A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo Israel Pharmaceuticals, Ltd. Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% to Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%), and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

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Protocol No.: PRG-NY-12-005

Confidential

[redacted]

PROTOCOL SIGNATURE PAGE

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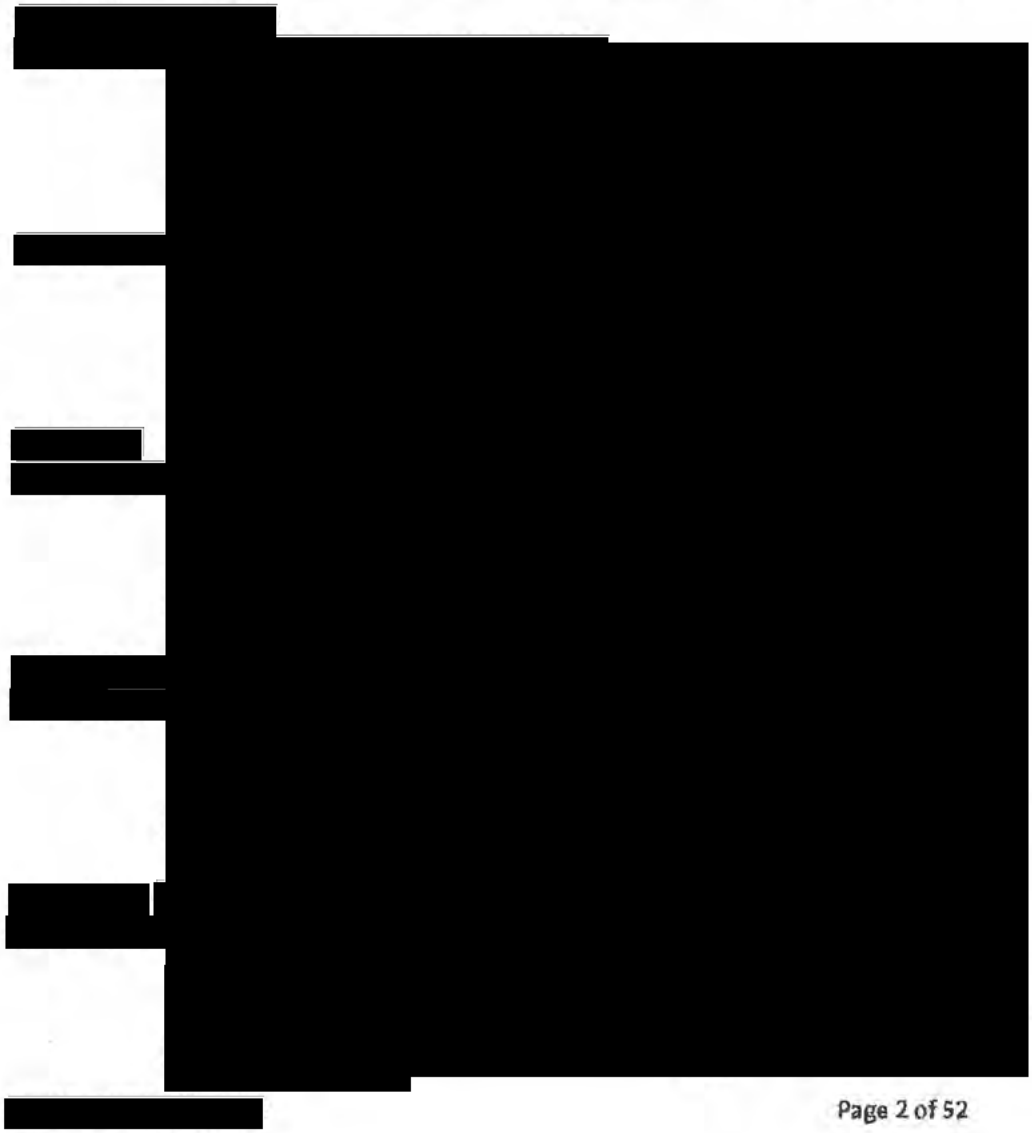
Signatures of representatives below indicate this is the agreed upon final version of the protocol:



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[redacted]

STUDY SYNOPSIS

Title:	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo Israel Pharmaceuticals, Ltd. Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% to Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%), and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris
Study Period:	12 weeks
Study Medication:	1. Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5%, Perrigo Israel Pharmaceuticals, Ltd. 2. Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%), Valeant Pharmaceuticals (Dow Pharmaceutical Sciences, Inc) 3. Vehicle of test product, Perrigo Israel Pharmaceuticals, Ltd.
Study Objectives:	To compare the safety and efficacy profiles of Perrigo Israel Pharmaceuticals, Ltd. Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% to Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%) 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 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] 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] to the affected areas of the face avoiding contact with the eyes, mouth, lips, inside and on angles of the nose, and mucous membranes once daily for 12 weeks.
Study Visits:	Clinical Evaluations will be performed at: 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) 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 (±4 days) Telephone Contact.
Evaluations:	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.

Endpoints:	The two primary efficacy endpoints will be the: 1) Mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion count and 2) Mean percent change from baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion count. 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.
Safety:	The incidence of all adverse events reported during the study will be summarized by treatment group. [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.

ABBREVIATIONS

PP	Per protocol population
IGA	Investigator's Global Assessment
ANOVA	Analysis of Variance
LOCF	Last Observation Carried Forward
mITT	Modified Intent To Treat population
ITT	Intent to treat population
FDA	US Food and Drug Administration
IRB	Institutional Review Board
AE	Adverse Event
SAE	Serious Adverse Event
IUD	Intra-Uterine Device
OTC	Over the counter
Rx	Prescription
CRF	Case Report Form
SPF	Sun Protection Factor
SAP	Statistical Analysis Plan
DCF	Data Clarification Form
ICH	International Conference on Harmonization
GCP	Good Clinical Practice
CMH	Cochran–Mantel–Haenszel test
PI	Principal Investigator

1. BACKGROUND

[redacted]

[redacted] Perrigo Israel Pharmaceuticals, Ltd. has developed a generic formulation of Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5%.

2. STUDY OBJECTIVES

The objectives of this study are to compare the efficacy and safety profiles of Perrigo Israel Pharmaceuticals, Ltd.; Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% and Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/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 in the inflammatory (papules and pustules) lesion count and
2) Mean percent change from baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion count.

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.

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. 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.

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]

[redacted] the assigned study medication will be applied topically [redacted] to the affected areas of the face, avoiding contact with the eyes, lips, mouth, inside and on angles of the nose, and mucous membranes once daily [redacted] for 12 weeks.

Subjects will be males and females, ≥ 12 to ≤ 40 years of age, with at [redacted] facial acne vulgaris with an inflammatory lesion (papules or pustules) [redacted] and a non-inflammatory lesion (open and closed comedones) [redacted] and no [redacted] nodulocystic lesions (i.e., nodules and cysts) on the face including those present on the nose. Visits to the study site are scheduled at baseline (Day 1) and Weeks 4, 8, and 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.

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 for this study. Subjects under the legal age of consent must sign an IRB approved written informed consent/assent in addition to a parent or legally authorized representative.
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) [redacted] and no [redacted] nodulocystic lesions (i.e., 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 topical acne medication or topical antibiotics 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]

[redacted]

4.2 Exclusion Criteria

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

1. Subjects, who are pregnant, breast feeding, or planning a pregnancy within the study participation period.
2. Presence of [redacted] facial nodulocystic lesions (i.e. nodules and cysts).
3. [redacted]
4. [redacted].
5. [redacted]
6. [redacted]
7. Presence of any other facial skin condition that might interfere with acne vulgaris diagnosis and/or assessment [redacted]
8. Excessive facial hair [redacted] that would interfere with diagnosis or assessment of acne vulgaris.
9. History of unresponsiveness to topical Clindamycin Phosphate and/or benzoyl peroxide therapy.
10. Use of systemic Clindamycin products [redacted] prior to baseline or throughout the study.
11. History of hypersensitivity or allergy to Clindamycin Phosphate, benzoyl peroxide and/or any ingredient in the study medication.
12. 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 [redacted]
13. Use [redacted] prior to baseline or during the study of therapeutic vitamin D supplement [redacted]
14. Use of medications known to exacerbate acne [redacted]
15. [redacted]
16. Use of medicated make-up throughout the study and significant change in the use of consumer products [redacted] and throughout the study (other than study supplied cleanser and lotion).
17. Use [redacted] prior to baseline or during the study of 1) systemic steroids*, 2) systemic (e.g., oral or injectable) antibiotics, 3) systemic treatment for acne vulgaris (other than oral retinoids which require a 6-month washout), or 4) systemic anti-inflammatory or immunosuppressive agents [redacted].

[redacted]

18. [redacted]

19. [redacted]

20. [redacted]

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

22. [redacted]

23. [redacted]

24. [redacted]

25. Previous enrollment in this current study.

26. [redacted]

4.3 Precautions

The following precautions are to be taken during this study:

1. Subjects should avoid contact of the study medication with the eyes, mouth, angles of and inside the nose, lips and other mucous membranes or on any cuts or open wounds. In case of accidental exposure, the eyes should be rinsed with plenty of water.
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. Subjects should consult the investigator with any questions regarding concomitant medications.
7. Due to the warning contained in the label of this product, subjects should be carefully monitored for adverse events associated with severe colitis (diarrhea and bloody diarrhea). If significant diarrhea occurs, the drug should be discontinued for that subject.
8. Subjects should wash hands before and after applying study medication.
9. [redacted]

10. [redacted]
11. Subjects should avoid getting the assigned treatment on their hair or on colored fabric. Product may bleach hair or colored fabric.
12. The product should not be applied to cuts, abrasions, eczematous or sunburned skin.
13. The product should not be applied more than once daily and subjects should not use more than the recommended amount.
14. [redacted]
15. [redacted].
16. Subjects should be informed that local skin reactions (erythema, scaling, itching, burning and stinging) may occur.
17. Subjects should be informed that more serious side effects such as diarrhea, stomach pain and allergic reactions (e.g. severe swelling, shortness of breath, and anaphylaxis) may occur and that they should report these symptoms to the study staff immediately.

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. A copy of the signed consent/assent will be given to every participant 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 a parent or legally authorized representative.

5.2 Assignment of Subject Number

An independent third-party dispenser will 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. The subject numbers will be assigned sequentially in the order in which subjects are enrolled at each center.

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 commencing the use of the study medication. A record of medication taken by the subject during the study is to be obtained at each study visit including the Week 2/Day 14 (±4days) telephone contact.

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. The exam will include heart, lung, abdomen evaluation as well as recording height, weight and vital signs. Vital signs are to include sitting blood pressure, oral temperature, heart rate, and respiratory rate.

5.6 Urine Pregnancy Test

[redacted]

5.7 Dermatological Assessment (Diagnosis)

Investigator or sub-investigator will examine the subject to establish the clinical diagnosis of facial acne vulgaris (a score of at least 3 (moderate severity) or 4 (severe), on the Investigator's Global Assessment is needed for enrollment).

5.8 Investigator's Global Assessment (IGA)

To the greatest extent possible, the same investigator who made baseline (Day 1) assessments will perform a Global Assessment of the subject's overall acne vulgaris condition at each subsequent visit. The IGA must be conducted by qualified investigators listed on the Form FDA 1572 who have been delegated this task by the Principal Investigator (PI). [redacted]. 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 Case Report Forms 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

Each subject's initial condition and course of acne vulgaris will be assessed by counting the inflammatory and non-inflammatory lesions as well as nodules/cysts including those present on the nose (excluding the angles of the nose) and documenting on the facial diagram as part of the source documentation. [redacted]

5.9.1 Inflammatory Lesion Count

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 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 ≤ 5mm diameter

Pustule = pus-filled inflammatory lesion ≤ 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 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

[redacted]

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

5.9.3 [redacted]

5.10 Application Site Reaction Assessment

At baseline and each subsequent visit, application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching are to be recorded. 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 trial visit.

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 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.

Site Reaction	DESCRIPTION
Erythema	[redacted]
Dryness	[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] pump bottle of study medication from the subject kit box will be dispensed 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). The initial application on Day 1 will be demonstrated and observed by study staff when the subject applies the mediation at the study site to ensure subjects understand the instructions. Subsequent applications of study medication should be applied as demonstrated starting Day 2. [redacted]. At all subsequent study visits the study medication will be collected to assess study medication accountability. After the compliance evaluation, empty pump bottles will be collected and kept by the site. [redacted] subject will receive a new pump bottle each at Visit 2/Week 4/Day 28 (±4days) and Visit 3/Week 8/Day 56 (±4days). However all subjects MUST switch to at least the second new pump bottle by Visit 2/Week 4/Day 28 (±4days) or Visit 3/Week 8/Day 56 (±4days). The sites must collect pump 1 from each subject by Visit 3/Week 8/Day 56 (±4days) . [redacted]

A non-medicated, mild cleanser and a facial lotion with sunscreen will be dispensed to the subjects at the baseline visit. Subjects will cleanse their face with the study provided non-medicated, mild cleanser [redacted]. [redacted] the study medication should be applied to the affected areas of the face [redacted] and avoiding contact with the eyes, lips, mouth, inside and on angles of the nose, and mucous membranes at approximately the same time once daily for 12 weeks. Subjects will be instructed to wash hands immediately after applying the study medication. Subjects will be instructed to not use any other topical treatments or products other than the study provided facial lotion with sunscreen.

A diary card will be dispensed to each enrolled subject at Visit 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, and dispense additional study medication as required and a new diary. 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.

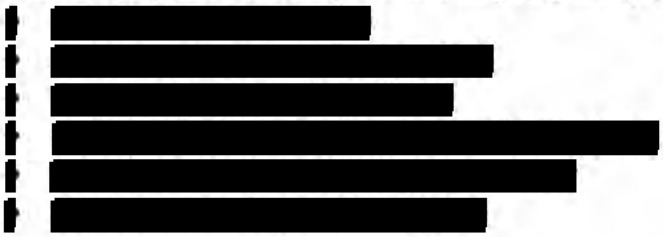
5.12 Visit Specific Procedures

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. The following procedures will be performed at the baseline visit:

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



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

[redacted]

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

[redacted]

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

[redacted]

5.12.6 Unscheduled Visit

An unscheduled visit is allowed at anytime 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, 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.

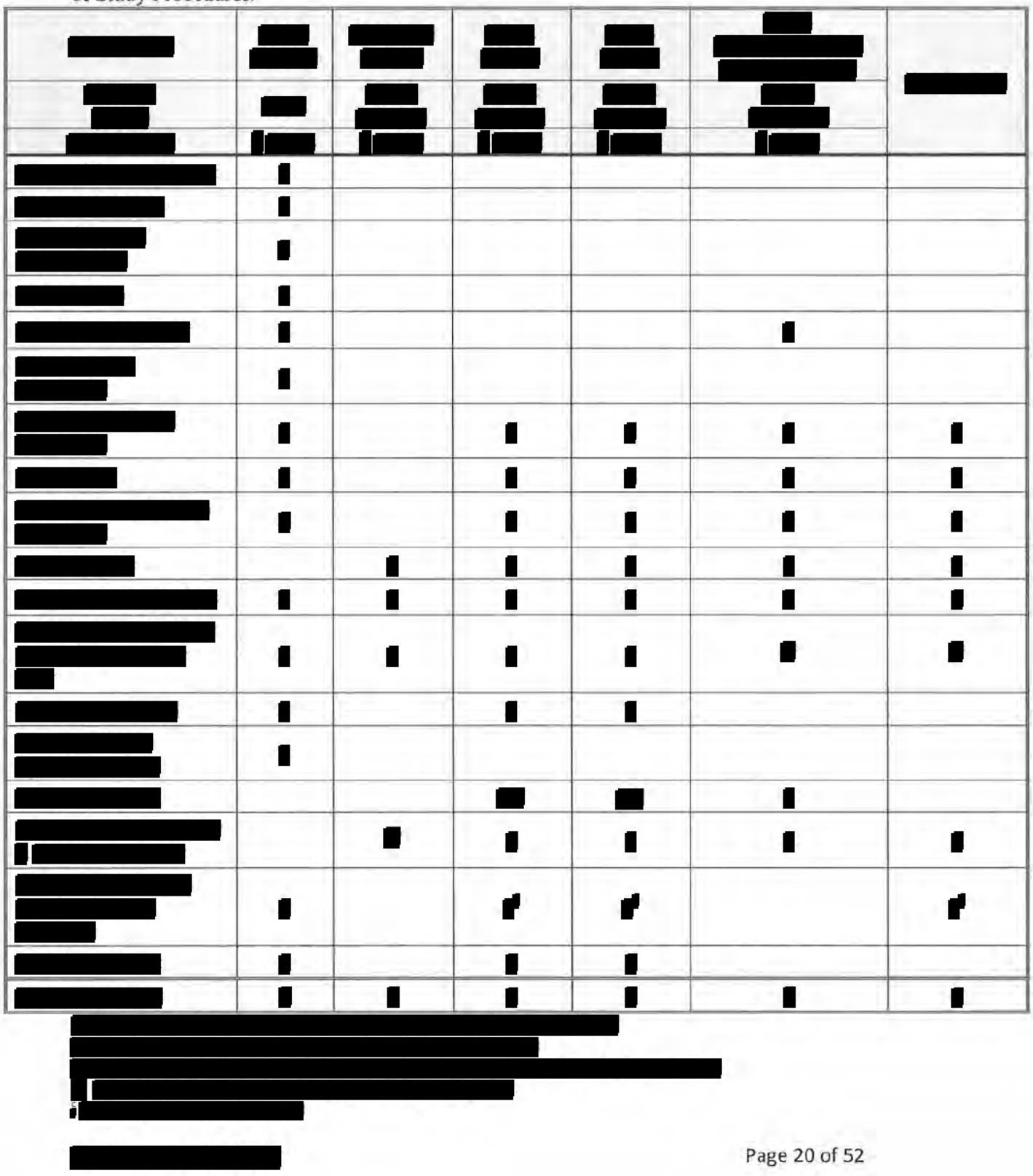
[redacted]

[redacted]

[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.



5.14 Screen Failures

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 received medication.

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 Pharmaceuticals/ contacts in Section 15 (Appendix A) at the earliest possible time.

[redacted]

[redacted]

5.16 Subject/Treatment Compliance

Subjects will apply the medication to the affected areas of the face including the nose at approximately the same time once daily for 12 weeks. On Day 1, subjects will apply their initial dose of study medication at the study site under the supervision of study staff. Compliance will be determined from the diary card, in which the subject will be instructed to record all applications made or missed. On Week 2 Day 14/ (±4 days), compliance will be assessed via telephone contact. The study co-ordinator will review Subject Instruction Sheet and Diary with the subject on the phone. The number of applications will be totaled by the study coordinator and recorded on the compliance page of the CRF. [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.

[redacted]

- The subject's medication code is unblinded.
- Subject did not meet or no longer meets the entry criteria.
- 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.
- 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]

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

If a subject is discontinued from the study for any reason, the Visit 4/ 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 End of Study Case Report Form.

[redacted]

6. MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by Perrigo Pharmaceuticals will consist of:

Test Product: Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5%, - [redacted]

Reference Product: Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%), - manufactured by Coria Labs (Valeant Pharmaceuticals).

Vehicle: Vehicle of test product - [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 random code, so that neither the subject nor the investigator can identify the treatment.

All study medications will be supplied to the subjects in [redacted] pump bottles. Each subject's treatment unit will consist of one kit box containing [redacted] pump bottles of study medication. [redacted]

In order to nullify any differences in product packaging, an independent third-party dispenser who is not collecting any patient data (e.g. adverse events or symptomatic assessments), performing any clinical evaluations such as IGA, lesion counting or evaluating diaries will dispense and collect study medication from the subjects. The third party dispenser will instruct the subject in study medication application, instruct the subject in diary card completion and oversee the study medication application (Note: Patient data does not include the collection of initial baseline medical history, contact information, or informed consent, etc., only those items/activities that may result in the independent third party dispenser becoming biased should be avoided). The 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 one randomly selected block of study medication for each shipment of study medication received. As per the Code of [redacted]

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. 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 was used." The investigator will store the retain sample study medication until such time as notification is received from Perrigo Pharmaceuticals that the samples are no longer required.

6.2.3 Storage and Test Article Accountability

Study articles used to conduct this study will be maintained under adequate security by the investigator. Study test articles will be stored in a refrigerator, 2-8°C (36-46°F) in a secured area with limited access. Each investigator site will ensure that the temperature of study medication is monitored and recorded throughout the study. The medication should not be frozen, should be protected from heat and kept tightly closed. 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. [redacted]

The clinic personnel will keep a running inventory of study test articles dispensed that will include subject numbers assigned and the date each is dispensed and used. 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 containers must be inventoried by the monitor and returned to Perrigo Pharmaceuticals, or designee, for destruction.

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, [redacted] to Test: Reference: Placebo [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 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 Pharmaceuticals or designee when possible.** The reason for breaking the blind must be clearly documented in the source documentation and CRF and the subject must be

discontinued from the study. Perrigo Pharmaceuticals must be notified immediately upon all unblinding situations.

7. ADVERSE REACTIONS

The potential adverse reactions of generic Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% are anticipated to be similar to those observed in Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5%). Adverse reactions related to treatment with Acanya Topical Gel include cutaneous irritation (erythema, scaling, itching, stinging and burning).

The following adverse reactions occurred in less than 0.2% of patients treated with Acanya gel: application site pain (0.1%), application site exfoliation (0.1%) and application site irritation (0.1%).

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudo membranous colitis) have been reported with the use of topical and systemic clindamycin. When significant diarrhea occurs, study medication should be discontinued. Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *Clostridium difficile* toxin may be helpful diagnostically.

Mild cases of pseudo membranous colitis usually respond to study medication discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Anaphylaxis, as well as allergic reactions leading to hospitalizations, has been reported in post-marketing use of products containing clindamycin/benzoyl peroxide.

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 Pharmaceuticals 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 (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
- 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, 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 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

[redacted]

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 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 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 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 CRF.

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 the sponsor. The adverse event term on the AE 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 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] 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 the sponsor, 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 Symbio's Medical Monitor for review. [redacted] will finalize the report and distribute it to the sponsor within 2 days 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] the sponsor, 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] 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 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]

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

[redacted]

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.

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 [redacted] responsibilities for the trial are completed before the outcome of the pregnancy is known, Perrigo Pharmaceuticals will assume the responsibility for following up on the pregnancy.

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 case report form (CRF) with the status of the AE noted.

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 case report form (CRF) page and reported to Perrigo Pharmaceuticals 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

Pharmaceuticals 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 Pharmaceuticals.

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,
  - Who was randomized and received and used study medication.
  - Who met the protocol criteria for compliance [redacted] and
  - Who completed Visit 4/Week 12 (End of Treatment/Early Termination Visit) within window [redacted]
  - Without 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

All randomized subjects who received study medication will be evaluated for safety. The efficacy analysis will be conducted on both the PP and the mITT subject populations. Two-sided hypothesis testing will be conducted for tests. Resulting p-values less than or equal to 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 Week 12 in the inflammatory (papules and pustules) lesion counts AND the mean percent change from baseline to Week 12 in the non-inflammatory (open and closed) lesions.

[redacted]

8.1.3 Sample Size Considerations

[redacted]

[redacted]

8.1.4 Efficacy Measures and Analysis

Clinical endpoints

The primary efficacy measure will be the mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts AND the mean percent change from baseline to 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 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 Center.

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.

[redacted]

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 via an Analysis of Variance using a statistical model containing terms for Treatment and Center.

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 $\alpha = 0.1$ (i.e. 90% coverage). [redacted]

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 [redacted]

treatments will be evaluated by statistical comparison of the proportion of subjects who reported any adverse events. The test and reference treatments' frequency and distribution of application site reactions of erythema, 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

The statistical significance of any treatment group difference in the distribution of categorical variables such as gender will be tested using Cochran–Mantel–Haenszel (CMH) test for general association adjusted for site. Continuous variables, such as age, will be analyzed using a two-way analysis of variance (ANOVA) model with site and treatment as a fixed effect.

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 Pharmaceuticals, 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 Pharmaceuticals.

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 Pharmaceuticals 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 Pharmaceuticals, it is required that the investigator permit the study monitor, any Sponsor 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 Pharmaceuticals 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 Pharmaceuticals 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 Pharmaceuticals 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 Pharmaceuticals 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.

It is agreed that, for reasonable cause, either the investigator or Perrigo Pharmaceuticals 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 Pharmaceuticals.

10.2 Protocol Amendments

The Investigator will not make any changes to this protocol without prior written consent from Perrigo Pharmaceuticals 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 Pharmaceuticals. If agreement is reached regarding the need for an amendment, the amendment will be written by Perrigo Pharmaceuticals. 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 Pharmaceuticals will submit protocol amendments to the FDA or other regulatory agencies.

When, in the judgment of the reviewing IRB, the investigators and/or Perrigo Pharmaceuticals, 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

All data collected in this study will be entered onto CRFs, verified by monitoring, submitted for double key entry into an appropriate database, 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 for appropriate Quality Assurance verifications before the treatment assignment 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 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 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 Pharmaceuticals, 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 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 Pharmaceuticals 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 Pharmaceuticals or (2) providing an opportunity for Perrigo Pharmaceuticals 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 [redacted]. Such documentation is subject to inspection by Perrigo Pharmaceuticals and the FDA.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

Perrigo Pharmaceuticals 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 Pharmaceuticals (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.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact Perrigo Pharmaceuticals 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 Pharmaceuticals 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 Pharmaceuticals 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 Pharmaceuticals, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of Perrigo Pharmaceuticals, 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 Pharmaceuticals in connection with the development of the drug. The information may be disclosed as deemed necessary by Perrigo Pharmaceuticals to allow the use of the information derived from this clinical study, the investigator is obliged to provide Perrigo Pharmaceuticals 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 Pharmaceuticals. [redacted]

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-12-005

PROTOCOL TITLE: A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo Israel Pharmaceuticals, Ltd. Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% to Acanya® Topical Gel (Clindamycin Phosphate-Benzoyl Peroxide Gel 1.2%/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 Pharmaceuticals 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]

15.2 Appendix B: Instructions for the Subject

Check Visit Dispensed: Visit 1: ☐ Visit 2: ☐ Visit 3: ☐ Visit 4: ☐ Unscheduled visit: ☐ Date: _____

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

1. [redacted]

2. At your visit today, you were instructed and shown how to use the medication. The medication should be applied at the same time once daily, for 12 weeks. Record each application on your Diary. Do NOT apply the product more than once daily and do NOT use more than the recommended amount.

Instructions for applying the study medication

[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)

_____ 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 DOCTOR'S OFFICE IMMEDIATELY.

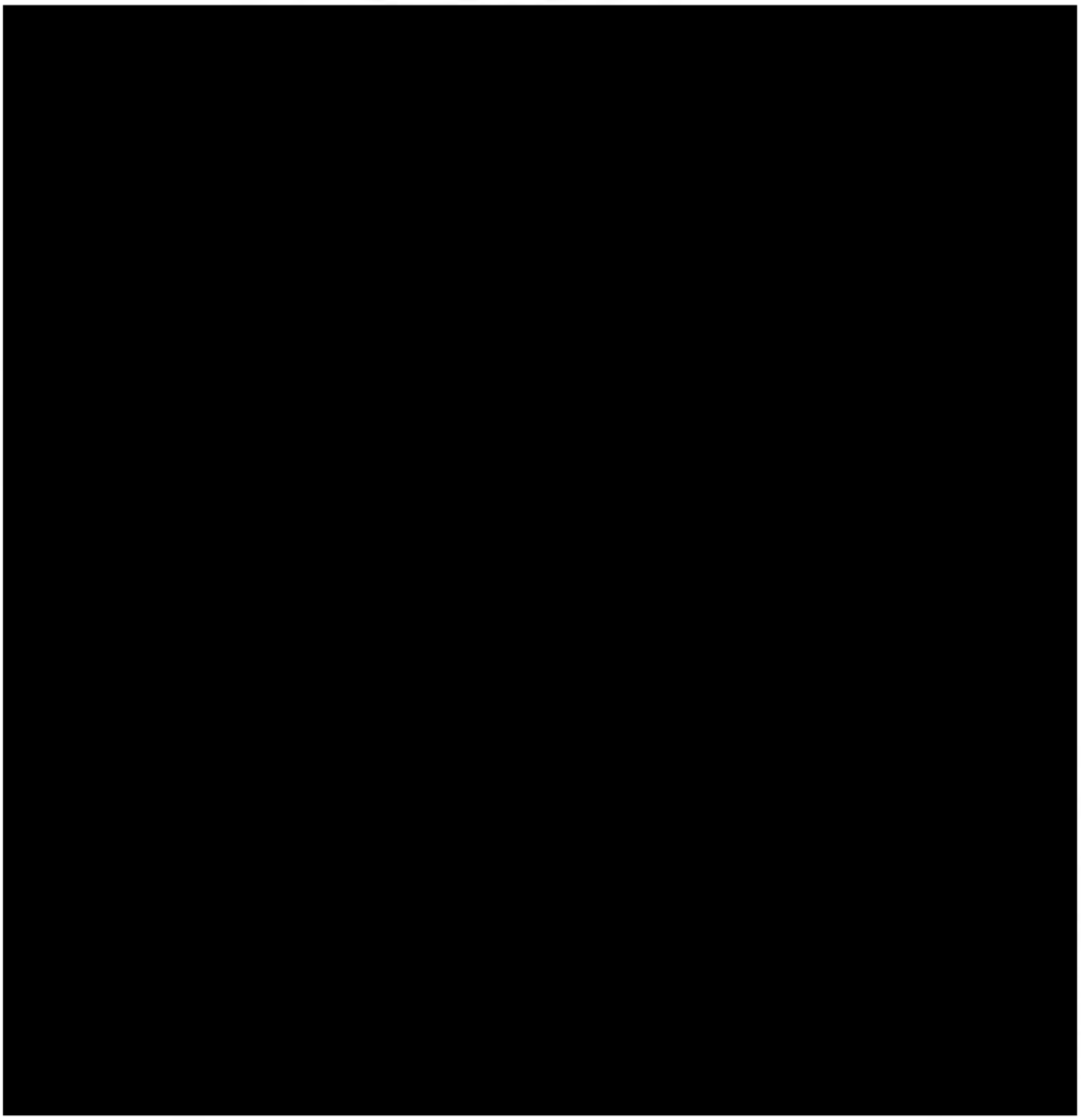
_____

Name and Telephone Number of Study Coordinator/Study Site

[redacted]

15.3 Appendix C: [redacted]

[redacted]



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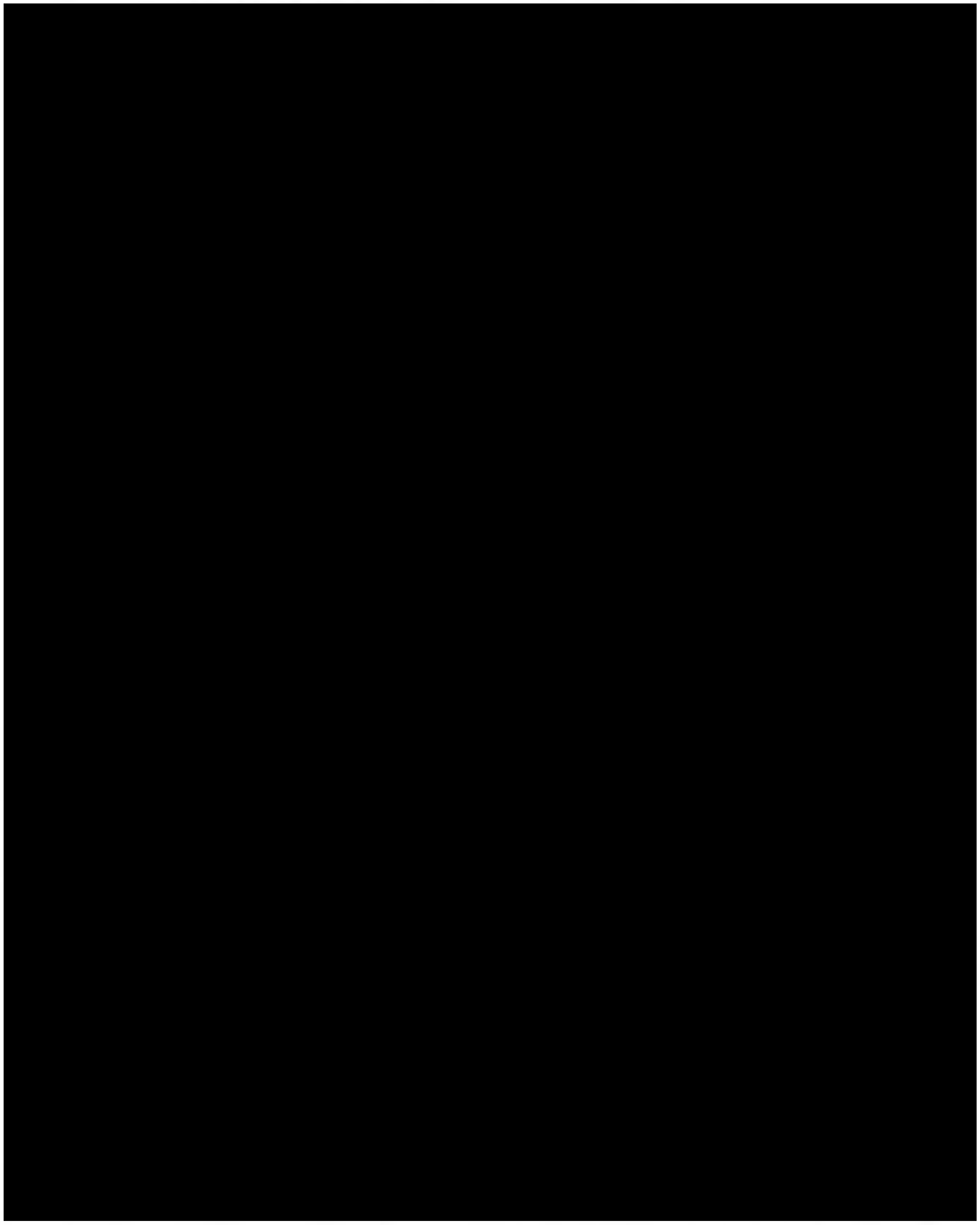

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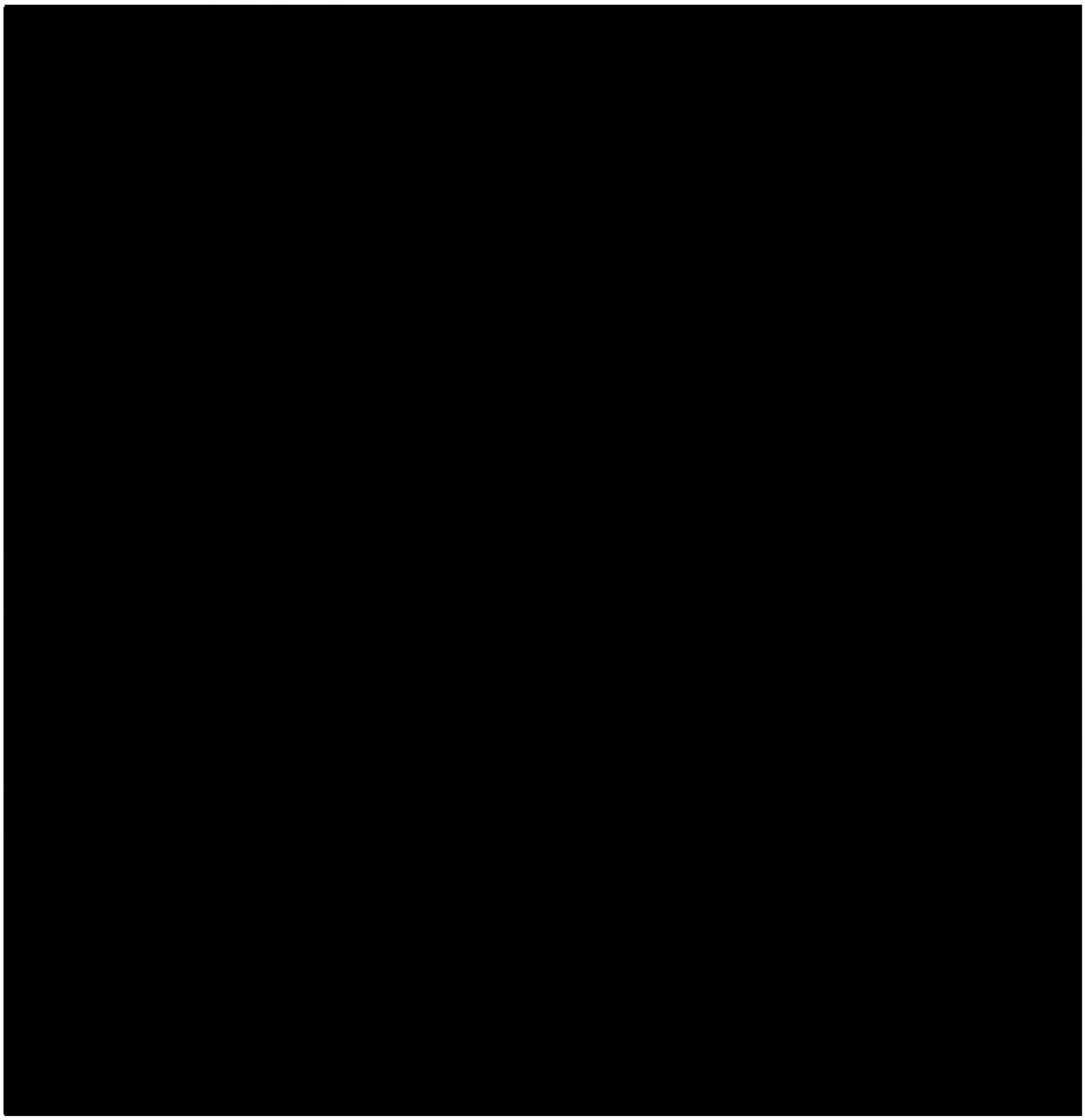

[redacted]

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16. REFERENCES

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