-dose and 12 post-dose

hours on Day 29. Overall interpretation (normal, abnormal not clinically significant or abnormal clinically significant) will also be recorded.

Vital sign measurements can be repeated. Repeats will be handled as follows. At the screening visit the latest repeat will be used for analysis. On Day 1 and Day 29 the latest repeat obtained prior to dosing will be used for analysis at the pre-dose time-point and the latest repeat obtained after dosing will be used for analysis at the 12-hour post-dose time-point.

Vital signs and their changes from baseline will be summarized descriptively by visit and treatment. Overall interpretation will also be summarized. All results will be listed.

7.7.4 Physical Examination

Physical examination will be performed at screening and Day 29 visit. The following body systems will be examined: General Appearance; Skin; HEENT; Heart; Lungs; Muscular-Skeletal; Lymph nodes; Neurological; Gastrointestinal; Genitourinary; Extremities as well as other if necessary. Each system will be classified as normal, abnormal not clinically significant or abnormal clinically significant.

Number and percentage of subjects with each classification will be presented by body system, visit and treatment. All results will be listed.

7.7.5 Exposure to Product

The subjects will be instructed to use the diary to document all doses taken. Dosing information will be summarized on the eCRF.

Compliance with scheduled application of the study drug will be determined as [Actual number of applications] / [Planned number of applications] * 100%, where

- Actual number of applications will be taken from the eCRF (“Total number of doses applied” field in the “Investigational Product Use Compliance” form)
- Planned number of applications is 29.

Number of missed doses will be calculated as follows. The number of doses missed in the dosing period (between the first and the last study drug application) will be taken directly from the eCRF. [redacted]

[redacted]

Duration of exposure will be calculated as Date of last use of study medication – Date of first use of study medication + 1. Duration of exposure will be summarized descriptively by treatment group.

Compliance and duration of exposure will be summarized for the Safety and mITT populations.

7.7.6 Exposure to Concomitant Medication

Prior and concomitant medications and concomitant non-drug therapies will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study will be provided in the data set, in addition to the reason for the medication use.

Medication or non-drug therapy will be classified as prior, if the end date is known and is prior to the first use of the study medication. Medications and non-drug therapies that are ongoing or ended after the first use of the study medication will be classified as concomitant. If the end date of the medication or non-drug therapy is unknown, it will also be considered concomitant.

Concomitant medications will be summarized by ATC class (the highest available level) and preferred name for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary March-2019 B3. Each subject will be counted only once for each applicable preferred name and ATC class. Concomitant medications will also be listed in a by-subject listing. Prior medications will be listed only.

8. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no changes from the protocol-specified analyses.

9. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

See separate document with the table, figure and listing shells.

10. LITERATURE CITATIONS / REFERENCES

1. Study Protocol: "A Randomized, Double-blind, Parallel-group, Three-arm, Placebo-controlled, Multi-Site Therapeutic Equivalence Study with Clinical End-points Comparing Test Product “Oxymetazoline hydrochloride Cream, 1%” to Reference Product “RHOFADE™ Cream, 1%” in the Treatment of Moderate to Severe Persistent Facial Erythema of Rosacea", version 3.0, dated January 29, 2020
2. Draft Guidance on Oxymetazoline Hydrochloride. FDA, November 2019.

11. APPENDICES

11.1 Study visit Schedule

	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4
Procedures	**Screening** [redacted]	**Screening** [redacted]	**Day 1 (Baseline)**	**Day 14 (Telephone follow-up)[a]** [redacted]	**Day 29 (EoT)** [redacted]
Written informed consent	X				
Demographics (height, weight, body mass index (BMI), gender, race, ethnicity)	X				
Pregnancy test (Urine)	X	X	X		X
Medical and surgical history	X	X			
Prior and concomitant medications and concurrent procedures	X	X	X	X	X
Vital signs measurements (blood pressure, heart rate, body temperature)	X	X	Pre-dose and 12 hrs		Pre-dose and 12 hrs
Clinician Erythema Assessment (CEA)	X	X	Pre-dose, 3, 6, 9, and 12 hrs (± 30 minutes at each timepoint)		Pre-dose, 3, 6, 9, and 12 hrs (± 30 minutes at each timepoint)
Subject Self-Assessment (SSA) for rosacea facial redness	X	X	Pre-dose, 3, 6, 9, and 12 hrs (± 30 minutes at each timepoint)		Pre-dose, 3, 6, 9, and 12 hrs (± 30 minutes at each timepoint)
Physical examination	X				X
Review of Inclusion/Exclusion	X	X	Pre-dose (confirm eligibility)		
Randomization			X		
Dispense study medication tube			X		
Dosing (Days 1-29)[b]			X		X
Adverse event monitoring[c]	X	X	X	X	X
Subject diary review			X		X
Confinement in study clinic			≥12 hrs in clinic		≥12 hrs in clinic
Collection of study medication tube					X

[a] 14 days after the first dose of study drug, a phone call will be made to follow-up on any changes in concomitant medications and check on compliance of study medication usage.

[b] Subject will apply study medication once daily preferably at the same time each day from Day 2 to Day 28 at home, as instructed.

[c] Including monitoring of application site dermatitis, application site pruritus, application site erythema, and application site pain, scaling or burning at Visit 2 and Visit 4.

11.2 Code Fragments

Therapeutic equivalence analysis in the primary endpoint

```
proc freq data=<dataset>
    tables <treatment>*<success> / riskdiffc;
run;
```

Note: this analysis needs to be performed on a dataset containing test and reference treatment subjects only.

Superiority analysis in the primary endpoint

```
ods output ExactTests=ExactTests;
proc logistic data=<dataset>;
  class <treatment> / param=ref;
  model <success> = <treatment>;
  strata <pooled site>;
  exact <treatment>;
run;
```

Note: p-value from exact CMH test is found in ExactTests dataset, variable ExactPValue.
Reference for exact CMH test: http://support.sas.com/kb/32/711.html.
This analysis needs to be performed separately for test and reference treatments on a dataset containing only test and placebo or reference and placebo treatment subjects.