A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER STUDY TO DEMONSTRATE THE SAFETY AND BIOEQUIVALENCE OF PERRIGO UK FINCO'S AZELASTINE HYDROCHLORIDE/FLUTICASONE PROPIONATE NASAL SPRAY 137MCG/50MCG PER ACTUATION COMPARED WITH MEDA PHARMACEUTICALS INC.'S DYMISTA® (AZELASTINE HYDROCHLORIDE/FLUTICASONE PROPIONATE) NASAL SPRAY 137MCG/50MCG PER ACTUATION IN THE RELIEF OF SEASONAL ALLERGIC RHINITIS (SAR) SYMPTOMS

NCT02230696

09-02-2014

Protocol/CIP No. PRG-NY-14-018

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER STUDY TO DEMONSTRATE THE SAFETY AND BIOEQUIVALENCE OF PERRIGO UK FINCO'S AZELASTINE HYDROCHLORIDE/FLUTICASONE PROPIONATE NASAL SPRAY 137MCG/50MCG PER ACTUATION COMPARED WITH MEDA PHARMACEUTICALS INC.'S DYMISTA® (AZELASTINE HYDROCHLORIDE/FLUTICASONE PROPIONATE) NASAL SPRAY 137MCG/50MCG PER ACTUATION IN THE RELIEF OF SEASONAL ALLERGIC RHINITIS (SAR) SYMPTOMS.

[redacted]

[redacted]

[redacted]

Table of Contents

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

AE(s)	Adverse event(s)
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Confidence interval
CIP	Clinical investigation plan
cm	Centimeters
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical Study Report
ENR	Enrolled
FDA	Food and Drug Administration
H_0	Null hypotheses
H_1	Alternative hypotheses
ICF	Informed consent form
IRAE	Immediately reportable adverse events
iTNSS	instantaneous Total Nasal Symptom Score
ITT	Intent-to-Treat
kg	Kilogram
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent-to-Treat
N	Number of subjects
NDA	New Drug Application
PP	Per-Protocol
PT	Preferred term
rTNSS	reflective Total Nasal Symptom Score
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Seasonal allergic rhinitis
SAS®	Statistical analysis software
SD	Standard Deviation
SOC	System organ class
SOP	Standard operating procedures
TCR	Theorem Clinical Research
TEAE	Treatment emergent adverse event
TNSS	Total Nasal Symptom Score

WHO	World Health Organization
UNIX	UNiplexed Information and Computing Service

2 INTRODUCTION

[redacted]

exposure.

This statistical analysis plan (SAP) describes the planned analyses to be included in the Clinical Study Report (CSR) PRG-NY-14-018 [redacted]

3 STUDY OBJECTIVES

The objectives of this study are:

1) To compare safety and efficacy profile of Perrigo UK FINCO's Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation, with Meda Pharmaceuticals Inc.'s Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray, 137mcg/50mcg per actuation.

2) To demonstrate the bioequivalence of Perrigo UK FINCO's Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation, to Meda Pharmaceuticals Inc.'s Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray, 137mcg/50mcg per actuation.

3) To demonstrate the superiority of efficacy of Perrigo UK FINCO's Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation, and Meda Pharmaceuticals Inc.'s Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray, 137mcg/50mcg per actuation over Perrigo UK FINCO's Placebo Nasal Spray.

4 STUDY DESIGN

4.1 General Design

This is a multi-center, double-blind, randomized, placebo-controlled, parallel-group study to be conducted in subjects with seasonal allergic rhinitis (SAR). The study will be performed [redacted] with [redacted] randomized subjects, to complete at least [redacted] per-protocol (PP) subjects. [redacted]

[redacted] eligible subjects will be randomly assigned [redacted] to the Test Product, Reference Product, or Placebo Product respectively:

1) Test Product: Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation - Perrigo UK FINCO

2) Reference Product: Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray 137mcg/50mcg per actuation - Meda Pharmaceuticals Inc.

3) Placebo: Placebo Nasal Spray - Perrigo UK FINCO

For the Treatment Period, subjects will be given the randomly assigned treatment nasal spray to be used twice daily for 14 days.

Subjects can be male or non-pregnant/nursing females, aged between 12 and 65 years (both inclusive). Subjects must have a history [redacted] of seasonal allergy to at least one allergen [redacted] known to be present during the study season. All subjects must have a qualifying rTNSS at both Screening Visit (a 12-hour reflective TNSS score [redacted] and Randomization Visit (mean baseline rTNSS value [redacted]

The visits to study site are scheduled at Screening (Visit 1, Day -7), Randomization and Onset of Action Evaluation (Visit 2, Day 1), Interim Visit for Compliance Monitoring (Visit 3, Day 7) and End of Treatment Period and Study Participation (Visit 4, Day 15).

4.2 Discussion of Study Design

This study is designed to compare the safety and efficacy profile of Test Product to Reference Product, to demonstrate the bioequivalence of Test Product to Reference Product, and to demonstrate the superiority of efficacy of the two active treatments (Test and Reference Products) over Placebo. This study has the following design characteristics:

- [redacted].
- Randomized: This is done in order to eliminate the allocation bias and balancing both known and unknown prognostic factors, in the assignment of treatments.
- Placebo controlled: This study involves a Placebo group that will be used to demonstrate the superiority of the test and reference product.
- Double-blind Treatment Period: This part of the study is designed as a double blind trial to facilitate blinding of the identity of treatments from investigators, participants, and assessors. This attempts to eliminate subjective, unrecognized biases carried by subjects and investigators.
- Parallel group: This is a parallel group study in which subjects are to be randomized either to Test Product or Reference Product or Placebo.
- Multi-center: This is designed as a multi-center study, in order to recruit the necessary number of subjects in a shorter timeframe. A multi-center trial is more likely to provide more representative results.
- Bioequivalence: This is designed as a bioequivalence study in order to demonstrate that the effect of the Test Product is similar to that of the Reference Product in the treatment of subjects with seasonal allergic rhinitis (SAR).
- Superiority: To determine adequate study sensitivity, the Test Product and Reference Product should both demonstrate that the treatment's mean change from baseline is statistically significantly greater ($p<0.05$, two-sided) than that of placebo. Hence, this study is designed to demonstrate the superiority of Test Product and Reference Product over Placebo.

4.3 Method of Assignment of Subjects to Treatment Groups

[redacted] eligible subjects will be randomized to the following treatment groups [redacted] (Test: Reference: Placebo) [redacted]

- Test Product: Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation - Perrigo UK FINCO
- Reference Product: Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray 137mcg/50mcg per actuation - Meda Pharmaceuticals Inc.
- Placebo: Placebo Nasal Spray - Perrigo UK FINCO

Randomization will be performed according to a computer generated randomization scheme where a treatment group designation has been assigned to each subjects' randomization bottle number. The treatment designation will remain blinded until the final database is closed. An independent third party will hold the randomization code throughout the study, until authorization is provided by a Perrigo representative to release the randomization schedule.

The block randomization technique will be used for randomization.

4.4 Blinding

This being a double blind study, the investigator and staff at the study site, study monitors, and data analysis/management personnel will be blinded to treatment assignment.

In the event of an emergency, the investigator can unblind specific subjects' treatment by removing the overlay of the blinded label, which is attached to the study medication log; however, every effort will be made to maintain the blind.

The investigator must not scratch off the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency situation only, and should seek prior authorization by the sponsor.

The reason for breaking the blind must be clearly documented in the source documentation and CRF, and the subject will be discontinued from the study. The sponsor must be notified immediately upon all unblinding situations.

4.5 Determination of Sample Size

[redacted]

[redacted]

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

[redacted]

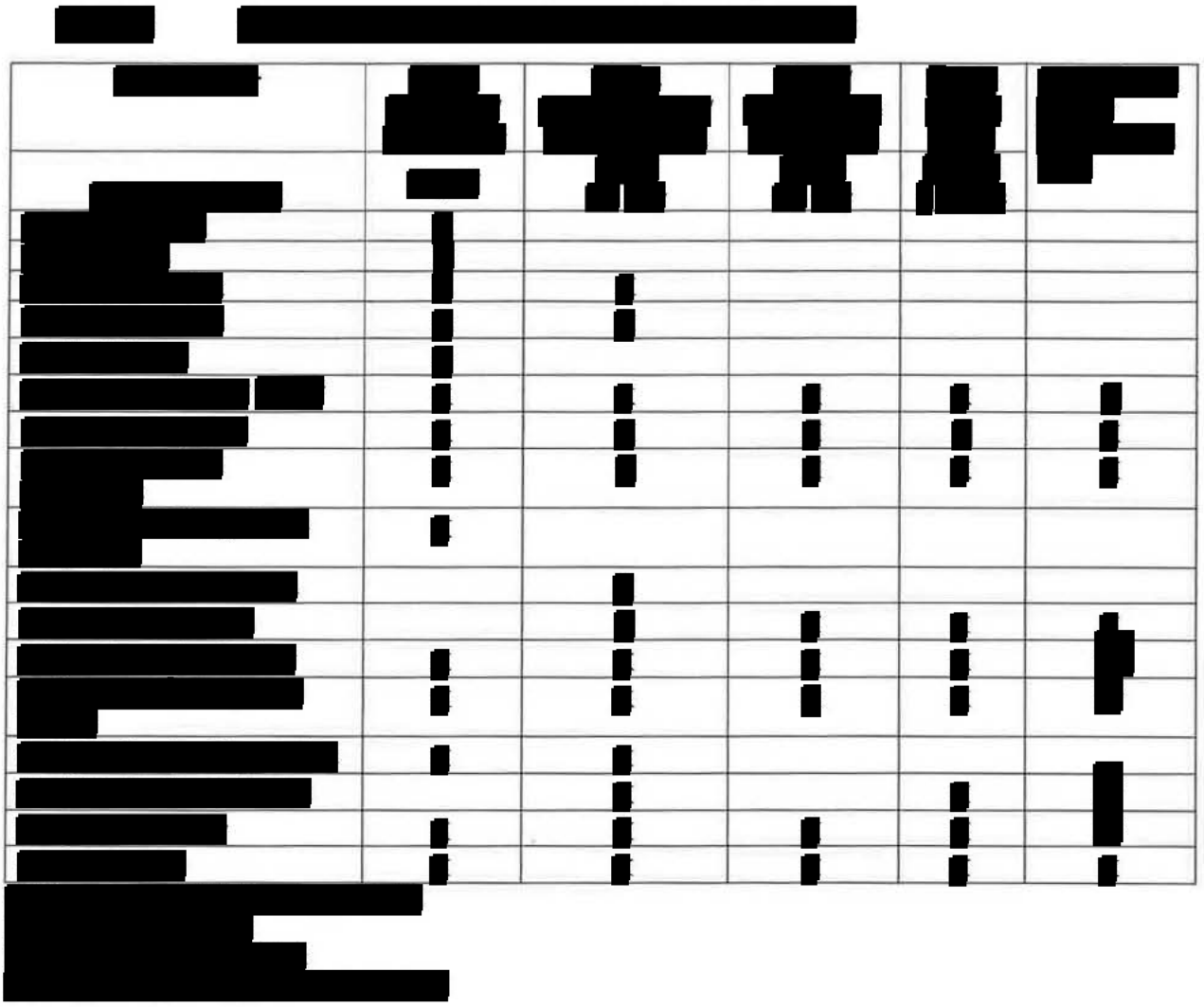
5.2 Changes from the Analyses Planned in the Protocol/CIP

There are no changes from the analyses planned in the protocol at the time of preparing this SAP.

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

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

6.1 Schedule of Evaluations



6.2 Time Point Algorithms

6.2.1 Relative Day

The date of first dose of study medication during treatment phase will be considered relative day 1, and the day before the first dose of study medication during the treatment phase will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

Relative day =
- Date of Assessment – Date of First Dose of Study Medication + 1. *For assessment on or after the first dose of study medication*
- Date of Assessment – Date of First Dose of Study Medication. *For assessment before the first dose of study medication*

6.2.2 Windows

The visits to study sites will be scheduled as per the following visit windows:

Table 3: Visit Windows

Visit	Scheduled Study Day
Visit 1 (Day -7)	Day -7
Visit 2 (Day 1)	Day 1
Visit 3 (Day 7)	Day 7 [redacted]
Visit 4 (Day 15)	Day 15 [redacted]

If a subject arrives on an unscheduled visit, then the assessment procedures will be completed as a scheduled visit.

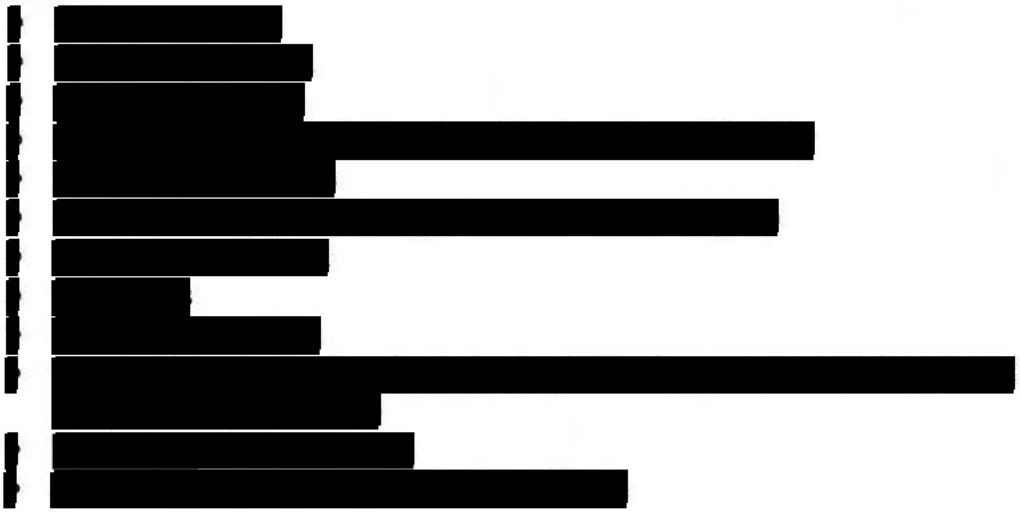
Data will be summarized as per scheduled study visits only. No windowing of visits will be performed for data analysis.

[redacted] The phases are defined as follows:

- [redacted] Day -7 to Day -1
- Treatment Phase: Day 1 to Day 15

6.3 Baseline Assessments

Baseline assessments will be the last assessment before the first dose of study medication during treatment phase. The following baseline information/assessments will be collected:



6.4 Efficacy Variables

6.4.3 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from baseline in reflective Total Nasal Symptom Score (rTNSS) during the 14-day treatment phase.

Symptom Scoring

Subjects will record instantaneous [redacted] and reflective [redacted] nasal symptom scores twice daily in the AM immediately before dosing, and approximately 12 hours later in the PM immediately before dosing.

Subjects will report the severity of their symptoms at Visit 1, and record symptom scores (instantaneous and reflective) twice daily thereafter, at about the same time each day in the AM and PM throughout the 3 weeks of the trial.

The symptoms include: nasal congestion/stuffy nose, nasal discharge/runny nose, sneezing, and itchy nose. Each symptom will be scored on the 4 point scale as described in table 4. Total Nasal Symptom Scores (rTNSS, iTNSS) for each assessment will be calculated by totaling these four symptom scores for a maximum score of 12.

Table 4: Symptom Score Description

Score	Assessment	Description
0	Absent	[redacted]
1	Mild	[redacted]
2	Moderate	[redacted]
3	Severe	[redacted]

reflective Total Nasal Symptom Score (rTNSS)

Baseline rTNSS

Baseline values for the individual symptom scores will be calculated. The[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4.4 Secondary Efficacy Endpoints

[redacted]

instantaneous Total Nasal Symptom Score (iTNSS)

The calculations for the "instantaneous" scores will be completed similar to rTNSS computations explained above.

[redacted]

[redacted]

6.5 Safety Assessments

6.5.1 Extent of Exposure and Compliance to Study Treatment

The extent of exposure to study medication will be quantified for the total number of doses administered during the course of the study.

[redacted]

6.5.2 Adverse Events

All adverse events occurring after signing the informed consent are to be recorded on the AE pages of the eCRF. Investigators' verbatim terms of adverse events will be mapped to system organ class and preferred term using MedDRA v 16.0 or higher.

6.5.2.1 Definitions

Adverse event (AE)
An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

Signs and symptoms of seasonal allergic rhinitis will not be considered adverse events, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/subject considers that it is in the subject's best interest to be dropped from continued participation in the study and given alternative therapy for their serious adverse event.

Serious adverse event (SAE)
Any untoward medical occurrence that meets any of the following criteria:

- Results in death
- Life-threatening event
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- Any other adverse events that may be considered serious based upon medical judgment

Immediately reportable adverse events (IRAE)
Immediately reportable adverse events are any AEs that necessitate discontinuation of study medication, including pregnancy.

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

Treatment emergent adverse event (TEAE)
Treatment-emergent adverse events (TEAE) are any AEs that occur or worsen (increase in severity and/or frequency) during or after the first dose of study medication during treatment phase.

For treatment-emergent status regarding events with partial or missing dates, please refer to Section 7.3.

6.5.2.2 Classifications of adverse events assessments

Intensity of adverse events
The maximum intensity of an AE during a day will be recorded on the CRF. If the intensity of an AE changes over a number of days, then separate entries will be made having distinct onset dates for the changes in severity. The intensity of an AE will be graded as follows:

- Mild
- Moderate
- Severe

For AEs with unknown or missing severity, the most severe assessment will be imputed for summary analyses.

Causal Relationship to Study Medication
Causal relationship of AE to study medication will be classified by the Investigator and will be reported as following:

- Definitely related
- Probably related
- Possibly related
- Unlikely related
- Not related

An AE will be considered related to study medication if the relationship is definitely related, probably related or possibly related. Any missing (unknown or missing) causal relationship of an AE to study medication will be summarized as related.

6.5.3 Clinical Laboratory Evaluations – Urine Pregnancy Test

Females of childbearing potential will have a urine pregnancy test at [redacted]

6.5.4 Other Observations Related to Safety

6.5.4.1 Physical Examination

[redacted]

6.5.4.2 Vital Signs

[redacted]

7 STATISTICAL METHODS

7.1 General Methodology

All analyses will be performed after the database is locked and access has been removed from the database and the study treatment codes are unblinded. Summary displays will be presented by treatment group. Subjects will be analyzed as treated.

All statistical tests will be two-sided with a significance level of α=0.05, unless specified otherwise.

[redacted]

7.2 Data Display Treatment and Other Sub-group Descriptors

In the clinical study report data displays, the treatment groups will be identified as follows:

Table 5: Treatment Descriptions

Study Phase	Treatment Group	Descriptor
[redacted]	[redacted]	[redacted]
Treatment Phase	Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation - Perrigo UK FINCO	AZ/FP 137mcg/50mcg – Perrigo
Treatment Phase	Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray 137mcg/50mcg per actuation - Meda Pharmaceuticals Inc.	AZ/FP 137mcg/50mcg – Meda
Treatment Phase	Placebo Nasal Spray - Perrigo UK FINCO	Perrigo UK FINCO Placebo

7.3 Adjustments for Covariates

[redacted]

7.4 Handling of Dropouts or Missing Data

[redacted]

[redacted]

[redacted]

[redacted]:

Table 6: Imputing Partial Start Dates

[redacted]

Once a partial date has been imputed as outlined above, the following will be performed to ensure the imputed dates are logical:

- In the case where an event of death occurs and the imputed date is later than the date of death, the imputed date should be set to date of death.
- If the event of imputed date is later than the date of study discontinuation, the imputed date should be set to date of study discontinuation.

When imputing partial dates of events for which both a start and stop date are collected, compare the start date and stop date following imputation. When the start date is imputed (and the stop date is not imputed) and the imputed start date is after the stop date, the imputed start date will be set to the stop date.

Imputation of start dates will be used in the assessment of treatment-emergent status. Imputation will not be used in the display of dates in data listings.

7.5 Interim Analyses and Data Monitoring

No interim analysis is planned for this study.

7.6 Multi-center Studies and Pooling of Centers

There will be no pooling of sites for this study.

7.7 Multiple Comparisons/Multiplicity

As this is a bioequivalence study for a generic drug product, no adjustment will be done for multiplicity of testing.

7.8 Use of an "Efficacy Subset" of Subjects

[redacted]

7.9 Active-Control Studies Intended to Show Equivalence

The objective of this study is to demonstrate the bioequivalence of Test Product to Reference Product assessed by mean change from baseline values. For the purpose of bioequivalence testing, bioequivalence can be assumed if the 90% confidence interval (CI) of the ratio of the mean change from baseline (Test/Reference) falls within the interval of 0.80 to 1.25.

Prior to testing bioequivalence, the superiority of efficacy of Test Product and Reference Product over Placebo will be demonstrated by comparing the mean change from baseline values of the two active treatments separately against the placebo control. This will be demonstrated if the Active Product's mean change from baseline is statistically significantly greater ($p<0.05$, two-sided) than that of the Placebo.

7.10 Examination of Subgroups

Not applicable to this study.

8 STATISTICAL ANALYSIS

8.1 Disposition of Subjects

The disposition of all subjects who sign an informed consent form (ICF) will be provided.

The frequencies and percentage of subjects randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations, will be summarized by treatment group.

All disposition data will be presented in subject listing.

[redacted].

8.2 Protocol Deviations

Protocol deviations will be evaluated based on the investigators' judgment. In the event of a significant deviation from the protocol due to an emergency, accident or mistake, the investigator must contact Perrigo at the earliest possible time.

Potential deviations will be identified prior to database lock. The total list of all recorded protocol deviations and programmatic deviations, if any, will be provided to the sponsor after database lock.

An overall protocol deviation listing will be reviewed in a blinded fashion just prior to database lock and access has been removed from the database, and deviations will be classified on an ongoing basis in a blinded fashion to determine as a major (violation) or minor classification (deviation).

A subject listing of all protocol deviations will be presented.

8.3 Analysis Populations

Table 7: Population Descriptions

Population	Definition	Displays
[redacted]	[redacted]	[redacted]
Intent-to-Treat (ITT)	Subjects who completed the [redacted] and were randomized into the study medication.	Demographics and baseline characteristics, disposition status, medical history, concomitant medication, major protocol deviations, allergy status, etc., will use this population.
Modified Intent-to-Treat (mITT)	Subjects who were randomized, received and used the study medication, and had at least one post-baseline efficacy assessment.	The bioequivalence and analyses of superiority will use this population.
Per-Protocol (PP)	Subjects who met the following criteria will be considered: • randomized into the study • met randomization inclusion/exclusion criteria • had a positive skin test, for the appropriate allergen • met the protocol criteria [redacted] • had not taken any concomitant medications prohibited by the protocol • had [redacted] reflective symptom scores from which the mean baseline rTNSS value and each mean baseline symptom score were calculated prior to randomization • had recorded [redacted] reflective symptom scores during the 14-day Treatment Period, OR was discontinued early due to treatment failure. • had no significant protocol violations that	The bioequivalence and analyses of superiority will use this population.

	could have interfered with the effect of the treatment or the precise evaluation of treatment efficacy.	

8.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using Intent-to-Treat (ITT) Population by treatment groups. Baseline characteristics will be summarized and presented as follows; if any differences arise then sensitivity/subgroup analyses will be conducted.

Age (years), height (cm), body weight (kg), body mass index (BMI) in kg/m^2, negative control measurement (mm), and wheal measurement (mm) will be summarized using descriptive statistics, and gender, race, ethnicity, allergy test conducted, allergens, suffered from at least one allergen for at least two previous seasons, and positive skin result will be summarized using frequencies and percentages.

Baseline comparability among the three treatment groups with respect to demographic and other baseline characteristics (age, gender, race, ethnicity, height, weight, BMI) will be assessed for quantitative variables with a two-way analysis of variance (ANOVA) using treatment group and center as fixed effects. For categorical variables the analysis will be conducted using the Cochran-Mantel-Haenszel (CMH) test for general association adjusted for center.

Birth control methods will not be summarized. A separate listing will be presented.

Medical history terms will be coded using MedDRA v 16.0 or higher to the preferred term (PT) and system organ class (SOC). Medical history will be summarized by frequencies and percentages of subjects by SOC and PT, within SOC and PT sorted by descending frequencies. Subjects with multiple events for the same SOC or PT will be counted only once for that SOC or PT.

[redacted]

All demographic and baseline characteristics described within this section will be presented in subject listings.

8.5 Prior and Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by Preferred Name and WHO anatomical therapeutic chemical (ATC) classification of ingredients.

Prior medications are defined as any medication given prior to and stopped before the first dose during [redacted] Concomitant medications are defined as any medication given to the subject starting on or after the day of first dose during the [redacted] or started prior to the first dose during the [redacted] and continuing during the study.

If the start date of medication is unknown and the end date is known, then the medication will be considered:

- Prior to study medication if the end date is prior to the first dose during the [redacted] of the study medication
- Concomitant to study medication if the end date is either on or after the first dose during [redacted] or the end date is unknown.

If both the start and end dates are unknown, then the medication will be considered to be "concomitant on-treatment". The partial and completely missing dates for prior and concomitant medications will be imputed as mentioned in section 7.3.

Prior and concomitant medications will be summarized by frequencies and percentages of subjects by preferred name within each ATC, with ATC and preferred names sorted by descending frequency.

ATC classification level 4 will be used in summary tables and listings. If ATC classification level 4 is missing then ATC classification level 3 will be used; if ATC classification level 3 is missing, then ATC classification level 2 will be used; if ATC classification level 2 is missing, then ATC classification level 1 will be used.

The prior and concomitant medications used will be presented in a subject listing.

8.6 Analysis of Efficacy Parameters

8.6.1 Analysis of Primary Efficacy Variable

8.6.1.1 Bioequivalence Testing of Mean Change from Baseline in Mean rTNSS between Test and Reference Product

The primary efficacy analysis is performed to demonstrate that Azelastine Hydrochloride/ Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation - Perrigo UK FINCO (Test) is bio-equivalent to Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray 137mcg/50mcg per actuation - Meda Pharmaceuticals Inc. (Reference).

The hypothesis to test the equivalence of Test Product to Reference Product will be:

H_0 (null hypothesis): $\mu_T / \mu_R < 0.80$ or $\mu_T / \mu_R > 1.25$

versus

H_1 (alternative hypothesis): $0.80 \leq \mu_T / \mu_R \leq 1.25$

Where, μ_T: The adjusted mean change from baseline in rTNSS of Test Product.

μ_R: The adjusted mean change from baseline in rTNSS of Reference Product.

The Test Product will be considered as therapeutically equivalent to the Reference Product if the 90% confidence interval (CI) for the ratio of the mean change from baseline (Test/Reference) falls within the interval of 0.80 to 1.25 using two one-sided tests.

[redacted]

A subject listing of individual and mean symptom scores, and overall rTNSS will be presented.

8.6.1.2 Superiority Testing of Mean Change from Baseline in Mean rTNSS of Active Products over Placebo

The test for superiority will be performed to show each of the active products i.e. Azelastine Hydrochloride/ Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation - Perrigo UK FINCO and Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray 137mcg/50mcg per actuation - Meda Pharmaceuticals Inc. is superior in efficacy over Placebo.

The hypothesis to test superiority of two Active Products over Placebo will be:

$$H_{0t}: \mu_T \leq \mu_P \text{ vs } H_{1t}: \mu_T > \mu_P$$
$$H_{0r}: \mu_R \leq \mu_P \text{ vs } H_{1r}: \mu_R > \mu_P$$

Where, H_{0t}: Null hypothesis for the Test Product
H_{1t}: Alternative hypothesis for Test Product
H_{0r}: Null hypothesis for the Reference Product
H_{1r}: Alternative hypothesis for Reference Product
μ_T: The adjusted mean change from baseline in rTNSS of Test Product
μ_R: The adjusted mean change from baseline in rTNSS of Reference Product
μ_P: The adjusted mean change from baseline in rTNSS of Placebo

[redacted]

[redacted]

[redacted].

8.6.2 Analysis of Secondary Efficacy Variables

8.6.2.1 Mean Change from Baseline in Mean iTNSS

The mean change from baseline in mean iTNSS value of Test product, Reference Product and Placebo will be analyzed using Analysis of Covariance (ANCOVA) with treatment and center as fixed effect and baseline iTNSS as covariate in the model. The 90% confidence interval for ratio (Test/Reference) of mean change from baseline in iTNSS scores over the 14 day treatment period will be calculated as described in the primary efficacy analysis.

The adjusted mean change from baseline of Test Product, Reference Product, and Placebo and their associated 95% confidence intervals will also be presented.

The statistical significance (p-value) of the mean change from baseline of Test Product vs Placebo and Reference Product vs Placebo will be determined. The difference in adjusted mean change from baseline, the adjusted mean change from baseline for each product, and the associated 95% CIs will also be presented.

[redacted]

A subject listing of individual and mean symptom scores and overall iTNSS will be presented.

[redacted]

[redacted]

[redacted]

[redacted]

8.6.3 Subgroup Analyses

No subgroup analyses of efficacy data are planned.

8.6.4 Exploratory Analyses

No exploratory analyses of efficacy data are planned.

8.7 Analysis of Safety

All safety analyses will be performed using the ITT population and will be summarized by treatment groups.

8.7.1 Extent of Exposure and Compliance to Study Treatment

8.7.1.1 Extent of Exposure

Total number of doses taken during [redacted] and Treatment Phase will be summarized descriptively.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.7.2 Adverse Events

All AE summary tables will include only TEAEs unless otherwise noted.

Adverse events will be summarized by system organ class and preferred term. A subject will only be counted once per system organ class and preferred term. AE's will also be presented by severity grades. In the case of multiple experiences with the same AE, the subject will be counted only once under the worst reported severity.

Adverse events will be presented in decreasing order of the incidences at SOC level and within each SOC, in decreasing order of the incidences at the preferred term level.

Should sufficient data exist, adverse event frequencies will be compared between treatments using Fisher's Exact test.

An overall summary of adverse events will be presented and will include:

- at least one TEAE
- any severe TEAE
- any treatment related TEAE
- any serious TEAE
- any serious related TEAE
- any TEAE resulting in death
- any TEAE resulting in study medication interruption/discontinuation
- any immediately reportable adverse events (IRAE)
- any unexpected adverse event

The subjects' frequencies and percentages will be presented by system organ class and preferred term for the following:

- All TEAEs
- TEAEs by severity
- Related TEAEs
- TEAEs leading to study medication interruption/discontinuation
- Related TEAEs leading to study medication interruption/discontinuation
- Serious TEAEs

- Serious related TEAEs
- Immediately reportable adverse events (IRAE)
- Unexpected adverse events

The overall event counts will also be presented for the above mentioned adverse event parameters.

The following subject listings will be presented:

- all AEs
- SAEs
- AEs leading to study medication interruption/discontinuation
- AEs leading to death
- non-TEAEs

8.7.3 Clinical Laboratory Evaluations – Urine Pregnancy Test

Females of childbearing potential will have a urine pregnancy test at Screening (Visit 1), Day 1 (Visit 2), Day 7 (Visit 3) and End of Study (Visit 4). The results will be displayed in a subject listing.

8.7.4 Other Observations Related to Safety

8.7.4.1 Physical Examination

The physical examination includes ENT, head, eyes, and lungs valuation, and will be performed at Screening (Visit 1), Day 1 (Visit 2), Day 7 (Visit 3) and End of Study (Visit 4).

The Physical examination parameters will be summarized by frequency counts and percentages for abnormalities.

A subject listing will be presented which will include:

- Whether physical examination was performed? (Yes/No)
- Were there any abnormal findings? (Normal/Abnormal)

8.7.4.2 Vital Signs

The vital signs assessment will be performed at Screening (Visit 1), Day 1 (Visit 2), Day 7 (Visit 3) and End of Study (Visit 4).The following parameters will be summarized descriptively by Visit:

- Blood pressure
- Body temperature

- Heart rate
- Respiratory rate

A subject listing will be presented for all vital signs parameters.

9 COMPUTER SOFTWARE

All analyses will be performed by Theorem Clinical Research using Version 9.2 of SAS® software or higher within a UNiplexed Information and Computing Service (UNIX) environment. All summary tables and data listings will be prepared using SAS® software.

10 REFERENCES

1. Summary Basis of Approval for Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray 137mcg/50mcg per actuation, NDA 202236.
2. Kleinman K. et al. - SAS and R - Data Management, Statistical Analysis and Graphics – 2010
3. Design and Analysis of Bioavailability and Bioequivalence Studies, Third Edition by Shein-Chung Chow, Jen-pei Liu.
4. "Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products," Food and Drug Administration, 2000.

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