

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Limited Partnership Adapalene and Benzoyl Peroxide Topical Gel 0.3%/2.5% to Galderma Laboratories, L.P. Epiduo[®] Forte (Adapalene and Benzoyl Peroxide) Gel, 0.3%/2.5%, and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

NCT03393494

09-28-2017

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Limited Partnership Adapalene and Benzoyl Peroxide Topical Gel 0.3%/2.5% to Galderma Laboratories, L.P. Epiduo[®] Forte (Adapalene and Benzoyl Peroxide) Gel, 0.3%/2.5%, and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

Protocol No.: PRG-NY-17-008



Confidential

The confidential information provided in this document is for use by parties directly involved in this investigation. By accepting this document, you agree that the information contained herein will not be disclosed to any person not directly involved in this investigation without written authorization from Perrigo UK FINCO's Limited Partnership.

Protocol No: PRG-NY-17-008

PROTOCOL SIGNATURE PAGE

PROTOCOL NUMBER: PRG-NY-17-008

PROTOCOL TITLE: A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Adapalene and Benzoyl Peroxide Topical Gel 0.3%/2.5% to Galderma Laboratories, L.P. Epiduo[®] Forte (Adapalene and Benzoyl Peroxide) Gel, 0.3%/2.5%, and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris.

Signatures of representatives below indicate this is the agreed upon final version of the protocol:

[Redacted signature area]

[Redacted text]

TABLE OF CONTENTS

TABLE OF CONTENTS 3

1. BACKGROUND 8

2. STUDY OBJECTIVES 8

 2.1 Endpoints 8

 2.2 Safety 8

3. STUDY DESIGN 9

 3.1 Type/Design of Study 9

 3.2 Study Population 9

4. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS 9

 4.1 Inclusion Criteria 9

 4.2 Exclusion Criteria 10

 4.3 Prohibited Medications 12

 4.4 Precautions 14

5. PROCEDURES 15

 5.1 Subject Screening and Enrollment 15

 5.2 Assignment of Subject Number 16

 5.3 Demographics/Medical History 16

 5.4 Concomitant Medications 16

 5.5 Physical Examination 16

 5.6 Urine Pregnancy Test 16

 5.7 Dermatological Assessment (Diagnosis) 17

 5.8 Investigator’s Global Assessment (IGA) 17

 5.9 Lesion Counting 18

 5.9.1 Inflammatory Lesion Count 18

 5.9.2 Non-inflammatory Lesion Count 18

 5.9.3 Nodulocystic Lesion Count 18

 5.10 Application Site Reaction Assessment 19

 5.11 Study Medication Use, Subject Instructions and Diary 20

 5.12 Visit Specific Procedures 21

 5.12.1 Baseline Visit/ Day 1 21

 5.12.2 Telephone Contact/Week 2/Day 14 (±4 days) 22

 5.12.3 Visit 2/Week 4/Day 28 (± 4 days) 22

 5.12.4 Visit 3/Week 8/Day 56 (± 4 days) 22

 5.12.5 Visit 4/Week 12/Day 84 (± 4 days) End of Treatment/Early Termination Visit 23

 5.12.6 Unscheduled Visit 23

 5.13 Summary of Assessments 24

 5.14 Screen Failures 26

 5.15 Protocol Deviations/Violations 26

 5.16 Subject/Treatment Compliance 26

 5.17 Discontinuation/Withdrawal of Study Subjects 27

6. MATERIALS AND SUPPLIES 28

 6.1 Study Medication 28

 6.2 Medication Management 28

 6.2.1 Labeling, Packaging and Distribution 28

6.2.2 Retention Samples29

6.2.3 Storage and Test Article Accountability.....29

6.2.4 Randomization30

6.2.5 Procedure for Breaking the Blind30

7. ADVERSE REACTIONS..... 30

7.1 Departure from the Protocol for Individual Subjects31

7.2 Definitions31

7.3 Eliciting and Reporting of Adverse Events33

7.3.1 Expedited Reporting Responsibilities of the Study Center.....33

7.3.2 Submitting an Expedited Safety Report to the IRB.....34

7.4 SAE & AEs Requiring Discontinuation of Study Drug, including Pregnancies34

7.4.1 Pregnancy35

7.5 Post Study Adverse Events.....36

7.5.1 Non-serious Adverse Events36

7.5.2 Serious Adverse Events.....36

8. STATISTICAL ANALYSIS 37

8.1 Statistical Analysis Plan37

8.1.1 Analysis Populations37

8.1.2 Planned Analysis38

8.1.3 Sample Size Considerations38

8.1.4 Efficacy Measures and Analysis39

8.1.5 Safety and Adverse Events Analysis.....39

8.2 Comparability of Subjects at Baseline.....40

9. CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES..... 40

9.1 Subject Confidentiality.....41

10. CONDUCT OF STUDY..... 41

10.1 Completion of Study41

10.2 Protocol Amendments42

11. RECORDS MANAGEMENT 42

11.1 Data Collection.....42

11.2 Source Documents43

11.3 File Management at the Study Site.....44

11.4 Records Retention at the Study Site44

12. QUALITY CONTROL AND QUALITY ASSURANCE..... 44

12.1 Monitoring44

12.2 Auditing.....44

13. ETHICS AND RESPONSIBILITY 44

14. USE OF INFORMATION AND PUBLICATION 45

15. APPENDICES..... 47

15.1 Appendix A: Study Personnel Contacts.....47

15.2 Appendix B: Instructions for the Subject48

15.3 Appendix C: Face Diagram52

16. REFERENCES..... 53

STUDY SYNOPSIS

Title:	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO’s Limited Partnership Adapalene and Benzoyl Peroxide Topical Gel 0.3%/2.5% to Galderma Laboratories, L.P. Epiduo® Forte (Adapalene and Benzoyl Peroxide) Gel,0.3%/2.5%, and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris.
Study Period:	12 weeks (84 Days)
Study Medication:	<ol style="list-style-type: none"> 1. Adapalene and Benzoyl Peroxide Topical Gel, 0.3%/2.5%, Perrigo UK FINCO Limited Partnership, [REDACTED] 2. Epiduo® Forte (Adapalene and Benzoyl Peroxide) Gel,0.3%/2.5%, manufactured by Galderma Laboratories, L.P. 3. Vehicle of test product, Perrigo UK FINCO Limited Partnership, [REDACTED]
Study Objectives:	To compare the safety and efficacy profiles of Perrigo UK FINCO’s Limited Partnership Adapalene and Benzoyl Peroxide Topical Gel, 0.3%/2.5% to Galderma Laboratories Epiduo® Forte (Adapalene and Benzoyl Peroxide) Gel, 0.3%/2.5%, in order to prove bioequivalence between them and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of Acne Vulgaris.
Study Design:	Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be admitted into the study only after written informed consent/assent (as applicable) has been obtained and after all inclusion/exclusion criteria have been met. Male and female subjects 12 years to 40 years of age, inclusive, with acne vulgaris [REDACTED] will be eligible for enrollment.
Study Population:	[REDACTED] healthy males and females, 12 to 40 years of age, inclusive, who meet the inclusion/exclusion criteria, will be enrolled to obtain [REDACTED] modified-Intent-To-Treat (mITT) and [REDACTED] per-protocol (PP) subjects.
Dosing:	Subjects will be randomized [REDACTED] to either the test product, reference product or vehicle treatment group, respectively, and will apply [REDACTED] the study medication onto each area of the face (forehead, chin, right cheek, left cheek and nose) [REDACTED] avoiding contact with the eyes, lips, inside your nose/nostrils, angles of the nose, broken skin areas and mucous membranes at approximately the same time once daily for 12 weeks. [REDACTED]
Study Visits:	<p>Clinical Evaluations will be performed at:</p> <ol style="list-style-type: none"> 1. Visit 1/Day 1 (Baseline) 2. Visit 2/Week 4/Day 28 (±4 days)(Interim) 3. Visit 3/Week 8/Day 56 (±4 days)(Interim)

	<p>4. Visit 4/Week 12/Day 84 (± 4 days)(End of treatment/End study) Safety will be assessed by monitoring adverse events at each visit and at the Week 2/Day 14(± 4days) Telephone Contact.</p>
Evaluations:	<p>The number of facial inflammatory and non-inflammatory lesions as well as the Investigator’s Global Assessment (IGA) will be recorded at baseline and all subsequent visits.</p>
Endpoints:	<p>The two primary efficacy endpoints will be the:</p> <ol style="list-style-type: none"> 1) Mean percent change from baseline to Week 12 (Day 84) in the inflammatory (papules and pustules) lesion count and 2) Mean percent change from baseline to Week 12 (Day 84) in the non-inflammatory (open and closed comedones) lesion count. <p>The secondary endpoint will be the proportion of subjects at Week 12 with a clinical response of “success”, defined as an IGA score that is at least 2 grades less than the baseline assessment.</p>
Safety:	<p>The incidence of all adverse events reported during the study will be summarized by treatment group. [REDACTED]</p> <p>[REDACTED] In addition, the test and reference treatments frequency and distribution of application site reactions of erythema, dryness, burning/stinging, erosion, edema, pain and itching will be summarized and compared descriptively.</p>

ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CMH	Cochran–Mantel–Haenszel test
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
ICH	International Conference on Harmonization
IGA	Investigator’s Global Assessment
IRB	Institutional Review Board
ITT	Intent- to-treat (population)
IU	International Unit
IUD	Intra-Uterine Device
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat (population)
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the counter
PI	Principal Investigator
PP	Per-protocol (population)
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPF	Sun Protection Factor
Sub-I	Sub-Investigator
UPT	Urine Pregnancy Test



1. BACKGROUND

[REDACTED]

[REDACTED] Perrigo UK FINCO Limited Partnership has developed a generic formulation of Adapalene and Benzoyl Peroxide Topical Gel 0.3%/2.5%.

2. STUDY OBJECTIVES

The objectives of this study are to compare the efficacy and safety profiles of Perrigo UK FINCO's Limited Partnership Adapalene and Benzoyl Peroxide Topical, Gel 0.3%/2.5% and Epiduo® Forte (Adapalene and Benzoyl Peroxide) Gel, 0.3%/2.5%, and to show the superior efficacy of the two active formulations over that of the vehicle in the treatment of Acne Vulgaris.

2.1 Endpoints

The two primary efficacy endpoints will be the:

- 1) Mean percent change from baseline to Week 12 (Day 84) in the inflammatory (papules and pustules) lesion count and
- 2) Mean percent change from baseline to Week 12 (Day 84) in the non-inflammatory (open and closed comedones) lesion count.

The secondary endpoint will be the proportion of subjects at Week 12 (Day 84) with a clinical response of "success", defined as an IGA score that is at least 2 grades less than the baseline assessment.

2.2 Safety

Safety of the test and reference products will be compared by evaluating the nature, severity and frequency of their adverse event profiles. All adverse events that occur during the study will be recorded whether or not they are considered to be related to the study medication. Descriptions of reactions or complaints will include the approximate date of onset, the date the adverse event ended, the severity of the adverse event, 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. Pearson's Chi-Square test or Fisher's Exact test, whichever is most appropriate, will be used to compare the proportion of subjects in each treatment group with any adverse event. The adverse events reported by at least five percent of the subjects in any treatment group will be summarized descriptively.

[REDACTED]

3. STUDY DESIGN

3.1 Type/Design of Study

Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be assigned [REDACTED] to test product, reference product, or vehicle, respectively. [REDACTED] the assigned study medication will be applied topically [REDACTED] onto each area of the face (forehead, chin, right cheek, left cheek and nose) avoiding contact with the eyes, lips, mouth, inside your nose/nostrils, angles of the nose, broken skin areas and mucous membranes once daily in the evening around the same time for 12 weeks.

Subjects will be males and females, 12 to 40 years of age inclusive, with at least moderate facial acne vulgaris with an inflammatory lesion (papules and pustules) [REDACTED] and a non-inflammatory lesion (open and closed comedones) [REDACTED] nodulocystic lesions (e.g., nodules and cysts) on the face including those present on the nose. Visits to the study site are scheduled at baseline (Day 1) and Days 28 (Week 4), Days 56 (Week 8), and Day 84 (Week 12). A telephone contact will be made at Week 2.

3.2 Study Population

Male and female subjects, 12 to 40 years of age, inclusive, with a clinical diagnosis of at least moderate facial acne vulgaris with an inflammatory lesion (papules and pustules) [REDACTED] and a non-inflammatory lesion (open and closed comedones) [REDACTED] nodulocystic lesions (e.g., nodules and cysts) on the face including those present on the nose.

4. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1 Inclusion Criteria

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

1. Subject must sign an Institutional Review Board (IRB) approved written informed consent /assent for this study and must be witnessed and signed by someone (other than the person explaining the consent/assent form during the signing of the consent/assent before enrolling into the study. [REDACTED].
2. Subjects must be male or female, 12 to 40 years of age, inclusive.
3. Subjects must have a definite clinical diagnosis of facial acne vulgaris with an inflammatory lesion (papules and pustules) [REDACTED] and a non-inflammatory (open and closed comedones) lesion [REDACTED] and [REDACTED] nodulocystic lesions (e.g., nodules and cysts) including those present on the nose.
4. [REDACTED]

5. Subjects must be willing and able to understand and comply with the requirements of the study, apply the medication as instructed, refrain from use of all other:

- [REDACTED]

during the 12-week treatment period, return for the required treatment period visits, comply with therapy prohibitions, and are able to complete the study.

6. Subjects must be in general good health and free from any clinically significant disease, other than acne vulgaris, that might interfere with the study evaluations.

7. [REDACTED]

4.2 Exclusion Criteria

Subjects may not be selected if any of the following criteria exist:

1. Subjects who are pregnant, breastfeeding or planning a pregnancy within the period of their study participation period.

- 2. [REDACTED]
- 3. [REDACTED]
- 4. [REDACTED]
- 5. [REDACTED]

[REDACTED]

- [REDACTED]
6. Any uncontrolled, chronic or serious disease or medical condition that would prevent participation in a clinical trial, or, in judgment of the investigator, would put the subject at undue risk or might confound the study assessments (such as planned hospitalizations during the study).
 7. Excessive facial hair [REDACTED] that would interfere with the diagnosis or assessment of acne vulgaris.
 8. [REDACTED]
 9. [REDACTED]
 10. History of unresponsiveness to topical adapalene and/or benzoyl peroxide therapy.
 11. [REDACTED]
 12. History of hypersensitivity or allergy to adapalene, benzoyl peroxide, retinoids and/or any ingredient in the study medication.
 13. Use [REDACTED] prior to baseline or during the study of oral retinoids (e.g. Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
 14. Use of radiation therapy and/or anti-neoplastic agents [REDACTED] prior to Visit 1/Day 1 (Baseline).
 15. Use [REDACTED] prior to baseline or during the study of therapeutic vitamin D supplements of greater than 2,000 units/day [REDACTED]
 16. Use of medications known to exacerbate acne [REDACTED]
 17. Start or change [REDACTED] of Visit 1 and throughout the study of:
 - [REDACTED]
 18. [REDACTED]
 19. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

20. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

23. Subject consumes excessive alcohol, abuses drugs, or has a condition that could compromise the subject's ability to comply with study requirements.

24. Previous enrollment in this study, current enrollment in this study at another participating site or current enrollment in another study (in parallel to this study) at another clinical research site.

[REDACTED]

[REDACTED]

26. Participation in any clinical study involving an investigational product, agent or device (that might influence the intended effects or mask the side effects of study medication) in the 4 weeks (30 days) prior Visit 1/Day 1 (Baseline) or throughout the study.

27. Employee (or employee's family member) of the research center or private practice, CRO or Sponsor, or subjects who have a conflict of interest.

28. [REDACTED]

[REDACTED]

29. [REDACTED]

30. Subjects who in the opinion of the investigator, are unlikely to be able to follow the restrictions of the protocol and complete the study.

4.3 Prohibited Medications

The following medications/procedures are prohibited during this study:

1. Use of any treatment for acne vulgaris of the face, other than the assigned study treatment.
2. Subjects should not apply the assigned study treatment inside their nose/nostrils, angles of the nose, on their eyes, mouth, lips, broken skin areas or mucous membranes, or on any cuts or open wounds.

[REDACTED]

3. The application of medicated make-up or change in cosmetics, new or changes of medicated cleansers, moisturizers, creams, lotions, powders, or any other topical product (other than the assigned study treatment or lotion with sunscreen, and cleanser provided by the Investigator) to the face are prohibited during this study.

4. [Redacted]

5. Initiation of or change of dose of hormonal treatment and/or drugs causing acneiform eruptions

[Redacted]

[Redacted]

treatments or chlorine exposure (swimming, etc.) within 24 hours of study visits. Use of niacin

[REDACTED]

4.4 Precautions

The following precautions are to be taken during this study:

1. Subjects should avoid contact of the study medication with the eyes (upper and lower eyelids), inside their nose/nostrils, mucous membranes, mouth and lips and or on any cuts or broken skin. In case of accidental exposure, the eyes should be rinsed with plenty of water and a physician should be consulted if eye irritation persists.
2. The study medication should not be applied to cuts, abrasions, eczematous or sunburned skin, or sites other than the treatment area.
3. Subjects should store the study medication pump bottle upright and tightly closed at room temperature 20°C-25°C (68°F to 77°F) in an upright position; with excursions permitted between 15-30°C (59-86°F), away from children and heat and protected from light.
4. Subjects should wash their hands before and immediately after applying study medication.
5. [REDACTED]
6. [REDACTED]
7. [REDACTED]
8. [REDACTED]
9. The study medication should be spread smoothly and evenly [REDACTED] on each area of the face (forehead, chin, and nose, left and right cheek); [REDACTED].
10. The product should not be applied more than once daily and subjects should not use more than the recommended amount on the entire face.
11. [REDACTED]
12. Subjects should use only the non-medicated, mild cleanser and facial lotion with sunscreen product given to them on their face during the course of the study. Irritating topical products such as medicated or abrasive soaps, cleansers or washes (e.g., exfoliating facial scrubs), alcoholic toners, astringents and adhesive cleansing strips (e.g., Bioré® Pore Strips) are prohibited throughout the study.

[REDACTED]

[REDACTED]

13. Subject should use protective apparel (e.g., wide-brimmed hat) when outdoors. Weather extremes, such as wind or cold, may be irritating to subjects receiving treatment.
14. Subjects should not cover the treated area with a bandage (occlusive dressing) or other types of dressing after applying the study medication.

15. [REDACTED]

20. Subjects should consult the investigator with any questions regarding concomitant medications.
21. Subjects should avoid getting the assigned treatment on their hair or on colored fabric. Product may bleach hair or colored fabric.
22. [REDACTED]
23. Subjects should be informed that local skin reactions such as erythema, scaling, dryness, and stinging/burning as well as irritant and allergic contact dermatitis may occur and depending on the severity that they should report these symptoms to the study staff immediately.
24. If a reaction suggesting sensitivity or irritation occurs, the Investigator should assess the subject's condition as soon as possible (e.g., by scheduling an Unscheduled Visit, if required) and determine whether treatment should be discontinued. If the subject is discontinued from the study during an Unscheduled Visit, procedures from Visit 4 should be followed and the visit will be referred to as an Early Discontinuation Visit.

5. PROCEDURES

5.1 Subject Screening and Enrollment

The study personnel will review the IRB approved informed consent form and assent form, if applicable, with each subject and give the subject an opportunity to have all questions answered before proceeding. The consent/assent form must be signed by each subject and witnessed before the subject is enrolled into the study. The witness can be anyone present during the signing of the consent form other than the individual explaining the consent. A copy of the signed consent/assent will be given to every participant (or legally authorized representative) and the original will be maintained with the participant's records. Subjects under the legal age of consent must sign an IRB approved written informed consent/assent in addition to consent provided by a parent or legally authorized representative.

[REDACTED]

[REDACTED]

5.2 Assignment of Subject Number

As possible an independent third-party dispenser will dispense and assign a subject number to each enrolled subject. The subject number will correspond to a computer-generated randomization schedule assigning the number to one of the three study treatment groups.

Once the subject has consented, met inclusion/ exclusion criteria, they will be assigned a subject number. The subject number will be taken from the study medication kit dispensed to the subject at each site.

5.3 Demographics/Medical History

A demographic profile and 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.

5.4 Concomitant Medications

Concomitant medications and any medications taken [REDACTED] prior to signing informed consent/assent will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on either a regular or "prn" basis, including vitamins, aspirin and acetaminophen, should be recorded on this page prior to starting the study medication. [REDACTED]

5.5 Physical Examination

The investigator, sub-investigator or appropriately delegated and qualified designee will perform a brief physical examination, prior to the subject starting study medication. [REDACTED]

5.6 Urine Pregnancy Test

A urine pregnancy test will be conducted at Baseline/Visit 1/Day 1 [REDACTED]

[REDACTED] An investigator may repeat the pregnancy test anytime during the study visit if there is any suspicion or possibility that the subject may be pregnant. [REDACTED]

[REDACTED]

[REDACTED]

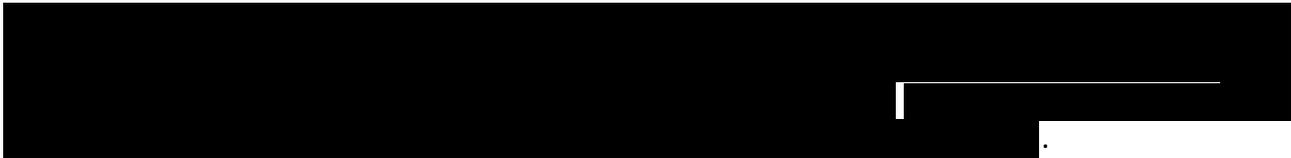


5.7 Dermatological Assessment (Diagnosis)

Investigator or sub-investigator will examine the subject to establish the clinical diagnosis of facial acne vulgaris.



5.8 Investigator’s Global Assessment (IGA)



The following scale will be used for the Investigator’s Global Assessment:

Grade	Category	Description
0	Clear	Clear skin with no inflammatory or noninflammatory lesions
1	Almost Clear	Rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild Severity	Greater than Grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate Severity	Greater than Grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe	Up to many noninflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions



*The electronic Case Report Form (eCRF) will allow for reporting by investigators of lesion worsening beyond Grade 4 with post-visit 1 treatment. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

5.9 Lesion Counting

The investigator should evaluate the treatment area before a subject applies the first dose of study medication. Each subject's initial condition and course of acne vulgaris will be assessed by 1) counting the inflammatory, non-inflammatory and nodulocystic lesions (e.g., nodules and cysts) including those present on the nose and documenting on the facial diagram ([Appendix C](#)) as part of the source documentation, 2) evaluation of the application site reaction.

[REDACTED]

5.9.1 Inflammatory Lesion Count (Papules and Pustules)

The numbers of facial papules and pustules, located above the jaw line to the hairline including those present on the nose, are to be counted at baseline and at each subsequent visit. The type, location and number of each lesion is to be recorded on the source document at each visit and the total count recorded.

Papule = solid palpable inflammatory lesion \leq 5mm diameter

Pustule = pus-filled inflammatory lesion \leq 5mm in diameter

5.9.2 Non-inflammatory Lesion Count

The numbers of facial open comedones and closed comedones, located above the jaw line to the hairline including those present on the nose, are to be counted at baseline and at each subsequent visit. The type, location and number of each lesion is to be recorded on the source document at each visit and the total count recorded.

Open Comedones: blackhead, surface of the plugged sebaceous follicle has a blackish appearance

Closed Comedones: whitehead, skin-colored or slightly inflamed "bump" in the skin

5.9.3 Nodulocystic Lesion Count

The numbers of facial nodules and cysts, located above the jaw line to the hairline including those present on the nose, are to be counted at baseline and at each subsequent visit. The total number of this type of lesion and location are to be recorded on the source document at each visit.

[REDACTED]

Nodule: Palpable solid or soft lesion $>$ 5mm in diameter.

[REDACTED]

Cysts: Pus filled lesion > 5mm in diameter

5.10 Application Site Reaction Assessment

At baseline (Visit 1/Day 1) and each subsequent visit, application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching are to be recorded on the source document. [REDACTED]

At Visit 1/Baseline (Day 1), the investigator should perform the application site reaction assessment before [REDACTED] the subject applies the first dose of the study medication at the site.

The Application Site Reaction Assessment must be conducted by qualified investigators listed on the Form FDA 1572 who have been delegated these tasks by the PI. [REDACTED]

Application site reactions (erythema, dryness, burning/stinging, erosion, edema, scaling/peeling, pain and itching) are not to be recorded as adverse events unless they result in either:

- The temporary discontinuation of the study medication.
- The discontinuation of the subject from the study.
- The use of a new concomitant medication in order to treat this event.

Any other application site reaction not listed above (such as infection) should be recorded as adverse events in the source document and eCRFs.

The investigator will assess a subject’s application site reaction by rating the following symptoms according to the scales provided below. Pain and itching symptoms will be assessed by discussion with the subject and will be reported as the severity experienced within 24 hours of the study visit.

Site Reaction	DESCRIPTION
Erythema	[REDACTED]
Dryness	[REDACTED]
Scaling/Peeling	[REDACTED]
Burning/Stinging	[REDACTED]
Erosion	[REDACTED]
Edema	[REDACTED]
Pain	[REDACTED]
Itching	[REDACTED]

SCORE	ASSESSMENT	DESCRIPTION
-------	------------	-------------

0	None	Absent
1	Mild	Slight, barely perceptible
2	Moderate	Distinct presence
3	Severe	Marked, intense

5.11 Study Medication Use, Subject Instructions and Diary

At the baseline visit, one [redacted] gm pump bottle of study medication from the subject kit box will be dispensed by the third-party dispenser (if possible) or designee, to enrolled subjects along with a diary card. Each subject will also receive a copy of written instructions, which detail the proper application method, and general instructions regarding the study (see [Appendix B](#)). At Visit 1/Baseline/Day 1, the third-party dispenser (if possible) or designee should ensure that all subjects met eligibility criteria and efficacy (IGA) and safety (application site reactions) assessments are conducted by the investigator before the subjects perform the initial application. The initial application on Day 1 will be demonstrated and observed by study staff when the subject applies the medication at the study site to ensure subject understands the instructions and is applying the medication appropriately. [redacted]

[redacted]. Subsequent applications of study medication should be applied as instructed by the subject at home. [redacted]. The study staff should instruct the subject to apply all subsequent doses of the study medication once daily (starting on the evening of Day 2 of the study treatment period) as demonstrated. At all subsequent study visits, the study medication and diary will be collected to visually inspect the pumps and diary completion. Empty pump bottles will be collected and kept by the site. Pump bottles with remaining medication will be redispensed to the subject. In addition to the re-dispensed pump bottle, the subject will receive a new pump bottle each at Visit 2/Week 4/Day 28 (±4days) and Visit 3/Week 8/Day 56 (±4days).

The dispenser will write the dispensing dates on the label of the study medication when it is dispensed to the subject. The study medication kits must be stored at room temperature at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) in a secure limited area at the investigator site. Subjects will be instructed to store the pump bottles at room temperature 20°C to 25°C (68°F to 77°F) in an upright position, away from children and heat, and should be protected from light.

A non-medicated, mild cleanser and a facial lotion with sunscreen will be dispensed to the subjects at the Visit 1/Day 1 (Baseline). Subjects will cleanse their face with the study provided non-medicated, mild cleanser using only the hands and pat dry with a soft clean towel and then wait an additional 15 minutes before applying the study medication. [redacted]

[redacted] the study medication onto each area of the face (forehead, chin, right cheek, left cheek, and nose) avoiding contact with the eyes, lips, angles of the nose, inside your nose/nostrials, broken skin and mucous membranes at approximately the same time once daily

in for 12 weeks. [REDACTED]

[REDACTED] Subjects will be instructed to wash hands immediately after applying the study medication. Subjects should continue to use the mild cleanser and facial lotion with sunscreen provided by the sponsor to wash the face for the duration of the study. Subjects will be instructed to not use any other topical treatments or products other than the study medication and sponsor provided non-medicated, mild cleanser and facial lotion with sunscreen.

A diary card will be dispensed to each enrolled subject at Visits 1, 2 & 3. The subjects will be instructed to complete the diary card after applying each daily dose of study medication. At each subsequent visit, study personnel will review and collect the diary card, determine whether the subject requires counseling for dosage compliance, confirm and record use of any prohibited medications, assess AEs, dispense additional study medication, cleanser or lotion and a new diary as required. In addition, each study subject will be reminded to bring with them all previously dispensed pump bottles (regardless of content) and the completed diary card at the next visit. Study personnel will schedule the subject's next visit prior to the subject's departure.

5.12 Visit Specific Procedures

The following sections outline the procedures required at each visit.

5.12.1 Baseline Visit/ Day 1

Prospective subjects will visit the study center and be examined by the study physician who will perform the procedures below at this visit.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.12.2 Telephone Contact/Week 2/Day 14 (± 4 days)

[REDACTED]

5.12.3 Visit 2/Week 4/Day 28 (± 4 days)

[REDACTED]

5.12.4 Visit 3/Week 8/Day 56 (± 4 days)

[REDACTED]

[REDACTED]

[REDACTED]

5.12.5 Visit 4/Week 12/Day 84 (\pm 4 days) End of Treatment/Early Termination Visit

[REDACTED]

5.12.6 Unscheduled Visit

An unscheduled visit is allowed at any time if in the investigator’s opinion it is warranted. If the investigator assesses the subject’s condition and determines that the subject’s condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as a treatment failure, an Early Termination Visit conducted, and a standard of care treatment may be advised at the investigator’s discretion. The following procedures may be performed at the Unscheduled Visit if required.

[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.

The following procedures: Informed Consent, Inclusion/Exclusion Criteria, Medical History/Demographics, collection and review of Concomitant medications, Physical exam, Vital signs, dermatological assessment (diagnosis), lesion counting, IGA, and Urine pregnancy test must be completed and documented on the source document before a subject is randomized on the study.

[REDACTED]

[REDACTED]

[REDACTED]

5.14 Screen Failures

Screen failures will not be entered in the database and included in any data analyses. A screen failure is a subject who received information about the study, including signing an informed consent/assent, and possibly performing some study related procedures, but was not enrolled, dispensed nor applied the investigational product.

5.15 Protocol Deviations/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 / [REDACTED] contacts in Section 15 ([Appendix A](#)) at the earliest possible time.

[REDACTED]

[REDACTED]

5.16 Subject/Treatment Compliance

[REDACTED] the study medication onto each area of the face (forehead, chin, right cheek, left cheek, and nose) [REDACTED] and avoiding contact with the eyes, lips, inside your nose/nostrils, angles of the nose, broken skin and mucous membranes at approximately the same time once daily [REDACTED] for 12 weeks. [REDACTED]

On Day 1, subjects will apply their initial dose of study medication at the study site under the supervision of the third-party dispenser staff or other designee. Compliance will be determined from the diary card, in which the subject will be instructed to record all applications made or

[REDACTED]

missed. On Week 2 Day 14/ (± 4 days), compliance will be assessed via telephone contact. The study coordinator, or designee, will review the Subject Instruction Sheet and Diary with the subject on the phone. The total number of study medication doses applied and/or missed will be determined based upon the first dose applied through and including the last dose applied. The first and last dates of treatment should be recorded in the source documents and eCRFs. The total of applied and missed study medication applications should also be recorded. By definition there are no missed applications before the first date of treatment or after the last date of treatment.

[REDACTED]

All used and unused pump bottles of study medication will be collected by the study site at appropriate visits or early termination.

5.17 Discontinuation/Withdrawal of Study Subjects

Subjects may be removed from the study for any of the following reasons:

- The subject withdraws his or her consent for any reason.
- The subject's condition has worsened to the degree that the investigator feels it is unsafe for the subject to continue in the study or requires an alternative therapy.
- The subject's medication code is unblinded.
- Subject did not meet or no longer meets the entry criteria.
- An adverse event including intercurrent illness, 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.
- 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.
- The subject becomes pregnant during the course of the trial.
- [REDACTED]
- Investigator discretion (e.g., non-compliant to study protocol requirements).

After a subject has been discontinued, he/she will not be allowed to re-enroll in the study at any facility.

The reasons for a subject being discontinued will be documented in the eCRFs and the enrollment log.

If a subject is discontinued from the study for any reason, the Visit 4 (Day 84)/End of Study Visit/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 on the Source Document and End of Study eCRF.

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

[REDACTED]

documented. For such a subject, the investigator must strive to follow the subject until the adverse event has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up.

[REDACTED]

6. MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by Perrigo will consist of:

Test Product: Adapalene and Benzoyl Peroxide Topical Gel 0.3%/2.5%,
Perrigo UK FINCO Limited Partnership [REDACTED]

Reference Product: Epiduo® Forte (Adapalene and Benzoyl Peroxide) Gel, 0.3%/2.5%,
Marketed by Galderma Laboratories, L.P.

Vehicle: Vehicle of test product
Perrigo UK FINCO Limited Partnership ([REDACTED])

[REDACTED]

6.2 Medication Management

6.2.1 Labeling, Packaging and Distribution

The study medication assigned to each subject number will be determined by a computer-generated randomization schedule. 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]

[REDACTED]

[REDACTED]

[REDACTED]

The investigator or sub-investigator performing the clinical evaluations will not dispense or collect study medication.

6.2.2 Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select [REDACTED] study medication ([REDACTED] subject treatment units) to be maintained as retain samples. The investigator will maintain [REDACTED] selected block of study medication from each shipment of study medication received. As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel (in an upright position away from children and heat and protected from light at room temperature, 20-25°C (68-77°F); with excursions permitted between 15°C to 30°C (59°F and 86°F) , even after the study has concluded. Each reserve sample shall be retained 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 or was used." The investigator will store the retain sample study medication until such time as notification is received from Perrigo that the samples are no longer required.

6.2.3 Storage and Test Article Accountability

[REDACTED]

Study articles used to conduct this study will be maintained under adequate security by the investigator or designee. Each investigator site will ensure that the temperature of study medication is monitored and recorded throughout the study. The study medication should be stored at room temperature in a secured area with limited access, 20-25°C (68-77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) and pumps must be kept in an upright position and tightly closed. The medication may bleach hair and colored fabric, should not be frozen, should be protected from light, kept away from children, heat and kept tightly closed. The investigator will not supply study medication to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

[REDACTED]

The clinic personnel at each investigator site will keep a running inventory of study medication dispensed that will include subject numbers assigned and the date each pump of study medication is dispensed, and returned. A study medication accountability form will be provided to the investigator to document all medications received, dispensed by and used by each subject. At the conclusion of the study all unused, partially used, and empty pumps must be inventoried by the monitor and returned to Perrigo, or designee, for destruction, with the exception of retention samples which shall remain at the Investigator site.

6.2.4 Randomization

Randomization will be performed according to a computer-generated randomization scheme where the treatment group designation has been assigned to the subject number. The treatment designation will remain blinded until the final database is closed. An independent third party will hold the randomization code throughout the study. The randomization scheme will be a block randomization, with [REDACTED] subjects assigned to Test: Reference: Vehicle [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 for each subject at each investigator site, which is attached to the study medication log; 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 only and should seek prior authorization by Perrigo or designee when possible.** The reason for breaking the blind must be clearly documented in the source documentation and eCRF and the subject must be discontinued from the study. Perrigo must be notified immediately upon all unblinding situations.

7. ADVERSE REACTIONS

[REDACTED]

Protocol No: PRG-NY-17-008

The potential adverse reactions of generic Adapalene and Benzoyl Peroxide Topical Gel, 0.3%/2.5%, are anticipated to be similar to those observed in EPIDUO[®] Forte (adapalene – benzoyl Peroxide Topical) Gel 0.3%/2.5%.

The following adverse reactions occurred in greater than 1% of patients treated with Epiduo[®] Forte Gel include local cutaneous irritation (erythema, scaling, dryness and stinging/burning,) skin irritation, eczema, atopic dermatitis and skin burning sensation. Irritant and allergic contact dermatitis may occur.

There is no post marketing experience with Epiduo[®] Forte gel. The following adverse reactions have been identified during post-approval use of EPIDUO gel, a similar drug containing 0.1% adapalene and 2.5% benzoyl peroxide as the active ingredients: eyelid edema, sunburn, blister, pain of skin, pruritus, swelling face, conjunctivitis, skin discoloration, rash, eczema, throat tightness and allergic contact dermatitis.

7.1 Departure from the Protocol for Individual Subjects

When an emergency occurs requiring a departure from the protocol for a subject, departure will be only for that subject. In such circumstances, the investigator or other physician in attendance will contact the Medical Monitor or Perrigo by telephone and follow up with a written description as soon as possible. The overseeing IRB should also be notified.

7.2 Definitions

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 temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

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

- Death
- Life-threatening event (e.g., 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
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- 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.

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 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.

Definitely - The AE:

- 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

Probably - The AE:

- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge)
- cannot be reasonably explained by the known characteristics of the subject's state.

Possible - The AE:

- follows a reasonable temporal sequence from study medication administration
- but that could readily be produced by a number of other factors.

Unlikely - The AE:

- 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 - The AE:

- does not have a reasonable temporal association with the administration of study medication
- has some other obvious explanation for the event.

7.3 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 visit. 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 document and the study reporting forms. When reporting an adverse event, the Investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study medication or procedure. Serious or unexpected 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 the source document and recorded in a timely manner on the eCRFs. Adverse events (e.g., worsening of acne*) that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF 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 eCRF.

7.3.1 Expedited Reporting Responsibilities of the Study Center

For any serious or unexpected 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 serious adverse events are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to Perrigo. The adverse event term on the AE eCRF 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, events determined to be chronic 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 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 [REDACTED] [REDACTED] immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier to [REDACTED] 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 (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.

7.3.2 Submitting an Expedited Safety Report to the IRB

Once [REDACTED] receives all supporting documentation for the reported event, the Medical Monitor, in conjunction with Perrigo, will determine if the safety report is eligible for expedited review. [REDACTED] will log the initial event and will notify the sponsor that an event has been reported within 1 business day after initial receipt. [REDACTED] will complete the review of the event, enter information into their safety database and generate the report. This form, as well as other supporting documentation, will be forwarded to [REDACTED] Medical Monitor for review. [REDACTED] will finalize the report and distribute it to the sponsor within 1 day (one) after initial receipt. When expedited safety reporting to regulatory authorities is indeed required, the Investigator should review and update any newly available materials at once. Follow-up queries may be sent to the study center to further clarify the event.

Each expedited safety report will routinely include a brief cover memorandum, the completed report, and any additional pertinent information recommended by [REDACTED] Perrigo, or study Medical Monitor. Once the report is assembled, the Principal Investigator must submit the expedited safety report to the IRB within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available.

When a Principal Investigator receives an expedited safety report from [REDACTED] or the sponsor detailing adverse events occurring at other study centers under this protocol, it must be promptly submitted to the study center's IRB. The Principal Investigator must retain a copy of such reports as submitted to their IRB in the site's study Regulatory Binder.

7.4 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 [REDACTED] AND PERRIGO IMMEDIATELY (WITHIN 24 HOURS) VIA TELEPHONE OR FACSIMILE. IF INITIALLY REPORTED VIA TELEPHONE, THIS MUST BE FOLLOWED-UP BY A FACSIMILE OF THE WRITTEN SAE REPORT WITHIN 24 HOURS OF THE CALL TO [REDACTED]

Non-serious events that require discontinuation of study medication (including laboratory abnormalities) should be reported to Perrigo immediately and within 1 working day.

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]

[REDACTED]

7.4.1 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/or by faxing a completed Pregnancy Report to [REDACTED] 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 [REDACTED] 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 [REDACTED] within one working day of being notified of the pregnancy report.

If the trial is completed before the outcome of the pregnancy is known, [REDACTED] will assume the responsibility for following up on the pregnancy. [REDACTED] will contact the Investigator or Study coordinator on or around the potential expected date of delivery to follow-up on the outcome of pregnancy and will also check on the status of the infant 8 weeks post-delivery. Upon awareness of the pregnancy outcome and known status of the infant following 8 weeks of delivery, the investigator will complete the applicable pregnancy report forms and fax to [REDACTED] within 1 day of being notified.

7.5 Post Study Adverse Events

7.5.1 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 eCRF with the status of the AE noted. These adverse events must be followed by the investigator until the events are resolved, events determined to be chronic 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.

7.5.2 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 eCRF page and reported to Perrigo 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 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.

8. STATISTICAL ANALYSIS

The sections that follow highlight sample size determination and the planned analyses for this study. 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.

8.1 Statistical Analysis Plan

8.1.1 Analysis Populations

The following populations are defined for the purpose of analyses:

- Intent-to-Treat (ITT) (safety population): Any subject that was randomized, received and used study medication.

- Modified Intent-to-Treat (mITT): Any subject, who met the inclusion/exclusion criteria, was randomized, received and used the study medication, and returned for at least one post-baseline efficacy assessment.

- Per Protocol (PP): Any subject who:
 - met inclusion/exclusion criteria,
 - was randomized, received and used study medication,
 - met the protocol criteria for compliance [REDACTED]
[REDACTED] and
 - completed Visit 4/Week 12/Day 84 (End of Treatment/Early Termination Visit) efficacy evaluations within the designated window (± 4 days) OR was discontinued from the study due to treatment failure and
 - had no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

[REDACTED]

[REDACTED]

[REDACTED]

8.1.2 Planned Analysis

The safety analysis will be performed for the ITT subjects. The efficacy analysis will be conducted on both the PP and the mITT subject populations. Two-sided hypothesis testing will be conducted. Resulting p-values less than 0.05 will be considered statistically significant. No adjustments of p-values for multiple comparisons will be made. No interim analyses are planned. SAS software will be used for all data analyses and tabulations.

The treatment response will be summarized by treatment group for the end-of-treatment evaluation.

The two primary efficacy endpoints will be the mean percent change from baseline to Visit 4/day 84/Week 12 in the inflammatory (papules and pustules) lesion counts AND the mean percent change from baseline to Visit 4/Day 84/Week 12 in the non-inflammatory (open and closed) lesions.

[REDACTED]

8.1.3 Sample Size Considerations

[REDACTED]

[REDACTED]

[REDACTED]

8.1.4 Efficacy Measures and Analysis

Clinical endpoints

The primary efficacy measure will be the mean percent change from baseline to Visit 4/Day 84/Week 12 in the inflammatory (papules and pustules) lesion counts AND the mean percent change from baseline to Visit 4/Day 84/Week 12 in the non-inflammatory (open and closed) lesion counts. The secondary efficacy measure will be the proportion of subjects with clinical success on the Investigator's Global Assessment (IGA) at Visit 4/Day 84/Week 12. Success is defined as an IGA score that is at least 2 grades less than the baseline assessment.

Equivalent efficacy

For the mean percent reduction from baseline in the inflammatory and non-inflammatory lesion counts, the Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the 90% confidence interval on the Test-to-Reference ratio of means, calculated by Fieller's Method, falls within the interval 0.80 to 1.25. The treatment means and estimate of residual variance for the confidence interval calculation will come from an Analysis of Variance of the Test and Reference results using a statistical model containing terms for Treatment and Site.

For the proportion of subjects with clinical success, the Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the 90% confidence interval on the difference between Test and the Reference proportions is contained within the interval -20% to +20%. The confidence interval will be constructed using Wald's method with Yates' continuity correction.



Superiority

For the percent reductions from baseline in the inflammatory and non-inflammatory lesion counts, each active treatment will be evaluated to determine if it has superior efficacy to that of the Vehicle at Visit 4/Week 12/Day 84 via an Analysis of Variance using a statistical model containing terms for Treatment and Site.

The proportion of subjects with clinical success for each active treatment will be compared to that of the Vehicle using a Z-test with Yates' continuity correction.



All hypothesis tests will be two-sided at a significance level of $\alpha = 0.05$, except confidence intervals which will be based on $\alpha = 0.1$ (e.g., 90% coverage).

8.1.5 Safety and Adverse Events Analysis

The frequency and percent of subjects with adverse events will be summarized by MedDRA system organ class and preferred term and by severity and relationship to study drug for all three treatment groups. The adverse events reported by at least five percent of the subjects in any treatment group will also be tabulated. The comparable safety of the Test and Reference treatments will be evaluated by statistical comparison of the proportion of subjects who reported any adverse events. The frequency and distribution of application site reactions of erythema, dryness, scaling/peeling, burning/stinging, erosion, edema, pain and itching will be summarized and compared descriptively. Safety comparisons will be performed only for the safety intent-to-treat population.

8.2 Comparability of Subjects at Baseline

Descriptive statistics will be presented, by treatment group, for subject baseline characteristics. The significance of any obvious treatment group differences will be discussed in the CSR.

9. CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES

It will be made clear to the subject that, for the purposes of the study, they are consenting only for topical application of medication or vehicle. 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, 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.

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 of any written informed consent/assent form used in the study, preferably prior to submission to the IRB.

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 screening phase, the subject will be withdrawn from screening. In the event that the subject is re-screened for study participation, a new informed consent/assent form must be signed.

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, it is required that the investigator permit the study monitor, any 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 or their 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 or their authorized representative 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 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 under adequate security and restricted accessibility.

10. CONDUCT OF STUDY

The investigational site is to maintain complete documentation of all events and the times at which they occur.

10.1 Completion of Study

The investigational site will complete the study and complete all documentation required, in satisfactory compliance with the protocol, within 3.5 months of enrollment of the last subject and extending beyond as needed to complete necessary data queries.

Protocol No: PRG-NY-17-008

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

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 between [REDACTED] 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 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

Database set-up will be performed by [REDACTED] in collaboration with the Electronic Data Capture (EDC) vendor, using an appropriate fully validated, 21 CFR Part 11 compliant EDC system. eCRFs will be provided to each site via a secured web link. All applicable study data collected on each subject will be recorded by approved site personnel into the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Approved staff at [REDACTED] will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual data queries to correct missing data or discrepancies found against the source within the EDC system.

Data validation will consist of automated and manual edit checks that are created directly into EDC. Automated edit checks will be executed on all data points defined and documented by the study team and data management. Study metrics will be reported from the EDC system.



Protocol No: PRG-NY-17-008

After all data have been verified by approved staff at [REDACTED] an Investigator or Sub-Investigator (listed on Form FDA 1572) is required to review and approve all eCRFs prior to database lock and breaking of the blind.

After database lock, each site will be provided with a password protected CD that will include the eCRF data from their site for local archival purposes.

Quality assurance verification via a 10% database audit of eCRF data will be conducted before the treatment assignment code is broken.

During each subject's visit to the clinic, a designee 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 Week 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, will be entered in **black or blue 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 database. The database 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).

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 21 CFR§312.57 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 a New Drug 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. 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 eCRFs.

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 electronic case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

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, any other countries regulations, and 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 (e.g., the clinical protocol, eCRFs), 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 used 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]

Protocol No: PRG-NY-17-008

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-17-008

PROTOCOL TITLE:

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Limited Partnership Adapalene and Benzoyl Peroxide Topical Gel 0.3%/2.5% to Galderma Laboratories, L.P. Epiduo® Forte (Adapalene and Benzoyl Peroxide) Gel 0.3%/2.5%, and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

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



15. APPENDICES

15.1 Appendix A: Study Personnel Contacts

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

15.2 Appendix B: Instructions for the Subject

Check Visit Dispensed: Visit 1: Visit 2: Visit 3: Unscheduled visit: Date: _____

SUBJECT INITIALS: _____ SUBJECT NUMBER: _____ SITE NUMBER: _____

[REDACTED]

[REDACTED]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[REDACTED]

Your study coordinator will call you in about 2 weeks to see how you are doing and to answer any questions you may have:

Your call is scheduled for: _____ (Week 2)
(Date)

You are scheduled to return at:

_____ on _____ (Visit 2, Study Week 4)
(Time) (Date)

[REDACTED]

_____ on _____ (Visit 3, Study Week 8)
(Time) (Date)

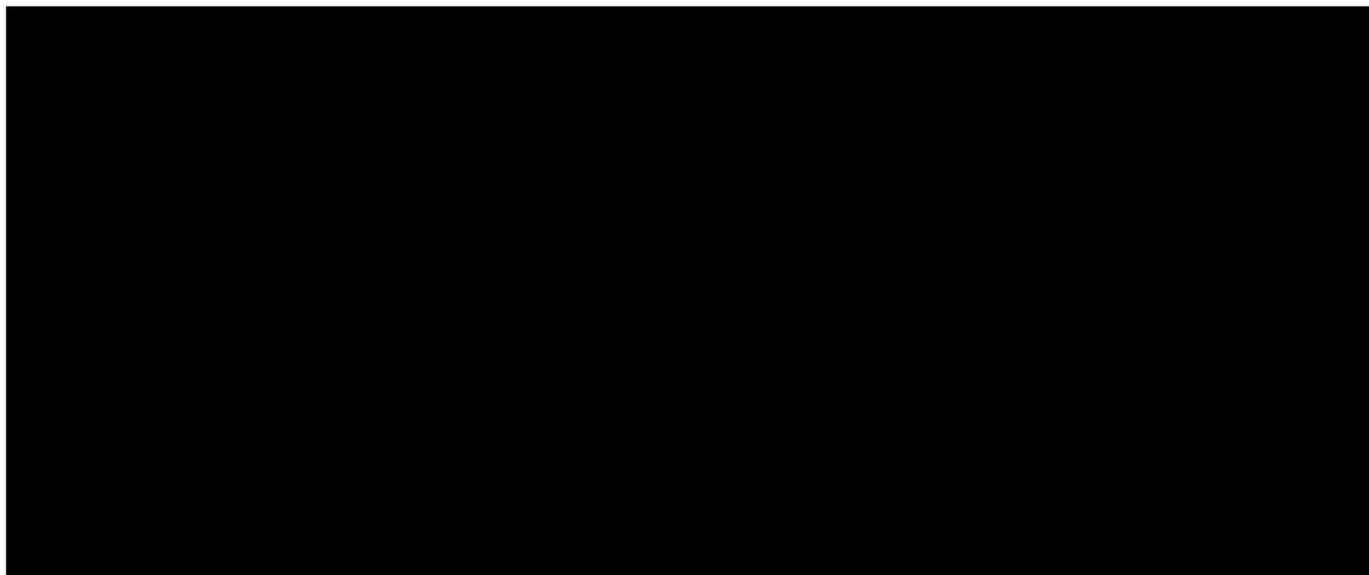
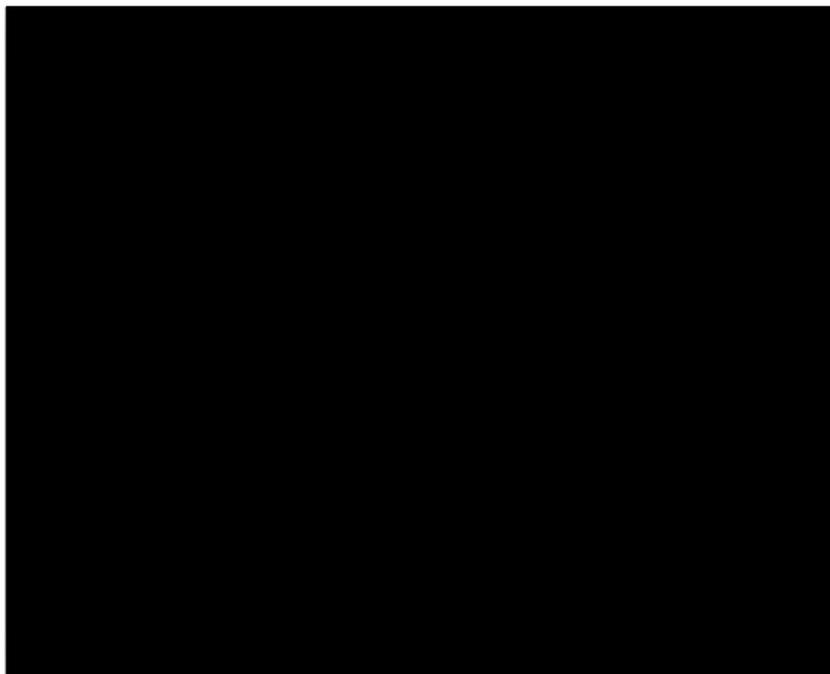
_____ on _____ (Visit 4, Study Week 12)
(Time) (Date)

ALL APPOINTMENTS ARE IMPORTANT! IF YOU NEED TO RE-SCHEDULE YOUR APPOINTMENT, PLEASE CALL YOUR STUDY DOCTOR'S OFFICE IMMEDIATELY.

Name and Telephone Number of Study Coordinator/Study Site



15.3 Appendix C: Face Diagram



16. REFERENCES

1. [Redacted]

[Redacted]