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

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

PROTOCOL NUMBER: PRG-NY-14-018

[redacted]

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[redacted]

PROTOCOL SIGNATURE PAGE

PROTOCOL NUMBER: PRG-NY-14-018

PROTOCOL TITLE: 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]

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STUDY SYNOPSIS

Title:	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
Study Period:	Approximately three (3) weeks (21 Days): 1 week (7-day) [redacted] 2 weeks (14-days) Treatment Period
Study Medications:	Test Product: Perrigo UK FINCO's Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray 137mcg/50mcg per actuation Reference Product: Meda Pharmaceuticals Inc.'s Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray 137mcg/50mcg per actuation Placebo: Placebo Nasal Spray
Study Objectives:	To compare safety and efficacy of Perrigo UK FINCO's Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray compared with Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray in the treatment of subjects with seasonal allergic rhinitis, and to demonstrate the bioequivalence of the test product to the reference product as well as the superiority of the two active treatments over placebo.
Study Design:	This is a randomized, double-blind, placebo-controlled, parallel-group study to be performed [redacted] randomized subjects, to complete [redacted] per-protocol (PP) subjects. Enrollment will continue until the number of PP subjects has been obtained. [redacted] qualified subjects will be randomly assigned [redacted] to the Test Product, Reference Product, or Placebo for a 2 week (14-day), twice-daily treatment regimen (Treatment Period). Subjects will visit the study center according to the following schedule: Visit 1/Day -7 prior to randomization (Screening) Visit 2/Day 1 [redacted] (Randomization and Onset of Action Evaluation) Visit 3/Day 7 [redacted] (Interim Visit for Compliance Monitoring) Visit 4/Day 15 [redacted] (End of Treatment Period and Study Participation) At Visit 1, potential subjects will be screened to ensure they meet all

[redacted]

	inclusion/exclusion criteria. [redacted] subjects will be given a [redacted] nasal spray bottle and instructed to use the product twice daily (AM and PM, approximately 12 hours apart and around the same times each day [redacted] for the 1 week (7 day) [redacted]. 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. Nasal symptom scores and dosing should be performed at about the same times each day in the AM and PM during the course of the [redacted] beginning from Day -7 (Screening). The four symptoms to be assessed are nasal congestion/stuffy nose, nasal discharge/runny nose, sneezing and itchy nose [redacted] These scores will be used to calculate instantaneous (iTNSS) and reflective (rTNSS) Total Nasal Symptom Scores. [redacted] [redacted] At Visit 2/ Day 1 (± 1 day) (Randomization [redacted]), subjects will return to the study center, return their medication bottle, and their diary data will be evaluated to establish baseline symptom scores. [redacted] The subject-assessed scores recorded twice daily during the 14-day Treatment Period will be used to evaluate treatment efficacy. Adverse event experiences will be used to evaluate treatment safety.

[redacted]

[redacted]

	[redacted] At Visit 3/Day 7 (± 1 days) (Interim Visit for Compliance Monitoring), subjects will return to the study center, [redacted] have the diary entries collected, reviewed for completeness, and evaluated for proper compliance. They will then take home the rest of their diary pages to record symptoms from days 8-15. At Visit 4/Day 15 (+ 3 days) (End of Treatment Period and Study Participation) subjects will return to the study center, return their study medication and the rest of their Treatment Period diary pages used to record symptoms from days 8-15, [redacted], and be discharged from the study.
Study Population:	Male and non-pregnant/nursing female subjects, between 12 to 65 years of age. Subjects should have with a documented history [redacted] of seasonal allergy to at least one allergen [redacted] present during the study season AND qualifying rTNSS and nasal congestion score at both Visits 1 and 2.
Dosing & administration:	During both the 7-day [redacted] and the 14-day Treatment Period, subjects will record their AM and PM instantaneous and reflective nasal symptom scores, then administer one spray in each nostril (AM and PM, approximately 12 hours apart and around the same time each day ± 2

[redacted]

[redacted]

	hours). [redacted] At Visits 1 and 2, following training/instruction on the proper use of the nasal spray bottle, eligible subjects will administer the first AM dose while at the study center in the presence of study staff to ensure that the subject understands proper administration technique.
Study Visits:	Subjects will return to the study center at the following points: 1. Visit 1/Day -7 prior to randomization (Screening) 2. Visit 2/Day 1 [redacted] (Randomization and Onset of Action Evaluation) 3. Visit 3/Day 7 [redacted] (Interim Visit for Compliance Monitoring) 4. Visit 4/Day 15 [redacted] (End of Treatment Period and Study Participation)
Evaluations:	The following evaluations will be performed by either study staff or the subject throughout the study: • Eligibility for entry into the study will be based primarily on history of seasonal allergic rhinitis [redacted] in conjunction with the current symptoms of SAR. • [redacted] • Study subjects will record severity of symptoms twice daily immediately prior to dosing (AM and PM, approximately 12 hours apart and around the same times [redacted]) throughout the 7-day [redacted] and the 14-day Treatment Period. Two assessments will be made at each time point: instantaneous and reflective. Four symptoms (nasal congestion/stuffy nose, nasal discharge/runny nose, sneezing, and itchy nose) will be assigned a score of 0, 1, 2, or 3 where 0 = none (no symptoms present) and 3 = severe (symptoms which are bothersome and interfere with activity OR nighttime sleep). • [redacted]

[redacted]

[redacted]

	[redacted] • Safety will be evaluated based on spontaneous and elicited reports of adverse events.
Endpoints:	The primary efficacy parameter is the mean change from baseline of the subject-reported mean rTNSS scores calculated over the entire 14-day Treatment Period. The secondary efficacy endpoints are: • Mean change from baseline for the iTNSS for the entire 14-day Treatment Period. • [redacted] The baseline value for each symptom and for each summary measure (i.e. iTNSS and rTNSS) will be calculated as the sum of the symptom/measure scores from the last 3 days before Visit 2/Day 1 (Randomization) and the AM score of the symptoms assessments recorded in the morning of Visit 2/Day 1 (Randomization) during the [redacted] prior to initial dosing at Visit 2/Day 1 (Randomization), divided by the total number of scores included in the sum. rTNSS and iTNSS scores obtained during the 14-day Treatment Period will include the PM score on Day 1, and the 26 AM and PM scores on Days 2 to 14 (total of 27 scores) and will be used to evaluate treatment efficacy.
Safety:	Adverse events will be classified using standard MedDRA terminology Version 16.0 or above, and summarized by treatment group. Summary tables comparing the type, incidence, severity and Investigator's opinion of relationship to the study drug will be prepared by treatment group. [redacted] Should sufficient data exist, adverse event frequencies will be compared

[redacted]

[redacted]

	between treatments using Fisher Exact test or similar. All study subjects who are randomized to the active Treatment Period of the study will be included in the comparative safety analysis. Adverse events and concomitant medication use reported during the [redacted] and the Treatment Period will be tabulated in a summary table listing the type, incidence, severity and Investigator's opinion of relationship to the study drug.

[redacted]

[redacted]

1. BACKGROUND

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2. STUDY OBJECTIVES

The objectives of this study are:

1) To compare safety and efficacy 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, in the treatment of subjects with seasonal allergic rhinitis when used twice daily, one actuation per nostril.
2) To demonstrate the superiority of each of the two active treatments to that of the placebo nasal spray.
3) To demonstrate the bioequivalence of the test product to the reference product.

2.1 Efficacy Endpoints

The primary endpoint is the mean change from baseline in the subject-reported reflective Total Nasal Symptom Score (rTNSS) calculated over the entire 14-day Treatment Period.

The secondary efficacy endpoints are:

- Mean change from baseline for the instantaneous Total Nasal Symptom Scores (iTNSS) for the entire 14-day Treatment Period.
- [redacted]

[redacted]

rTNSS and iTNSS scores obtained during the 14-day Treatment Period will include the PM score on Day 1, and 26 AM and PM scores on Days 2 to 14 (total of 27 scores) and will be used to evaluate treatment efficacy.

2.2 Safety

Comparative safety analysis will be performed on all subjects who are randomized. Safety analysis will be based on reported adverse events. Safety of the test and reference products will be compared by evaluating the nature, severity and frequency of their adverse event profiles as described in section 7. All adverse events that occur during the study will be recorded. Descriptions of reactions or complaints will include the date of onset, the date the adverse event ended, the severity of the adverse event, the relationship to study medication,

[redacted]

and the outcome. Comparisons between the treatment groups will be made by tabulating the frequency of subjects with one or more adverse events (classified into MedDRA terms) during the study. The Fisher's Exact test (or similar) will be used to compare the proportion of subjects in each treatment group who report any adverse event.

Adverse events and concomitant medication use reported during the [redacted] and Treatment Period will be tabulated in a summary table listing the type, incidence, severity, and Investigator's opinion of drug relationship.

[redacted]

3. STUDY DESIGN

3.1 Type/Design of Study

This is a randomized, double-blind, placebo-controlled, parallel-group study to be performed in [redacted] study centers with [redacted] randomized subjects, to complete [redacted] per-protocol (PP) subjects. Enrollment will continue until the number of PP subjects has been obtained. [redacted] qualified subjects will be randomly assigned [redacted] to the Test Product, Reference Product, or Placebo Product respectively for a 14-day, twice daily Treatment Period.

Subjects will visit the study center according to the following schedule:

Visit 1/Day -7 prior to randomization (Screening)
Visit 2/Day 1 [redacted] (Randomization and Onset of Action Evaluation)
Visit 3/Day 7 [redacted] (Interim Visit for Compliance Monitoring)
Visit 4/Day 15 [redacted] (End of Treatment Period and Study Participation)

[redacted].

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. Nasal symptom scores and dosing should be performed at about the same time each day in the AM and PM during the

[redacted]

[redacted]

course of the [redacted] beginning from Day -7 (Screening). The four symptoms to be assessed are nasal congestion/stuffy nose, nasal discharge/runny nose, sneezing, and itchy nose and will be graded on a 4 point scale.

These scores will be used to calculate instantaneous (iTNSS) and reflective (rTNSS) Total Nasal Symptom Scores. The minimum and maximum possible scores per symptom are 0 and 3, respectively, and the total minimum and maximum possible scores are 0 and 12, respectively, when all 4 symptoms are added together.

[redacted]

At Visit 2/Day 1 (± 1 day) (Randomization [redacted]), subjects will return to the study center, return their medication bottle, and their diary data will be evaluated to establish baseline symptom scores. [redacted].

The subject-assessed scores obtained twice daily during the 14-day Treatment Period will be used to evaluate treatment efficacy.

Adverse event experiences will be used to evaluate treatment safety.

[redacted]

[redacted]

[redacted]

[redacted]

At Visit 3/Day 7 (± 1 days) (Interim Visit for Compliance Monitoring), subjects will return to the study center, [redacted], and have the first 7 days of their diary entries collected, reviewed for completeness, and evaluated for proper compliance. They will then take home the rest of their diary pages to record symptoms from days 8-15.

At Visit 4/Day 15 (+ 3 days) (End of Treatment Period and Study Participation), subjects will return to the study center with their study medication and the rest of their diary pages used to record symptoms from days 8-15, [redacted], and be discharged from the study.

3.2 Study Population

Male and non-pregnant/nursing female subjects, between 12 to 65 years of age. Subjects should have a documented history [redacted] of seasonal allergy to at least one allergen [redacted] known to be present during the study season AND qualifying rTNSS and nasal congestion score at both Visits 1 and 2.

4. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1 Inclusion Criteria

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

1. Complete the informed consent process and the subject or parent/legal guardian as appropriate must sign the informed consent form. [redacted].
2. Male or female between 12 to 65 years of age, inclusive.
3. [redacted]

[redacted]

[redacted]

4. Moderate-to-severe rhinitis[redacted]
5. At Screening (Visit 1), subjects should record both the instantaneous and reflective symptom scores on the [redacted] diary in the office before the first nasal application of study medication. [redacted]
6. At Randomization (Visit 2), subjects will be randomized only if:
   - [redacted]
7. Subject must have a history [redacted] of seasonal allergy to at least one allergen known to be present during the study season, [redacted]
8. Subject must be in general good health with no clinically significant disease other than SAR that may interfere with the interpretation of study results, as determined by the Investigator.
9. Subject must be willing and able to understand and comply with the requirements of the study, use the study medication as instructed, diary symptom management, refrain from use of all other SAR medications or antibiotics during the three (3) weeks study period, return for the required Treatment Period visits, comply with therapy prohibitions, and be able to complete the study.
10. [redacted]
11. [redacted]

4.2 Exclusion Criteria

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

[redacted]

[redacted]

1. Female who is pregnant or nursing, who is not using or does not agree to use an acceptable form of contraception during the study, or who intends to become pregnant during the study. If a study subject becomes pregnant or is discovered to be pregnant at any time during the study, she must discontinue treatment immediately, return to the research facility for a safety examination, and be followed through the term or termination of the pregnancy (whether by medical intervention, miscarriage or birth).
2. Subject has a history of hypersensitivity or allergy to Azelastine Hydrochloride and/or Fluticasone Propionate, drugs similar to Azelastine Hydrochloride and/or Fluticasone Propionate or to any of the other medication ingredients.
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. Subject has any condition or abnormality of the upper airway [redacted] that, in the opinion of the Investigator, could interfere with administration of the product, evaluation of the subject's condition, or other aspect of the trial.
8. [redacted].
9. [redacted]
10. [redacted]
11. Subject lacks history of seasonal allergy to at least one allergen known to be present during the study season [redacted].
12. [redacted]
13. [redacted]
14. [redacted]

[redacted]

15. [redacted]

16. [redacted]

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

[redacted]

[redacted]

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

17. Currently receiving or plans to receive Radiation therapy during the study duration.
18. [redacted]
19. [redacted]
20. [redacted]
21. [redacted]
22. [redacted]
23. [redacted]
24. [redacted]
25. [redacted]
26. [redacted]
27. [redacted]
28. Subject has a history of alcoholism, drug abuse, or problems which would likely make him/her unreliable for the study.

[redacted]

At the discretion of the Investigator, subjects with a history of alcoholism, substance abuse or other issues may be enrolled provided the subject has been abstinent (or problems otherwise resolved, as appropriate) for the 24 months (or longer) preceding Visit 1.

29. [redacted]
30. [redacted]
31. Subject has previously enrolled in this study or is enrolled in this study with another participating investigator site.
32. Subject is concurrently participating in another investigational study or using any investigational drug (or biologic) or device within the 30 days prior to Visit 1.
33. [redacted]
34. [redacted]
35. [redacted]
36. [redacted]
37. [redacted]

5. PROCEDURES

5.1 Written Informed Consent

The study personnel will review the IRB approved informed consent/assent form with each subject (and subject's guardian as applicable) and give the subject (and subject's guardian as applicable) an opportunity to have all questions answered before proceeding. The consent form must be signed by each subject and witnessed before the subject is enrolled into the study or study related procedures are performed. If a subject is considered a minor by the state law in which the clinical site is located, the subject must complete the assent process, and sign the appropriate form. A copy of the signed consent/assent will be given to every participant and the original will be maintained with the participant's records.

5.2 Demographics/Medical History

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

[redacted]

5.3 Concurrent & Prohibited Medications

Concurrent medications and any medications taken [redacted] prior to the start of the study will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications to be recorded include prescription (Rx), over-the-counter (OTC) medications, and dietary and herbal supplements. All medications taken on a regular basis, including vitamins, aspirin and acetaminophen, should be recorded prior to commencing the use of the study medication. Any changes in concurrent medications during the study will also be recorded.

Subjects taking any of the prohibited medications in Exclusion Criteria #16 (Section 4.2) may be considered for enrollment provided the medication is stopped based on the withdrawal period(s relative to Visit 1.

5.4 Restrictions During the Study

[redacted]

5.5 Physical Examination

The investigator, sub-investigator or designee will perform a brief physical examination, [redacted]

5.6 Urine Pregnancy Test

[redacted]

5.7 Evaluation of Allergy Status (Diagnosis)

Diagnosis will be made based on both of the criteria below:

[redacted]

[redacted]

1. **History:** A detailed history of each subject's allergic responses, including seasonal (SAR) and Perennial Allergic Rhinitis (PAR), will be obtained. Whenever possible, historical documentation should be kept in the source documents.

[redacted]

5.8 Symptoms Scoring

Subjects will report the severity of their symptoms at Visit 1, and record symptoms scores (instantaneous and reflective) twice daily thereafter, throughout the 3 weeks of the trial.

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

Score	Assessment	Description
0	Absent	No sign/symptom evident
1	Mild	Sign/symptom is noticeable but does not interfere with any activity
2	Moderate	Sign/symptom is slightly bothersome and slightly interferes with activity OR nighttime sleep
3	Severe	Sign/symptom is bothersome and interferes with activity OR nighttime sleep

[redacted]

[redacted]

[redacted]

[redacted]

5.9 Assignment of Subject Number

An independent third-party dispenser should dispense the study medication. The randomization number will correspond to a computer-generated randomization schedule assigning the kit number to one of the three treatment groups. [redacted] Kits are randomly distributed and are not pre-assigned for distribution to subjects.

5.10 Study Medication Use, Subject Instructions and Subject Diary

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] Qualified subjects will be issued the Treatment Period study medication along with a new Treatment Period diary. Items recorded in this diary are similar to the [redacted] diary and include the instantaneous and reflective nasal symptom scores, date/time score is recorded, date/time of dose administration. Subjects should document any changes in health status or concomitant medications taken between Visits 2, 3, and 4. [redacted]

At Visit 3/Day 7 (± 1 days) (Interim Visit for Compliance Monitoring), subjects will return to the study center, [redacted], and have the first 7 days of their Treatment Period diary entries collected, reviewed for completeness, and evaluated for proper compliance.

5.11 Visit Specific Procedures

The following sections outline the procedures required at each visit.

5.11.1 Visit 1/Day -7 (Screening)

[redacted]

[redacted]

5.11.2 Visit 2/Day 1 (± 1 day) (Randomization and Onset of Action Evaluation)

[redacted]

[redacted]

[redacted]

5.11.3 Visit 3/Day 7 (± 1 day) (Interim Visit for Compliance Monitoring)

[redacted]

5.11.4 Visit 4/Day 15 (+ 3 days) (End of Treatment Period and Study Participation)

[redacted]

5.11.5 Unscheduled/ Early Termination Visit

[redacted]

[redacted]

[redacted]

[redacted]

5.12 Pollen counts

[redacted]

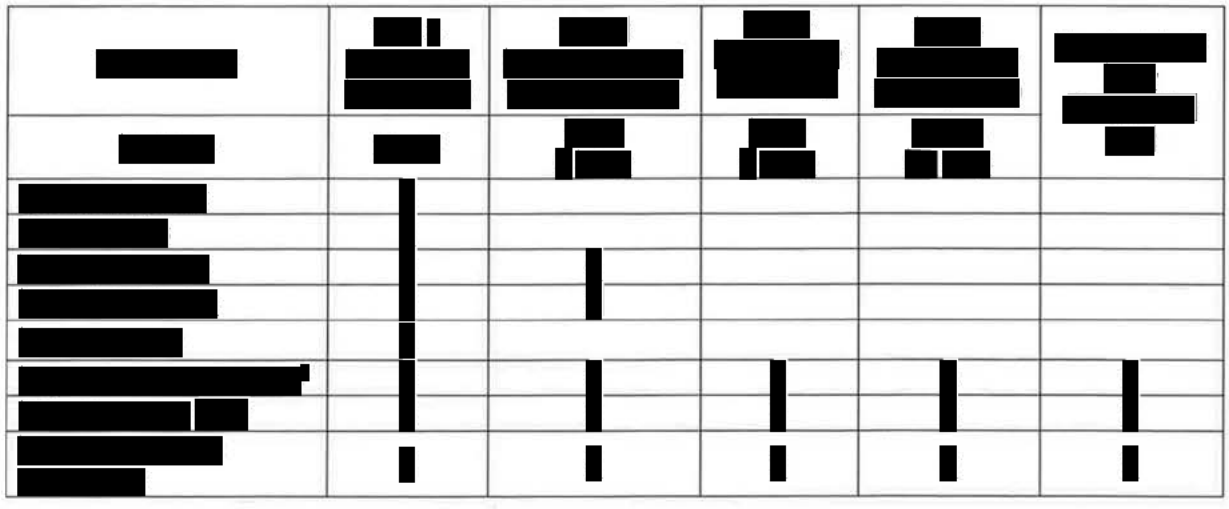
[redacted]

[redacted]

5.13 Summary of Assessments

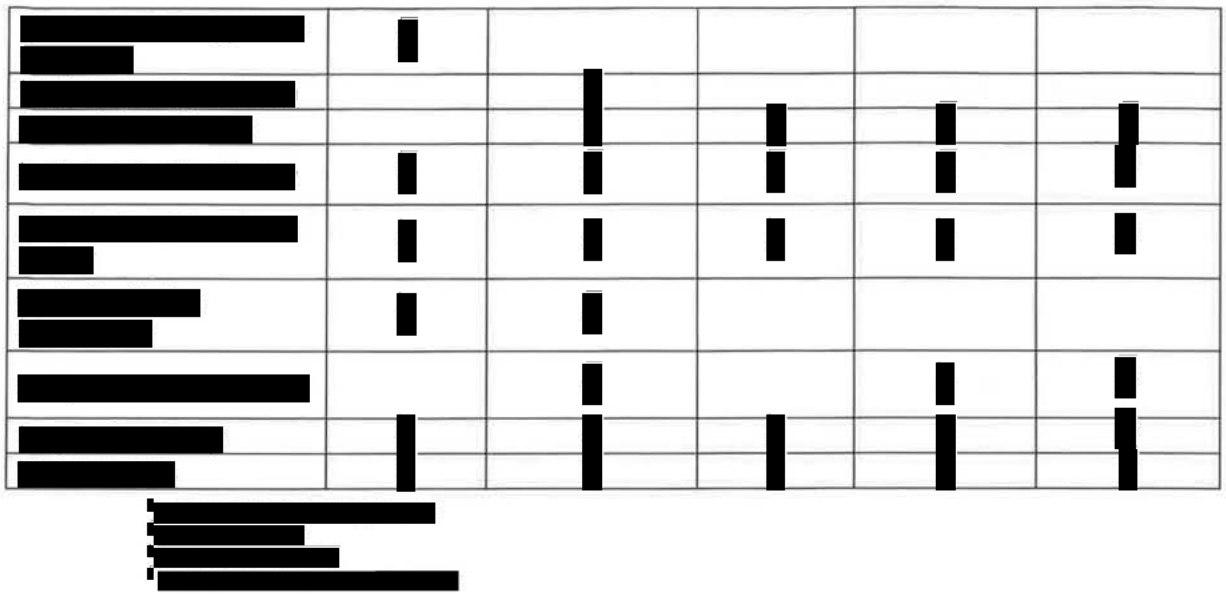
The schedule of visits and procedures to be conducted at each visit are summarized in the Schedule of Study Procedures below.

Schedule of Study Procedures



[redacted]

[redacted]



[redacted]

Screen failures will not be included in any data analyses. A screen failure is a subject who received information about the study, including signing an informed consent, but never administered a dose of the study medication.

5.15 Protocol Deviations and Violations

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.16 Subject/Treatment Compliance

[redacted]

Subjects will administer their assigned study medication twice daily, in the morning (AM) and approximately 12 hours later in the evening (PM), for 14 days during the Treatment Period. The history of administration will be recorded in subjects' diaries. Copies of the diaries will become part of the CRF for the study. The number of total applications will be recorded in the CRF.

[redacted]

[redacted]

5.17 Discontinuation/Withdrawal of Study Subjects

When a subject withdraws prior to completing the study, the primary reason for withdrawal must be documented on the source document and on the eCRF. Subjects may be discontinued from the study for the following reasons:

1. The subject withdraws his or her consent for any reason.
2. The subject's condition has worsened to the degree that the investigator feels it is unsafe for the subject to continue in the study.
3. Subject did not meet entry criteria.
4. The subject's medication code is unblinded.
5. An adverse event occurs for which the subject desires to discontinue treatment or the investigator determines that it is in the subject's best interest to be discontinued.

[redacted]

[redacted]

6. The subject is lost to follow-up. The investigator will document efforts to attempt to reach the subject twice by telephone and will send a certified follow-up letter before considering that subject lost to follow-up. All attempts must be thoroughly recorded.
7. The subject becomes pregnant during the course of the trial.
8. [redacted]
9. [redacted]

In the event that a subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a subject, the Investigator must strive to follow the subject until the adverse event has either resolved (including following a pregnancy to term or termination), becomes clinically insignificant, the event is stabilized, or the subject is lost to follow-up. For any serious adverse event, follow procedures stated in Section 7.3.

If a subject is discontinued from the study for any reason, the Unscheduled/Early Termination Visit procedures should be completed and any outstanding data and study medication should be collected. Data, in addition to the reason for discontinuation and the date of removal, will be recorded.

6. MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by the Sponsor will consist of:

Test Product:	Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray, 137mcg/50mcg per actuation Perrigo UK FINCO Limited Partnership [redacted]
Reference Product:	Dymista® (Azelastine Hydrochloride/Fluticasone Propionate) Nasal Spray 137mcg/50mcg per actuation Meda Pharmaceuticals Inc. [redacted]
Placebo:	Placebo (of the Test product) Nasal Spray Perrigo UK FINCO Limited Partnership [redacted]

[redacted]

[redacted]

[redacted]

6.2 Drug Management

6.2.1 Labeling, Packaging and Distribution

Study medications will be supplied in [redacted] bottles by the Sponsor. The original labels on the bottle will be masked with an opaque label for blinding purposes. Study staff at each site will be trained in practices that will minimize any opportunity for the Investigator/Sub-investigator to become unblinded. In order to nullify any remaining differences in product packaging and to maintain investigator blinding, the Principal Investigator/Sub-Investigator performing the subject clinical evaluations will not be involved with the dispensing or return of study medication. The integrity of the blinded label portion identifying the product will be checked at each visit by study staff and by study monitors during their visits.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.2 Retention Samples

Each investigational site where [redacted] medication and Treatment Period study medication is dispensed to at least one subject will be required to randomly select [redacted] As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with the product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Retain samples shall be stored for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used." The investigator will store the retain sample study medication until such time as notification is received from Perrigo the samples are no longer required. [redacted]

6.2.3 Storage and Test Article Accountability

Study medication will be maintained under adequate security by the investigator. Study medication will be stored upright, with the dust cap in place, at USP controlled room temperature 20°C-25°C (68°F-77°F), and, protected from light in a secured area. Do not store in the freezer or refrigerator. The investigator will not supply study test articles to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

The clinic personnel will keep a current inventory of study test articles dispensed that will include subject numbers assigned and the date each is dispensed and used. At the conclusion of the study all unused, partially used, and empty bottles must be inventoried by the monitor and returned to Perrigo for destruction.

In the event the retained samples must be moved from the study center, the Investigator must provide the Sponsor with written notification of the transfer of the samples and include all relevant contact information regarding the new storage location.

6.2.4 Randomization

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

[redacted]

[redacted]

6.2.5 Procedure for Breaking the Blind

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

7. ADVERSE REACTIONS

The potential adverse reactions of generic Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray 137mcg/50mcg per actuation are anticipated to be similar to those observed in Dymista® (Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray 137mcg/50mcg per actuation). Adverse reactions related to treatment with Dymista® include somnolence, local nasal effects (epistaxis, nasal ulceration, nasal septal perforation, impaired wound healing, Candida albicans infection), cataracts and glaucoma, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis effects (weakness, fatigue, nausea, vomiting, hypotension, growth reduction). More common adverse reactions include headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory infection, pharyngitis, pain, and diarrhea.

7.1 Definitions

Adverse Event (AE)

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

Serious Adverse Event (SAE)

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

- Death;
- Life-threatening event (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death;
- Requires in-subject hospitalization or prolongs hospitalization;

[redacted]

[redacted]

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Congenital anomaly/birth defect; or
- Other adverse events that may be considered serious based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, e.g. allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Immediately Reportable Adverse Events (IRAE)

Any serious AE or any AE that necessitates discontinuation of study medication, including pregnancy.

Unexpected Adverse Event

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

Intensity of Adverse Events

The maximum intensity of an AE during a day should be recorded on the source document/CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates for the changes in severity.

Mild	AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.
Moderate	AEs typically introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
Severe	AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Causal Relationship to Study Medication

The following criteria should be used in assessing the apparent causal relationship of an AE to study medication.

Definite	• Follows a reasonable temporal sequence from study medication administration; • Abates upon discontinuation of the study medication (dechallenge); • Is confirmed by reappearance of the reaction on repeat exposure.
Probable	• Follows a reasonable temporal sequence from study medication administration; • Abates upon discontinuation of the study medication (dechallenge);

[redacted]

[redacted]

	• Cannot be reasonably explained by the known characteristics of the subject's state.
Possible	• Follows a reasonable temporal sequence from study medication administration; • But that could readily be produced by a number of other factors.
Unlikely	• Follows a reasonable temporal sequence from study medication administration; • Could have been produced by either the subject's clinical state or by study medication administration.
Not related	• Does not have a reasonable temporal association with the administration of study medication; • Has some other obvious explanation for the event.

7.2 Eliciting and Reporting of Adverse Events

The investigator will periodically assess subjects for the occurrence of adverse events. In order to avoid bias in eliciting adverse events, the subject or parent/legally authorized representative should be asked a non-specific question (e.g., "How have you been feeling since your last visit?") to assess whether any AE has been experienced since the last assessment. All adverse events (as defined in section 7.2), either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported and documented in the source and the study reporting forms. When reporting an adverse event, the Investigator must assign a severity/intensity of Adverse Events (as defined in section 7.2 of the protocol) to each event and declare an opinion on the relatedness/causal relationship of the event to the study medication or procedure. Serious adverse events must be reported to Perrigo **within 24 hours** of when the Investigator first learns of the occurrence of the event.

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

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

7.3 Expedited Reporting Responsibilities of the Study Center

For any serious adverse event, the sponsor must be notified ***within 24 hours*** of when the Investigator first learns of the occurrence of the event. Expedited reporting requirements for

[redacted]

[redacted]

serious adverse events are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to the sponsor. The adverse event term on the AE source document/case report form and the SAE report should agree exactly. Special attention should be given to recording hospitalizations and concomitant medications.

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

When reporting a serious adverse event (SAE) the Investigator (or the Study Coordinator) will promptly report any serious adverse event or pregnancy by telephone to sponsor representative immediately after the investigator becomes aware of the event.

[redacted]

An SAE form should be completed and sent by fax, email, or overnight courier to the sponsor within 24 hours of knowledge of the event by the site. In many cases, only preliminary information will be available. Appropriate follow up information should be sought (e.g. hospital discharge summaries, operative reports etc.) and a follow up SAE report form submitted. A designation of causality from the study medication should always be included with a follow up report. Assess and report the causality of the event.

7.4 Submitting an Expedited Safety Report to the IRB

Upon notification of an SAE by [redacted] the Clinical Affairs Project Manager at Perrigo will notify Perrigo's pharmacovigilance group of the received information.

[redacted] will report the SAE to the appropriate IRB in accordance with the applicable SOP and regulatory requirements.

[redacted]

[redacted]

7.5 SAE & AEs Requiring Discontinuation of Study Drug, Including Pregnancies

Any SAE, which occurs after a subject has entered the study, whether or not related to study medication, must be reported to Perrigo IMMEDIATELY (WITHIN 24 HOURS) VIA TELEPHONE OR FACSIMILE.

Non-serious events that require discontinuation of study medication (including laboratory abnormalities) should be reported to the sponsor immediately and within 3 working days.

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

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

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

[redacted]

7.6 Pregnancy

At the time a Principal Investigator or site personnel becomes aware that a study participant became pregnant following study participation, the Principal Investigator or designee will report the pregnancy immediately by phone and by faxing a completed Pregnancy Report to Sponsor within one working day of being notified of the pregnancy report.

The report will include the following elements:

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

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

[redacted]

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

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

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

If CRO's responsibilities for the trial are completed before the outcome of the pregnancy is known, the sponsor will assume the responsibility for following up on the pregnancy.

7.7 Post Study Adverse Events

7.7.1 Non-serious Adverse Events

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE source document/case report form (CRF) with the status of the AE noted.

7.7.2 Serious Adverse Events

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

7.8 Adverse Event Follow-up

Subjects experiencing adverse events will be followed up until the events have resolved.

[redacted]

8. STATISTICAL ANALYSIS

The sections that follow highlight sample size determination and the planned analyses for this study. The objectives of this study are to establish comparable safety and efficacy of the Test and Reference treatments, to show that both active treatments have superior efficacy over that of the Placebo, and to demonstrate the bioequivalence of the test product to the reference product.

8.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be prepared separately from this protocol which gives descriptions of the statistical methods, models, hypotheses and subject populations to be analyzed. The SAP will be completed and approved before locking the database and unblinding the study and will serve as a companion to the protocol and the *de facto* documentation of the proposed statistical evaluation. The SAP will be completed and finalized prior to breaking the blind.

8.2 General Considerations

Statistical analyses will be conducted by the Sponsor or its designee. The mITT and PP populations will be used in the analysis of efficacy endpoints and the safety population for safety endpoints. Summary displays will be presented by treatment group. Subjects will be analyzed as treated.

Baseline is defined as the last measurement for a variable prior to the initial dose of study treatment. Hypotheses will be tested at the 5% statistical significance level, unless otherwise specified. No interim analysis is planned. Efficacy and safety analyses will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC), or comparable software.

All data collected on the eCRF will be listed in the appendices of the final clinical study report. Routine data listing or tabulation review of blinded data during the study conduct will be performed to identify missing data, anomalies, outliers, etc. A complete description of data handling rules and planned statistical analyses will be described in a separate statistical analysis plan (SAP) prior to data lock and unblinding procedures are completed at the end of the study.

8.3 Analysis Populations

The following populations are defined for the purpose of analyses:

1. Run-In Only Population (RIOP): Any subject who was enrolled and entered into the [redacted] of the study but were not randomized.
2. Intent-to-Treat (ITT): Any subject who completed the [redacted] and was randomized into the study.

[redacted]

[redacted]

3. Modified Intent-to-Treat (mITT): Any subject that was randomized, received and used study medication, and that has at least one post-baseline efficacy assessment.
4. Per-protocol (PP): Any subject, consistent with the protocol, that:
   (a) was randomized into the study,
   (b) met randomization inclusion/exclusion criteria,
   (c) had a positive skin test, for the appropriate allergen
   (d) was compliant with study treatment [redacted] during the 14-day Treatment Period,
   (e) had not taken any concomitant medications prohibited by the protocol or had any other significant protocol violations,
   (f) [redacted],
   (g) [redacted].

[redacted]

- [redacted]
- [redacted]

8.4 Sample Size Considerations

[redacted]

[redacted]

[redacted]

8.5 Efficacy Measures and Analysis

The mean baseline score/value for each symptom and summary measure (i.e. iTNSS or rTNSS) will be calculated by taking the sum of the recorded observations during the last 3 days before randomization (Visit 2) and the score on the morning score of randomization (Visit 2) and dividing by the number of observations included in that sum.

Efficacy endpoints will be expressed in terms of their mean response, calculated as the sum of observed responses divided by the number of observations over the 14-day Treatment Period. All calculations for mean scores will be done programmatically. [redacted]

[redacted]

8.5.1.1 Primary Analyses

The primary analyses for determining the bioequivalence of the Test and Reference treatments, and the superiority of each active treatment over the Placebo, will be based on each treatment's mean and median change from baseline for mean rTNSS calculated from the symptom scores for the 14-day Treatment Period.

The statistical analyses for both bioequivalence and superiority of the active treatments over placebo will involve Analysis of Covariance (ANCOVA) with terms for Treatment and Center, using mean baseline rTNSS as the covariate.

For the bioequivalence comparison, Analyses of Covariance using only the two active treatment's results will be used to calculate the 90% confidence intervals on the Test-to-Reference ratio at the mean change from baseline and median change from baseline values, using Fieller's method. The mean and median change values will be determined from the baseline values of all subjects, without regard to treatment received. If the 90% confidence intervals are contained within the interval 80.0% to 125.0%, then the two products will be considered to be therapeutically equivalent.

The superiority of treatment over the placebo will be concluded if the treatment's mean change from baseline is statistically significantly greater ($p<0.05$) than that of the placebo in the ANCOVA based on the treatment and placebo results. The superiority of Test and Reference treatments over the Placebo will be evaluated identically in a separate ANCOVA. [redacted]

[redacted]

[redacted]

[redacted]

8.5.1.2 Secondary Analyses

Secondary efficacy endpoint will be the mean change from baseline in mean iTNSS over the 14-day Treatment Period.

Mean values will be presented for the secondary efficacy variable. Statistical analyses will be performed by ANCOVA, as described for the primary endpoint analyses. The statistical significance of the Test-to-Reference, Test-to-Placebo and Reference-to-Placebo comparisons will be determined. In addition, the 90% confidence interval for the Test-to-Reference iTNSS scores over the 14-day Treatment Period will be calculated and presented as described for the primary efficacy analysis.

[redacted]

8.5.1.3 Safety Analysis

Adverse events will be classified using standard MedDRA terminology Version 16.0 or above, and summarized by treatment group. Summary tables comparing the type, incidence, severity and Investigator's opinion of relationship to the study drug will be prepared by treatment group. 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 SAR.

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

Concomitant medication use will be tabulated by subject.

All study subjects who are randomized to the active Treatment Period of the study will be included in the comparative safety analysis (Safety Population Randomized).

Adverse events and concomitant medication use reported during the [redacted] (Run-In Only population) and Treatment Period (including Intent-To-Treat, Modified Intent-to-

[redacted]

[redacted]

Treat and Per-protocol populations) will be tabulated in a summary table listing the type, incidence, severity and Investigator's opinion of relationship to the study drug.

8.6 Comparability of Subjects at Baseline

Baseline variables will be compared between treatment groups to identify differences which may not have been eliminated by randomization. The comparison will be done using a two-way analysis of variance (ANOVA) using Treatment and Center as fixed effects for quantitative variables while for categorical variables (such as gender) the analysis will be conducted using the Cochran-Mantel-Haenszel (CMH) test for general association adjusted for Center. Any significant baseline differences will be reviewed for their potential impact on the efficacy findings.

9. CONSENT CONSIDERATIONS AND PROCEDURES

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

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

Periodic status reports must be submitted to the IRB at least annually as required by the site's IRB, as well as notification of completion of the study and a final report within three months of study completion or termination. A copy of all reports submitted to the IRB must be sent to Perrigo UK FINCO Limited Partnership.

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

[redacted]

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

If the subject fails to meet the inclusion/exclusion criteria at the conclusion of the Placebo Run-In Phase, the subject will be withdrawn from the study.

9.1 Subject Confidentiality

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

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

To preserve the subject's confidentiality, the data collected will be available only to the investigators of the study, their support staff, Perrigo UK FINCO Limited Partnership, and possibly the FDA.

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

[redacted]

[redacted]

10. CONDUCT OF STUDY

The investigational site is to maintain complete documentation of all events and the dates on which they occur including source documents such as appointment books, investigator's notes etc.

10.1 Completion of Study

The investigational site will complete the study and complete all documentation required, in satisfactory compliance with the protocol, within 1 month of enrollment of the last subject and extending beyond as needed to complete necessary data queries.

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

10.2 Protocol Amendments

Neither the investigator nor Perrigo will modify this protocol without first obtaining the concurrence of the other. The party initiating a modification will confirm it in writing. Modifications of the protocol may require IRB approval.

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

When, in the judgment of the reviewing IRB, the investigators and/or Perrigo, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent form will require similar

[redacted]

[redacted]

modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before expecting continued participation.

11. RECORDS MANAGEMENT

11.1 Data Collection

All data collected in this study will be entered onto eCRFs, verified by monitoring, and submitted for statistical evaluation as described below. Checks will be run on the data and queries issued as needed. Once all data is cleaned, full quality control verification will be done prior to breaking the blind. After all data are correctly entered, the database will be locked and submitted to appropriate Quality Assurance verifications before the treatment code is broken. All data collected in the CRFs will be documented in subject data listings and summarized in tables, as appropriate.

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

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

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

Any changes to information in the study progress notes and other source documents, should be entered in **blue** or **black ink**, **initialed** and **dated** by the authorized person making the correction/addition. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. (e.g., ~~wrong data~~ right data). Entries may not be erased or masked with white-out fluid. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

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

[redacted]

[redacted]

11.2 Source Documents

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

11.3 File Management at the Study Site

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

11.4 Records Retention at the Study Site

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

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

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

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

12.2 Auditing

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

[redacted]

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

13. ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the United States Food and Drug Administration (FDA) regulations, Health Protection Bureau (HPB) and with the ICH GCP Guidelines.

14. USE OF INFORMATION AND PUBLICATION

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

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

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

[redacted]

[redacted]

15. INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-14-018

PROTOCOL TITLE: 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

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

_____
Principal Investigator's Printed Name

_____
Principal Investigator's Signature

_____
Date

[redacted]

[redacted]

16. REFERENCES

1. [redacted]

[redacted]

[redacted]

17. APPENDICES

17.1 Appendix A: Study Personnel Contacts

[redacted]

[redacted]

[redacted]

[redacted]

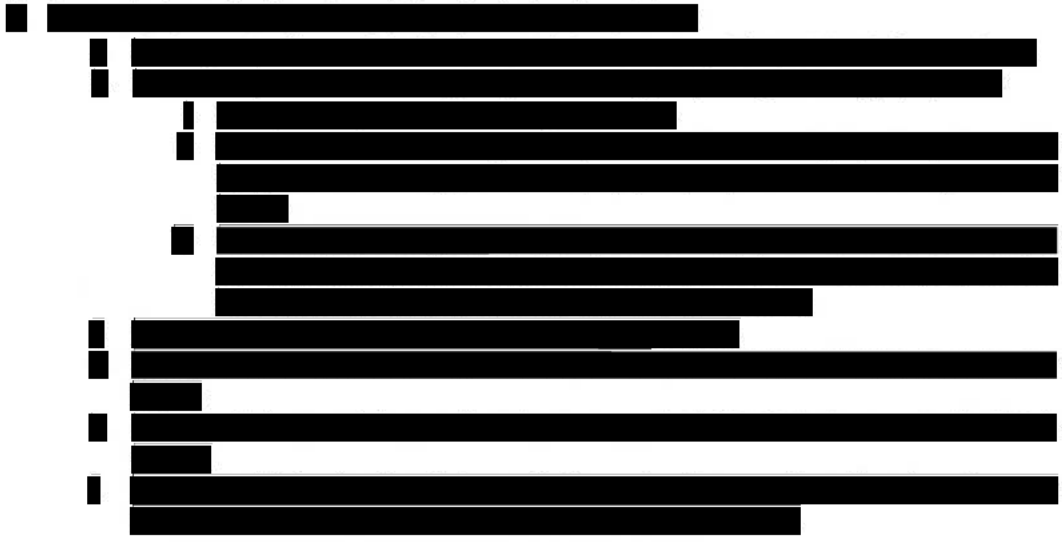
[redacted]

[redacted]

17.2 Appendix B: [redacted]

[redacted]

[redacted]



[redacted]

[redacted]

You are scheduled to return at:

_____ on _____ for Visit 2/Day 1
Time Date

_____ on _____ for Visit 3/Day 7
Time Date

[redacted]

[redacted]

_____ on _____ for Visit 4/Day 15
Time Date

If you cannot make your appointment, please contact:

_____ at _____
Name Phone number

ALL APPOINTMENTS ARE IMPORTANT AND SHOULD BE MAINTAINED AS SCHEDULED! IF YOU NEED TO CHANGE YOUR APPOINTMENT, PLEASE CALL YOUR STUDY DOCTOR'S OFFICE.

[redacted]

[redacted]

17.3 Appendix C: Nasal spray project acronyms and definitions

AAAAI	American Academy of Allergy, Asthma and Immunology
AE	Adverse Event
ANOVA	Analysis of Variance
AR	Allergic Rhinitis
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
FDA	Food & Drug Administration
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic-Pituitary Axis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IND	Investigational New Drug (application)
INH	Inhaled
IRB	Institutional Review Board
iTNSS	Instantaneous Total Nasal Symptom Score
ITT	Intent to Treat
IUD	Intra Uterine Device
LOCF	Last Observation Carried Forward
mcg	Microgram
OTC	Over the Counter
PP	Per Protocol
rTNSS	Reflective Total Nasal Symptom Score
SAE	Serious Adverse Event
SAR	Seasonal Allergic Rhinitis
TNSS	Total Nasal Symptom Score
USP	United States Pharmacopoeia

[redacted]