A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP COMPARISON STUDY TO DETERMINE THE THERAPEUTIC EQUIVALENCE OF GDC 268 AND CLINDAMYCIN PHOSPHATE TOPICAL LOTION, 1% IN SUBJECTS WITH ACNE VULGARIS

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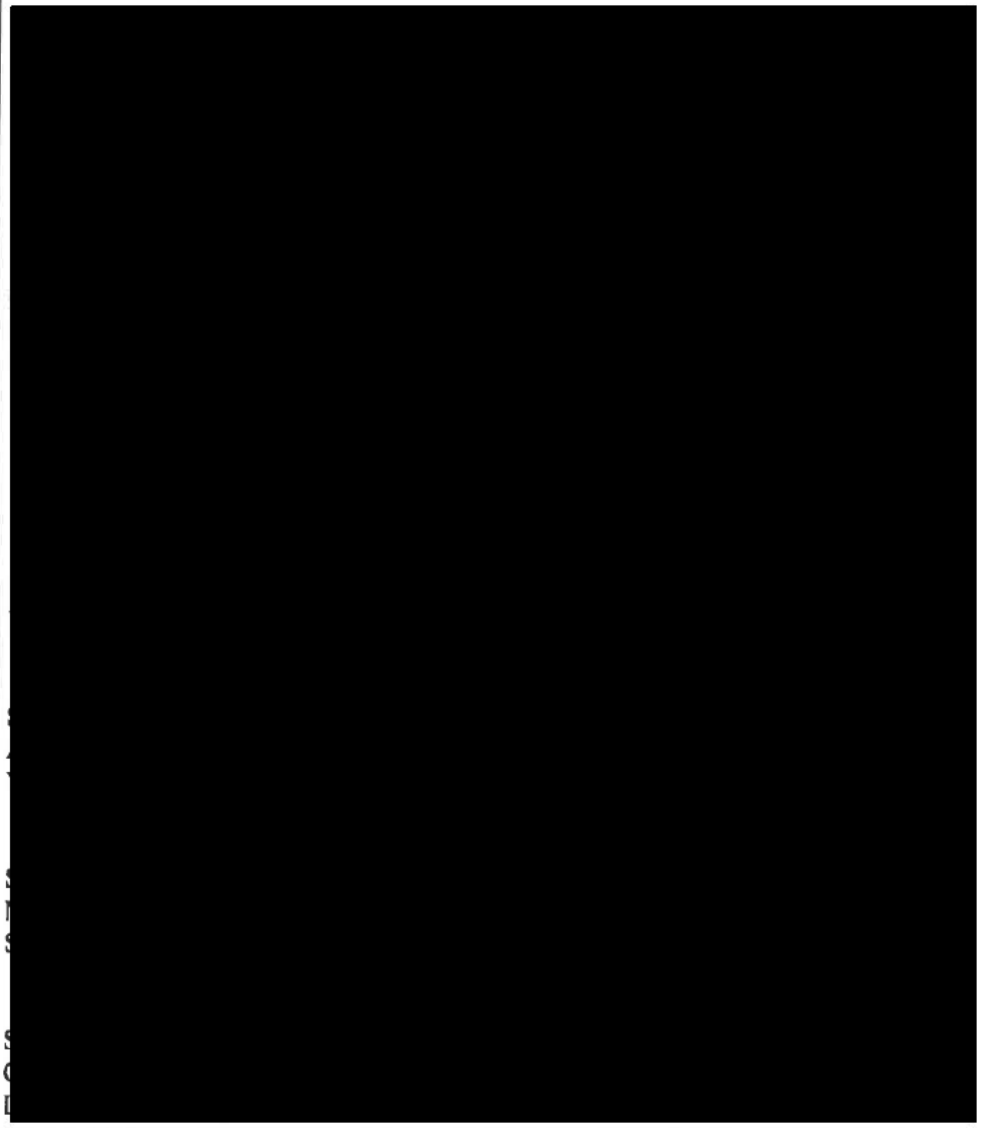
PROTOCOL APPROVAL

The following individuals approve version 3.0 of the GDC-268-001 protocol dated September 6, 2019. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.



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STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Gage Development Company, LLC, the Sponsor.

I have read this protocol, agree that it contains all the details necessary to conduct the study as described, and will conduct this study following this protocol.

I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from Gage Development Company, LLC. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to Gage Development Company, LLC of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by Gage Development Company, LLC, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

Any additional information added to this protocol is also confidential and proprietary to Gage Development Company, LLC and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Investigator Signature Date

Protocol number: GDC-268-001 Site number: _____

PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Comparison Study to Determine the Therapeutic Equivalence of GDC 268 and Clindamycin Phosphate Topical Lotion, 1% in Subjects with Acne Vulgaris
Study Type	Bioequivalence with Clinical Endpoint
Test Articles	1. Test product: GDC 268 (Gage Development Company, LLC) 2. Reference Product: Clindamycin Phosphate Topical Lotion, 1% (GREENSTONE® BRAND) 3. Placebo: GDC Vehicle (Gage Development Company, LLC)
Study Objective	To evaluate the safety, tolerability, and therapeutic equivalence of GDC 268 to Clindamycin Phosphate Topical Lotion, 1% and to compare the efficacy of these two products to the GDC vehicle lotion (i.e., placebo) in the treatment of acne vulgaris.
Study Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group comparison.
Treatment Groups	Eligible subjects will be randomized (2:2:1) to treatment with GDC 268, Clindamycin Phosphate Topical Lotion, or GDC Vehicle.
Duration of Treatment	Twice daily for 12 weeks.
Duration of Study	Each subject will participate for approximately 12 weeks, in addition to the screening visit.
Study Population	Healthy male or female subjects 12 to 40 years of age (inclusive) with a clinical diagnosis of mild to severe facial acne vulgaris (Grade 2, 3, or 4 on the Investigator's Global Assessment [IGA]), 25-100 non-inflammatory lesions (i.e., open and closed comedones), 20-70 inflammatory lesions (i.e., papules and pustules), and ≤2 nodulocystic lesions (nodules and cysts) on the face.
Total Number of Subjects	Approximately 1200 subjects will be enrolled to obtain at least 1153 modified intent-to-treat (mITT) and at least 865 per-protocol (PP) subjects in the study.
Number of Sites	Approximately 50 sites will participate in the study.
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is a healthy male or non-pregnant, non-breastfeeding female 12 to 40 years of age (inclusive) at the time of consent/assent. 2. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide

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	informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation. 3. Subject has a clinical diagnosis of mild to severe facial acne vulgaris defined as Grade 2, 3, or 4 on the IGA at Baseline. 4. Subject must have ≥ 25 but ≤ 100 non-inflammatory lesions (open and closed comedones) AND ≥ 20 but ≤ 70 inflammatory lesions (papules and pustules) AND ≤ 2 nodulocystic lesions (nodules and cysts) on the face (e.g., forehead, nose, cheeks, chin, upper lip) at Baseline. 5. Subject and parent/guardian (if applicable) are willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study. 6. Subject must be willing and able to refrain from use of all other topical products in the Treatment Area, all acne medications other than test article, and all antibiotics (other than test article) during the 12-week treatment period. 7. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of facial acne vulgaris or otherwise impact the integrity of the study, or exposes the subject to an unacceptable risk by study participation. 8. Females must be surgically sterile[1] or use an effective method of birth control.[2,3] Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[4] at Baseline. 9. Subject has used the same type and brand of make-up, cleanser or other non-medicated facial products and hair products (e.g., Clinique foundation, Cetaphil soap, shampoo, hair gel, hairspray, mousse, etc.) for at least 4 weeks prior to Visit 1/Baseline and agrees to continue and not change his/her other general skin care and hair care products and regimen for the entire study. NOTE: Subjects who change from using a medicated acne cleanser that contains benzoyl peroxide, salicylic acid, etc. to using a bland non-medicated/non-acne cleanser

[1] Hysterectomy, bilateral tubal ligation (at least 6 months prior to initiation of treatment), or bilateral oophorectomy.

[2] Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, implantable, or vaginal ring] (see next footnote), b) intrauterine device (IUD), c) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], d) monogamous relationship with a partner who is sterile [e.g., vasectomy performed at least 6 months prior to study entry], or e) total abstinence for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a partner of the opposite sex who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.

[3] WOCBP taking hormonal therapy (e.g., oral, transdermal, injectable, implantable, vaginal ring) must be on treatment prior to study entry, continued per label, and must not change their dosing regimen during the study. **WOCBP taking hormonal therapy for any reason must be on the same treatment for at least 3 months prior to study entry.** Those who have used hormonal therapy prior to study entry must have discontinued use at least 8 weeks prior to the start of the study. NOTE: Subjects using hormonal therapy for acne management should not be allowed to enroll unless they have washed out of this therapy for at least 8 weeks prior to study entry.

[4] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

	prior to Visit 1/Baseline will only be required to have used the new non-acne cleanser for at least 2 weeks in order to establish a stable skin care regimen.
Exclusion Criteria	A subject is ineligible to enter the study if he/she meets one or more of the following criteria: 1. Subject is pregnant, breastfeeding, or is planning to become pregnant or breastfeed during the study. 2. Subject has active nodulocystic acne or acne conglobata, acne fulminans, or other forms of acne (e.g., acne mechanica). 3. Subject has more than 2 facial nodules/cysts (where nodule/cyst is defined as an inflammatory lesion greater than or equal to 0.5 cm in size with or without cystic changes). 4. Subject has any skin condition that, in the investigator's opinion, could interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis). 5. Subject has excessive facial hair (e.g., beards, sideburns, moustaches), facial tattoos, or other facial attributes that would interfere with diagnosis or assessment of acne vulgaris in the opinion of the investigator. 6. Subject has a history of hypersensitivity or allergy to clindamycin or lincomycin and/or any of the ingredients in the test articles. 7. Subject has a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis. 8. Subject is atopic (e.g., atopic dermatitis, allergic rhinitis, allergic asthma). Note: Subjects that are not atopic but have a component(s) of this syndrome may be enrolled (e.g., a person with allergic rhinitis or allergic asthma). 9. Subject has used any of the following <u>topical</u> preparations or procedures on the face: • Topical retinoids (e.g., tazarotene, adapalene, and tretinoin) within 2 weeks prior to Baseline; • Topical anti-acne treatments including, but not limited to, over-the-counter (OTC) acne cleansers, soaps, washes or treatments, benzoyl peroxide, antibiotics, azelaic acid, dapsone, sulfa based products, corticosteroids, and salicylic acid within 2 weeks prior to Baseline; • Topical steroids within 2 weeks prior to Baseline. • Topical antibiotics within 2 weeks prior to Baseline. • Topical anti-inflammatory agents within 2 weeks prior to Baseline; • Cryodestruction or chemodestruction, dermabrasion, photodynamic therapy including other light-based and laser therapies, acne surgery, intralesional steroids, or x-ray therapy within 4 weeks prior to Baseline; • Other topical therapy, which may materially affect the subject's acne, in the investigator's opinion. 10. Subject has used any of the following <u>systemic</u> medications:

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	• Corticosteroids (including intramuscular, intra-articular, and intralesional injections) for any indication within 4 weeks prior to Baseline; • Antibiotics[5] for any indication or other systemic anti-acne medications within 4 weeks prior to Baseline; • Androgen receptor blockers (e.g., spironolactone, flutamide) within 4 weeks prior to Baseline; • Retinoid therapy (e.g., isotretinoin) within 6 months prior to Baseline; • Vitamin A supplements (greater than 10,000 units per day) within 6 months prior to Baseline; • Anti-inflammatory agents or immunosuppressive drugs within 4 weeks prior to Baseline; • Neuromuscular blocking agents such as botulinum toxin type A (e.g., BOTOX, DYSPORT) within 2 weeks prior to Baseline; • Other systemic therapy, which may materially affect the subject's acne, in the investigator's opinion. 11. Subject has used oral contraceptives or estrogen for less than 3 months prior to Baseline. 12. Subject is planning surgery during the study. 13. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study. 14. Subject is currently enrolled in an investigational drug, device, or biologic study. 15. Subject has used an investigational drug or investigational device treatment within 30 days prior to first application of the test article. 16. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator. 17. Subject and parent/guardian (if applicable) are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
Study Procedures	Subjects can be screened for the study up to 45 days before Baseline. During screening, the study requirements will be reviewed, written informed consent/assent obtained, and eligibility confirmed. These procedures may be combined with the Baseline Visit if wash out from prohibited medications is not required. If applicable, qualified subjects can wash out from prohibited acne medications or treatments prior to their Baseline Visit once they have been consented. Subjects who require washout for longer than 45 days will be re-consented. The study will consist of a Screening/Baseline Visit, a follow-up telephone call at Week 2, and follow-up visits at Weeks 4, 8, and 12. An unscheduled in-office follow-up visit may be done at the discretion of the investigator for subjects with tolerability issues or a material adverse event (AE) concern.

[5] Contact the Medical Monitor if a subject requires concomitant antibiotic therapy.

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	Visit 1 (Day 1): Screening/Baseline. The following will be obtained at this visit: signed written informed consent/assent (or re-consent/assent if washout period exceeds 45 days), confirmation of eligibility, medical history, demographics, review of concomitant medications and procedures/therapies, dermatologic exam, vital signs (with height and weight), a UPT for WOCBP, clinical evaluations (IGA and lesion counts), local skin reaction (LSR) assessment, and standardized photography of the face. Qualified subjects will be randomly assigned to one of three treatment groups (GDC 268, Reference Product, or GDC Vehicle). Randomization will be blocked from a centralized schedule and stratified by the number of non-inflammatory lesions (≤70 / > 70) present at the Baseline visit. Subject kits will be dispensed according to the kit number assigned by an Interactive Web Response System (IWRS) as subjects are enrolled. Test article application will be demonstrated using the non-medicated samples provided to the site and, as part of training, the subject will apply the non-medicated sample in the clinic under staff supervision to ensure proper application. The subject will be instructed not to open study supplies at the site. Test article will be dispensed along with application instructions, and a Subject Diary will be provided to document applied or missed doses. Subjects will be instructed to apply the test article twice daily, once in the morning and once in the evening, for 12 weeks with the first dose to be applied on the evening of the Baseline Visit. The subject will be scheduled for a follow-up telephone call. Visit 2 (Week 2): Follow-Up Telephone Call. The site staff will contact the subject to confirm the next visit appointment, review the Subject Diary and test article compliance, review of concomitant medications and procedures/therapies, and query the subject about AEs. The site staff will remind the subject to continue to apply test article twice daily, once in the morning and once in the evening and to bring all bottles (used and unused) of test article with him/her to the next clinic visit and to not apply test article or other products to the face within 4 hours of the next clinic visit. Subjects with tolerability issues or a material AE concern of any type may be seen for an in-office follow-up as an unscheduled visit at the discretion of the investigator. Visits 3 and 4 (Weeks 4 and 8): Follow-Up. The subject will return to the clinic for review of concomitant medications and procedures/therapies, LSRs, and AEs. Clinical evaluations (IGA and lesion counts) will be performed. The Subject Diary will be reviewed/collected/distributed as necessary and test article compliance will be reviewed; the site staff will remind the subject to continue to apply test article twice daily, once in the morning and once in the evening, until the next clinic visit and to not apply test article or other products to the face within 4 hours of the next clinic visit. Test article application will be demonstrated if deemed necessary. Test article accountability will be documented. The subject will be scheduled for the next visit. Visit 5 (Week 12): End of Study (EOS) or Early Termination (ET). The subject will return to the clinic for review of concomitant medications and procedures/therapies, LSRs, and AEs. A UPT for WOCBP and clinical evaluations (IGA and lesion counts) will be performed. The Subject Diary will be reviewed and test article compliance will be reviewed. Test article

	accountability will be documented; all test articles and subject diaries will be collected. The subject will exit the study. Unscheduled Visit. The investigator may see the subject at an unscheduled visit to manage any AEs or LSRs (if applicable). The subject will return to the clinic for review of concomitant medications and procedures/therapies, LSRs, and AEs. The Subject Diary and test article compliance will be reviewed. The subject's next appointment will be confirmed.
Study Measurements	Dosing Compliance: Measures of test article compliance will include the duration (days) of treatment (defined as last dose date – first dose date +1), the total number of applications applied and missed (determined from the doses reported in the Subject Diary), and the percent of expected doses applied. A subject will be considered compliant with the dosing regimen if the subject applies at least 75% and no more than 125% of the expected test article applications for the specified duration of the study and does not miss the scheduled applications for more than 3 consecutive days. Efficacy and safety measurements will be assessed according to the schedule of events. Efficacy: *Investigator's Global Assessment* Overall severity of acne will be assessed using a five-point scale where 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, and 4=Severe. This is a static morphological scale that refers to a point in time and not a comparison to Baseline. *Acne Lesion Counts* The number of non-inflammatory lesions (open and closed comedones) and inflammatory lesions (papules and pustules) on the face (including those present on the nose) will be counted. Counts of nodules and cysts will be reported separately and are not to be included in the inflammatory or non-inflammatory lesion counts. Safety: *Adverse Events* All reported or observed AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any ongoing AEs. Untoward events that occur prior to the first dose of test article will be captured in the Medical History section of the electronic case report form (eCRF) unless they are related to a study-specific procedure. *Local Skin Reactions* At each visit, LSRs (erythema, edema, scaling/dryness, stinging/burning, pruritus, erosion, and pain) will be assessed. Erythema, edema, scaling/dryness, and erosion will be assessed by the investigator and stinging/burning, pain, and pruritus will be assessed by the subject. Assessments will be made using a 4-point ordinal scale where 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). Only LSRs that require medical intervention

	(e.g., prescription medication), require withholding or discontinuation of the application of the test article, or extend 2 cm beyond the Treatment Area will be documented as AEs. Any LSRs that are not listed above will be recorded as an AE. *Vital Signs* Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured at Visit 1/Baseline. Assessments will be made after the subject has rested in a seated position for at least 5 minutes. Height and weight will also be measured at Visit 1/Baseline. *Urine Pregnancy Tests* A UPT will be performed at Visit 1/Baseline and at Visit 5/Week 12/EOS for WOCBP.
Study Endpoints	Co-Primary Efficacy Endpoints: • Percent change from Baseline to Week 12 in the inflammatory (papules and pustules) lesion count. • Percent change from Baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion count. Safety Endpoints: • Incidence (severity and causality) of any reported or observed treatment emergent AEs, whether or not they are considered to be related to the test article. • Number of subjects with improved/same versus worsened severities compared to Baseline of the following LSRs: erythema, edema, scaling/dryness, stinging/burning, pruritus, erosion, and pain at each onsite treatment visit.
Sample Size Calculations	Based on the assumption of a 40% reduction in inflammatory and non-inflammatory lesions counts for the Reference Product and a 38% reduction for GDC 268, 346 PP subjects per active arm will provide 85% probability of demonstrating therapeutic equivalence between the two active treatments at an alpha=0.05 (two one-sided tests) with 90% confidence interval bounds of the ratio of means being 0.08 and 1.25. Assuming a 25% reduction in inflammatory and non-inflammatory lesions counts for the VEH, 231 mITT subjects in the VEH arm and 462 mITT subjects in each of the active treatment arms will provide at least an 85% probability of demonstrating that each active treatment is statistically superior to vehicle treatment at a two-sided alpha of 0.05. Therefore, approximately 1200 subjects will be enrolled using a 2:2:1 randomization ratio (GDC 268:Reference Product:VEH) to obtain a total of 1155 mITT subjects and 865 PP subjects.
Statistical Methods	All statistical processing will be performed using SAS® Version 9.4 unless otherwise stated. **Study Populations:** The Safety population will include all randomized subjects who applied at least one dose of test article.

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	The mITT population will include all randomized subjects who applied at least one dose of test article. The PP population will include all mITT subjects who met all inclusion/exclusion criteria, were compliant with the assigned test articles based on the subject diaries (applied at least 75% and no more than 125% of the expected test article applications for the specified duration of the study), did not miss the scheduled test article applications for more than 3 consecutive days (i.e., 3 consecutive days with no test article application), have no other evidence of material dosing noncompliance, and completed the primary endpoint evaluation at Week 12 within the designated visit window (Day 85 ± 4 days) with no protocol violations that would affect the treatment evaluation including use of the prohibited medications. Subject randomization will be stratified by the number of non-inflammatory lesions (≤70 / >70) present at the Baseline Visit in order to ensure balanced enrollment of subjects across the treatment groups by non-inflammatory lesion count. No subset analyses are planned based on baseline non-inflammatory lesion counts. **Dosing Compliance**: Descriptive statistics will be used to summarize test article compliance for each analysis population. Compliant subjects are defined as those who apply at least 75% and no more than 125% of the expected test article applications, and did not miss scheduled applications for more than 3 consecutive days. The percentage of compliant subjects will be also presented. **Efficacy Analyses:** The efficacy analyses will be conducted on the mITT and PP populations. <u>Primary Endpoints</u> For each of the co-primary endpoints (percent change from Baseline at Week 12 in the inflammatory lesion counts and in the non-inflammatory lesion counts), the 90% confidence interval of the ratio of the mean percent reduction in lesion counts between the GDC 268 group and the Reference Product group will be assessed in the PP population. If the 90% confidence intervals are contained within the interval [0.8, 1.25] for both inflammatory and non-inflammatory lesions, bioequivalence between GDC 268 and the Reference Product will be demonstrated. The percent change from Baseline at Week 12 in the inflammatory lesion counts and in the non-inflammatory lesion counts for each GDC 268 and Reference Product group will be compared against VEH group at an alpha=0.05 ($p<0.05$) in the mITT population using last observation carried forward (LOCF) imputation using analysis of variance (ANOVA) with factor of treatment in the statistical model using original percent change values. If the distribution of percent change from Baseline in the lesion counts are significantly skewed, the analyses will be performed based on rank transformed data.

	Exploratory Endpoint The frequency distribution of the observed and change from Baseline IGA scores will be presented at each visit by treatment group for the mITT and PP populations. **Safety Analyses:** All safety analyses will be performed in the Safety population unless otherwise stated. Adverse Events All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percent of unique subjects reporting each treatment-emergent AE will be summarized by MedDRA system organ class (SOC), MedDRA preferred term (PT), and treatment group. AEs will also be similarly summarized by SOC, PT, maximum severity, and treatment group as well as by SOC, PT, closest relationship to test article, and treatment group. All AEs reported during the study will be listed. Local Skin Reactions The frequency of the individual LSRs (erythema, edema, scaling/dryness, stinging/burning, pruritus, erosion, and pain) will be tabulated by severity and treatment group at each onsite clinic visit. Subject counts for improved/same versus worsened compared to Baseline value will be also presented for the post-baseline visits.

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SCHEDULE OF EVENTS

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Unscheduled Visit[1]
	Screening/ Baseline	Week 2 Telephone	Week 4	Week 8	Week 12 EOS or ET	
Days	1	15 ± 3	29 ± 3	57 ± 4	85 ± 4	
Informed Consent/Assent[2]	X					
Demographics	X					
Eligibility	X					
Medical History	X					
Concomitant Medications and Procedures/Therapies	X	X	X	X	X	X
Dermatological Exam	X					
Vital Signs including height and weight[3]	X					
UPT[4] for WOCBP[5]	X				X	
Clinical Evaluations (IGA and lesion counts)	X		X	X	X	
LSR Assessment	X		X	X	X	X
Photography	X					
Randomize the subject	X					
Test Article Accountability	X		X	X	X	
Demonstrate how to apply test article	X[6]					
Subject Diary and Compliance Review[7]: Dispense (D), Review (R), and/or Collect (C)	D	R	C+R+D	C+R+D	C+R	R
Adverse Events		X	X	X	X	X

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[1] An unscheduled in-office follow-up visit may be done at the discretion of the investigator for subjects with tolerability issues or a material AE concern.
[2] Consent/assent may be performed up to 45 days prior to Baseline. Subjects who require "washout" for longer than 45 days will be re-consented.
[3] Vital signs assessment will be performed after the subject has rested in a seated position for at least 5 minutes and will include temperature, systolic and diastolic blood pressure, heart rate, and respiration rate. Height and weight will also be measured at Visit 1/Baseline.
[4] UPTs must have a minimum sensitivity of 25 mIU ß-hCG/mL.
[5] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
[6] Study staff will provide a Subject Instruction Sheet to the subject and parent/guardian (if applicable) and test article application will be demonstrated using the non-medicated samples provided to the site.
[7] Review Subject Diary and amount of test article used since last visit to determine subject compliance. Re-educate subject on use of the test article with particular attention to inappropriate prior use of test article – be it amount of product applied and/or frequency of use.

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ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
AV	Acne Vulgaris
β-hCG	Beta-Human Chorionic Gonadotropin
C. difficile	*Clostridium difficile*
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GDC 268	Clindamycin phosphate topical lotion, 1% (Gage Development Company)
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
I/E	Inclusion/Exclusion
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mIU	Milli International Units
mL	Milliliter
NSAID	Nonsteroidal Anti-inflammatory Drug
OTC	Over-the-Counter
PP	Per-Protocol
PT	Preferred Term
rRNA	Ribosomal Ribonucleic Acid
SAE	Serious Adverse Event
SE	Self-Emulsifying
SOC	System Organ Class
TI	Therapeutics, Inc.
UPT	Urine Pregnancy Test
VEH	Vehicle
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

TABLE OF CONTENTS

1. BACKGROUND

Acne vulgaris (AV) is a chronic inflammatory dermatosis notable for open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules (also known as cysts). Lesions are most common on the face, but the neck, chest, upper back, and shoulders may also be affected. Acne is a common skin disease, especially in adolescents and young adults. Approximately 50 million people in the United States have AV [1]. Acne affects approximately 89% of teenagers, but can occur in most age groups [2] and can persist into adulthood.

Acne is a multifactorial inflammatory disease affecting the pilosebaceous follicles of the skin. The current understanding of acne pathogenesis is continuously evolving. Key pathogenic factors that play an important role in the development of acne are follicular hyperkeratinization, microbial colonization with *Propionibacterium acnes*, sebum production, and complex inflammatory mechanisms involving both innate and acquired immunity. In addition, studies have suggested that neuroendocrine regulatory mechanisms, diet, and genetic and nongenetic factors all may contribute to the multifactorial process of acne pathogenesis [3].

Topical clindamycin is commonly used to treat acne. Clindamycin belongs to a class of medications called lincomycin antibiotics. It works by slowing or stopping the growth of bacteria that cause acne and by decreasing swelling. Clindamycin has a primarily bacteriostatic effect. It is a bacterial protein synthesis inhibitor that inhibits ribosomal translocation, in a similar way to macrolides. It does so by binding to the 50S rRNA of the large bacterial ribosome subunit, overlapping with the binding sites of the oxazolidinone, pleuromutilin, and macrolide antibiotics, among others. Topical clindamycin is available in several formulations: a foam, a gel, a solution (liquid), a lotion, and a pledget (swab) to apply to the skin.

Clindamycin Phosphate Topical Lotion, 1% (Cleocin T) was approved by the FDA in 1989 for the topical treatment of acne vulgaris. The reference product is currently available as an authorized generic product (GREENSTONE® BRAND). The FDA-approved regimen for the treatment of acne vulgaris is application of clindamycin phosphate topical lotion, 1% twice daily to the affected area. A generic clindamycin phosphate topical lotion, 1% (GDC 268) has been developed by Gage Development Company, LLC for the topical treatment of acne vulgaris.

2. RATIONALE

Gage Development Company, LLC has developed GDC 268, a generic clindamycin phosphate topical lotion, 1% formulation, and the current clinical study is designed to evaluate the therapeutic equivalence of this formulation with the currently marketed Clindamycin Phosphate Topical Lotion, 1% (GREENSTONE® BRAND), the reference product. The dosage form, dosing frequency, treatment duration, and study design are

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consistent with the Reference Product package insert and with the FDA Office of Generic Drugs recommendation for a bioequivalence study with a clinical endpoint in the treatment of acne vulgaris with topical clindamycin phosphate lotion, 1% [4].

3. OBJECTIVE

The objective of the study is to evaluate the safety, tolerability, and therapeutic equivalence of GDC 268 to Clindamycin Phosphate Topical Lotion, 1% and to compare the efficacy of these two products to the GDC vehicle lotion (i.e., placebo) in the treatment of acne vulgaris.

4. STUDY DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, parallel group comparison study of GDC 268 and Clindamycin Phosphate Topical Lotion, 1% (GREEENSTONE® BRAND) in healthy male and non-pregnant, non-breastfeeding female subjects 12 to 40 years of age (inclusive) with facial acne vulgaris. Eligible subjects must have a clinical diagnosis of facial acne vulgaris with an Investigator's Global Assessment (IGA) score of at least 2 (mild), a minimum of 25 but no more than 100 non-inflammatory lesions (open and closed comedones), a minimum of 20 but no more than 70 inflammatory lesions (papules and pustules) and ≤2 nodulocystic lesions (nodules and cysts) on the face at Baseline. Approximately 1200 subjects will be enrolled at approximately 50 study sites. Subjects will be randomized to one of three treatment groups on a 2:2:1 basis as follows:

1. GDC 268 (Gage) (generic clindamycin phosphate topical lotion)
2. Clindamycin Phosphate Topical Lotion, 1% (GREEENSTONE® BRAND) (Reference Product)
3. GDC Vehicle (Gage)

All subjects will be instructed to apply the assigned test article twice daily to the entire face, once in the morning and once in the evening, for 12 weeks. The study will consist of a Screening/Baseline Visit, a follow-up telephone call at Week 2, and follow-up visits at Weeks 4, 8, and 12/End of Study (EOS) or Early Termination (ET). An unscheduled in-office follow-up visit may be completed at the discretion of the investigator for subjects with tolerability issues or a material adverse event (AE) concern. At EOS, safety and efficacy outcome measures will be compared to a) determine if treatment with GDC 268 is clinically equivalent to the currently marketed Clindamycin Phosphate Topical Lotion, 1% and b) both clindamycin phosphate 1% topical lotions are statistically superior in comparison to the GDC Vehicle.

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5. STUDY POPULATION

5.1 Subject Eligibility

To be included in the study, subjects must meet the following inclusion and none of the exclusion criteria.

5.1.1 Inclusion Criteria

1. Subject is a healthy male or non-pregnant, non-breastfeeding female 12 to 40 years of age (inclusive) at the time of consent/assent.
2. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation.
3. Subject has a clinical diagnosis of mild to severe facial acne vulgaris defined as Grade 2, 3, or 4 on the IGA at Baseline.
4. Subject must have ≥ of 25 but ≤ 100 non-inflammatory lesions (open and closed comedones) AND ≥ 20 but ≤ 70 inflammatory lesions (papules and pustules) AND ≤ 2 nodulocystic lesions (nodules and cysts) on the face (e.g., forehead, nose, cheeks, chin, upper lip) at Baseline.
5. Subject and parent/guardian (if applicable) are willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.
6. Subject must be willing and able to refrain from use of all other topical products in the Treatment Area, all acne medications other than test article, and all antibiotics (other than test article) during the 12-week treatment period.
7. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of facial acne vulgaris or otherwise impact the integrity of the study, or exposes the subject to an unacceptable risk by study participation.

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8. Females must surgically sterile[6] or use an effective method of birth control.[7,8] Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[9] at Baseline.
9. Subject has used the same type and brand of make-up, cleanser or other non-medicated facial products and hair products (e.g., Clinique foundation, Cetaphil soap, shampoo, hair gel, hairspray, mousse, etc.) for at least 4 weeks prior to Visit 1/Baseline and agrees to continue and not change his/her other general skin care and hair care products and regimen for the entire study. NOTE: Subjects who change from using a medicated acne cleanser that contains benzoyl peroxide, salicylic acid, etc. to using a bland non-medicated/non-acne cleanser prior to Visit 1/Baseline will only be required to have used the new non-acne cleanser for at least 2 weeks in order to establish a stable skin care regimen.

5.1.2 Exclusion Criteria

1. Subject is pregnant, breastfeeding, or is planning to become pregnant or breastfeed during the study.
2. Subject has active nodulocystic acne or acne conglobata, acne fulminans, or other forms of acne (e.g., acne mechanica).
3. Subject has more than 2 facial nodules/cysts (where nodule/cyst is defined as an inflammatory lesion greater than or equal to 0.5 cm in size with or without cystic changes).
4. Subject has any skin condition that, in the investigator's opinion, could interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis).

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[6] Hysterectomy, bilateral tubal ligation (at least 6 months prior to initiation of treatment), or bilateral oophorectomy.

[7] Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, implantable, or vaginal ring] (see next footnote), b) intrauterine device (IUD), c) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], d) monogamous relationship with a partner who is sterile [e.g., vasectomy performed at least 6 months prior to study entry], or e) total abstinence for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a partner of the opposite sex who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.

[8] WOCBP taking hormonal therapy (e.g., oral, transdermal, injectable, implantable, vaginal ring) must be on treatment prior to study entry, continued per label, and must not change their dosing regimen during the study. **WOCBP taking hormonal therapy for any reason must be on the same treatment for at least 3 months prior to study entry.** Those who have used hormonal therapy prior to study entry must have discontinued use at least 8 weeks prior to the start of the study. NOTE: Subjects using hormonal therapy for acne management should not be allowed to enroll unless they have washed out for at least 8 weeks prior to study entry.

[9] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

5. Subject has excessive facial hair (e.g., beards, sideburns, moustaches, etc.), facial tattoos, or other facial attributes that would interfere with diagnosis or assessment of acne vulgaris in the opinion of the investigator.
6. Subject has a history of hypersensitivity or allergy to clindamycin or lincomycin and/or any of the ingredients in the test articles (see Section 6.1).
7. Subject has a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.
8. Subject is atopic (e.g., atopic dermatitis, allergic rhinitis, allergic asthma). Note: Subjects that are not atopic but have a component(s) of this syndrome may be enrolled (e.g., a person with allergic rhinitis or allergic asthma).
9. Subject has used any of the following topical preparations or procedures on the face:
    - Topical retinoids (e.g., tazarotene, adapalene, and tretinoin) within 2 weeks prior to Baseline;
    - Topical anti-acne treatments including, but not limited to, over-the-counter (OTC) acne cleansers, soaps, washes or treatments, benzoyl peroxide, antibiotics, azelaic acid, dapsone, sulfa based products, corticosteroids, and salicylic acid within 2 weeks prior to Baseline;
    - Topical steroids within 2 weeks prior to Baseline.
    - Topical antibiotics within 2 weeks prior to Baseline.
    - Topical anti-inflammatory agents within 2 weeks prior to Baseline;
    - Cryodestruction or chemodestruction, dermabrasion, photodynamic therapy including other light-based and laser therapies, acne surgery, intralesional steroids, or x-ray therapy within 4 weeks prior to Baseline;
    - Other topical therapy, which may materially affect the subject's acne, in the investigator's opinion.
10. Subject has used any of the following systemic medications:
    - Corticosteroids (including intramuscular, intra-articular, and intralesional injections) for any indication within 4 weeks prior to Baseline;
    - Antibiotics[10] for any indication or other systemic anti-acne medications within 4 weeks prior to Baseline;
    - Androgen receptor blockers (e.g., spironolactone, flutamide) within 4 weeks prior to Baseline;
    - Retinoid therapy (e.g., isotretinoin) within 6 months prior to Baseline;
    - Vitamin A supplements (greater than 10,000 units per day) within 6 months prior to Baseline;
    - Anti-inflammatory agents or immunosuppressive drugs within 4 weeks prior to Baseline;
    - Neuromuscular blocking agents such as botulinum toxin type A (e.g., BOTOX, DYSPORT) within 2 weeks prior to Baseline;

[10] Contact the Medical Monitor if a subject requires concomitant antibiotic therapy.

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- Other systemic therapy, which may materially affect the subject's acne, in the investigator's opinion.

11. Subject has used oral contraceptives or estrogen for less than 3 months prior to Baseline.
12. Subject is planning surgery during the study.
13. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study.
14. Subject is currently enrolled in an investigational drug, device, or biologic study.
15. Subject has used an investigational drug or investigational device treatment within 30 days prior to first application of the test article.
16. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
17. Subject and parent/guardian (if applicable) are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the study are described in Section 13.2. Subjects who are discontinued will not be replaced.

5.1.4 Enrollment of Protected Population

Employees of the study site will be allowed to participate in this study if they wish to do so only if they are not involved with the conduct of this study and do not have access to study materials or documents. Family members of employees of the study site will also be allowed to participate in this study if they wish to do so and if they meet all of the inclusion and none of the exclusion criteria. Both employees and their family members are considered a protected population which requires the study site to obtain and use a modified informed consent/assent from the Institutional Review Board (IRB). Special care will be taken to ensure the following:

For an employee, the decision to participate or not participate will NOT affect:

- performance evaluations,
- possible promotions, and
- salary or benefits.

For a family member of an employee, the decision to participate or not participate will NOT affect the employee's:

- performance evaluations,
- possible promotions, and
- salary or benefits.

5.1.5 Subjects from the Same Household

Subjects from the same household will be allowed to participate in this study; however, no more than 2 subjects may be enrolled from the same household. Ideally, these subjects should not be enrolled in the study at the same time. If 2 subjects from the same household are enrolled concurrently, every effort shall be made to keep all test article and study documents (e.g., subject diaries) separate for each subject. Sites should carefully review each subject's returned test article at each visit and question each subject as to whether they only used the test article assigned to them.

6. TEST ARTICLES AND REGIMEN

The test articles used in this study are described below.

6.1 Description

Reference product:	Clindamycin Phosphate Topical Lotion, 1% (GREEENSTONE® BRAND)
Active ingredient:	Clindamycin phosphate
Other ingredients:	Cetostearyl alcohol; glycerin; glyceryl stearate SE (with potassium monostearate); isostearyl alcohol; methylparaben; sodium lauroyl sarcosinate; stearic acid; and purified water.
Test product:	GDC 268 (Gage)
Active ingredient:	Clindamycin phosphate
Other ingredients:	Cetostearyl alcohol; glycerin; glyceryl stearate SE (with potassium monostearate); isostearyl alcohol; methylparaben; sodium lauroyl sarcosinate; stearic acid; and purified water.
Placebo:	GDC Vehicle (Gage)
Active ingredient:	None
Other ingredients:	Cetostearyl alcohol; glycerin; glyceryl stearate SE (with potassium monostearate); isostearyl alcohol; methylparaben; sodium lauroyl sarcosinate; stearic acid; and purified water.

6.2 Instructions for Use and Application

At the Baseline Visit, the subject and parent/guardian (if applicable) will be instructed on how to apply the test article and, as part of training, the subject will apply the non-medicated sample in the clinic under staff supervision to ensure proper application. The bottle of test article should be shaken well immediately before each application. A disc about the size of a quarter of the test article will be dispensed and the test article will be

applied using the fingertip by gently dabbing small amounts to the entire face (inclusive; i.e., forehead, nose, cheeks, chin, upper lip) and spreading the test article in a thin, uniform layer across the entire face, not just on individual lesions, with each application.

Subjects will be instructed to apply the test article to the entire face twice daily, once in the morning and once in the evening, with approximately 8 to 12 hours in between applications for 12 weeks with the first dose of test article to be applied on the evening of the Baseline Visit. Note: Subjects who have an alternate sleep-wake schedule may adjust their twice daily dosing according to their schedule as long as their twice daily applications are approximately 8 to 12 hours apart. Subjects should not wash the treated area for at least 4 hours following test article application and should not apply the test article within 4 hours before any study visit. After test article application, allow a 10 minute dry-down period before applying any other approved facial product.

Subjects will be provided with a Subject Instruction Sheet detailing how to apply the test article (see Appendix 1) and a Subject Diary (see Appendix 2) to record dates and times of applications and any missed doses. Subjects will be instructed to bring all test article bottles (used and unused) and the Subject Diary to each study visit. At each visit, the Subject Diary will be collected, reviewed, and a new one will be provided to the subject (as needed).

6.3 Warnings, Precautions, and Contraindications

The safety information in this section is derived from the US Prescribing Information for Clindamycin Phosphate Topical Lotion, 1% reference product (GREEENSTONE® BRAND).

6.3.1 Contraindications

Clindamycin phosphate topical lotion is contraindicated in subjects with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

6.3.2 Warnings

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

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 *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the test article should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile*. The usual adult dosage is 500 milligrams to 2 grams of vancomycin orally per day in 3 to 4 divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

6.3.3 Precautions

General
Clindamycin phosphate topical products should be prescribed with caution in atopic individuals.

Drug Interactions
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution in patients receiving such agents.

Pregnancy
Teratogenic effects
In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. There are no adequate studies in pregnant women during the first trimester of pregnancy. Clindamycin should be used during the first trimester of pregnancy only if clearly needed.

Nursing Mothers
It is not known whether clindamycin is excreted in human milk following use of clindamycin phosphate. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora. If oral or intravenous clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. Monitor the infant for possible adverse effects on the gastrointestinal flora, such as diarrhea, candidiasis (thrush, diaper rash) or rarely, blood in the stool indicating possible antibiotic-associated colitis.

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The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breastfed child from clindamycin or from the underlying maternal condition.

6.3.4 Adverse Events with Use of Topical Clindamycin

Per the Reference Product package insert, in 18 clinical studies of various formulations of clindamycin phosphate using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events including burning, itching, dryness, erythema, oiliness/oily skin, and peeling. Abdominal pain, gastrointestinal disturbances, gram-negative folliculitis, eye pain, and contact dermatitis have also been reported in association with the use of topical formulations of clindamycin.

7. RANDOMIZATION ASSIGNMENT

Subjects will be randomized on a 2:2:1 basis to one of three treatment groups:

1. GDC 268 (Test)
2. Clindamycin Phosphate Topical Lotion, 1% (Reference Product)
3. GDC Vehicle (Placebo)

The study will use a central randomization scheme and stratified by the number of non-inflammatory lesions (≤70 / > 70) present at the Baseline visit. Subjects who are eligible for enrollment into the study will be randomized at Visit 1/Baseline; subject kits will be dispensed according to the kit number assigned by an Interactive Web Response System (IWRS) as subjects are enrolled. Treatment group designation will remain blinded until the final database is locked (see Section 15).

A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken within 30 days prior to the start of the study (Baseline) will be recorded as prior/concomitant medications with the dose (in source documents only) and corresponding indication. The medications to be recorded include prescription, OTC medications, and vitamins, minerals, and dietary supplements being taken for a therapeutic indication. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health and will not be recorded on the electronic case report forms (eCRFs). All concomitant medications will be coded with the current version of the WHO Drug Dictionary.

Any changes in concomitant medications and/or procedures/therapies during the study must be recorded. The reason for any changes in concomitant medications and/or procedures/therapies should be reported and should reflect either a baseline medical condition documented in the medical history or in conjunction with an AE.

8.1 Prohibited Medications or Therapies

Subjects must not use the medications or procedures in the timeframe noted below.

Within 24 hours of study visits during the study:

- Antipruritics, including antihistamines.

Within 2 weeks prior to Baseline and during the study:

- Topical retinoids (e.g., tazarotene, adapalene, and tretinoin) on the face;
- Topical anti-acne treatments including, but not limited to, OTC acne cleansers, soaps, washes or treatments, benzoyl peroxide, antibiotics, azelaic acid, dapsone, sulfa based products, corticosteroids, and salicylic acid on the face;
- Topical steroids on the face;
- Topical antibiotics on the face;
- Topical anti-inflammatory agents on the face;
- Neuromuscular blocking agents such as botulinum toxin type A (e.g., BOTOX, DYSPORT) at any body site.

Within 30 days prior to Baseline and during the study:

- Investigational drugs, devices, or biologics.

Within 4 weeks prior to Baseline and during the study:

- Cryodestruction or chemodestruction, dermabrasion, photodynamic therapy including other light-based and laser therapies, acne surgery, intralesional steroids, or x-ray therapy on the face;
- Systemic corticosteroids (including intramuscular, intra-articular, and intralesional injections) for any indication;
- Systemic antibiotics[11] for any indication or other systemic anti-acne medications;
- Androgen receptor blockers (e.g., spironolactone, flutamide);
- Anti-inflammatory agents or immunosuppressive drugs.

Within 6 months prior to Baseline and during the study:

- Systemic retinoid therapy (e.g., isotretinoin);
- Vitamin A supplements (greater than 10,000 units per day).

[11] Contact the Medical Monitor if a subject requires concomitant antibiotic therapy.

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During the study, the following are prohibited:

- Any other topical or systemic therapy, which may materially affect the subject's acne, in the investigator's opinion;
- Exposure to excessive sunlight or artificial tanning devices.

8.2 Allowed Medications or Therapies

Contraception for WOCBP is required per Inclusion Criterion #8 (see Section 5.1.1). Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health and will not be recorded in the eCRFs.

Subjects must be on a consistent skin care regimen for at least 4 weeks prior to Visit 1/Baseline and must not alter the regimen for the entire study. NOTE: Subjects who change from using a medicated acne cleanser that contains benzoyl peroxide, salicylic acid, etc. to using a bland non-medicated/non-acne cleanser prior to Visit 1/Baseline will only be required to have used the new non-acne cleanser for at least 2 weeks in order to establish a stable skin care regimen. Allowed skin care products include any type or brand of make-up, cleanser, non-medicated facial product, or hair product (e.g., Clinique foundation, Cetaphil soap, shampoo, hair gel, hairspray, mousse). General skin/hair care products (e.g., shampoo, hairspray, Cetaphil soap) and minimal use of non-medicated facial products and make-up (e.g., light powder, light foundation, lip stick, mascara, sunscreen) is permitted after test article application and a 10-minute dry-down period, provided that the subject has been using the products for at least 4 weeks prior to Visit 1/Baseline. Changes in the use of type or brand of eyeliner for use on the eyes, lipstick, and/or mascara for the eyelashes are allowed prior to and during the study since these products do not involve facial areas typically affected by acne and thus, do not materially impact the Treatment Area. These and other allowed skin care products do not need to be recorded in the eCRFs. With respect to sunscreen, if sunscreen is not part of the subject's stable skin care regimen, sunscreen may be used in the Treatment Area for significant sun exposure events (e.g., out on a boat all day); however, such use of sunscreen should be listed as a concomitant medication or therapy and recorded in the eCRFs.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health.

Non-prohibited chronic therapies being used at Visit 1/Baseline may be continued, but must be recorded.

Intranasal steroids as well as inhaled (puffer) or ophthalmic steroid preparations are allowed.

Reasonable use of OTC medications such as NSAIDs (e.g., aspirin, ibuprofen) or analgesics or antipyretics (e.g., acetaminophen) for relief of headache, muscle ache, etc. is allowed during the study and must be recorded.

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9. STUDY PROCEDURES

Specific activities for each study visit are listed below.

9.1 Visit 1 (Day 1): Screening/Baseline

At Screening, the investigator or qualified designee will:

- Obtain a signed, written informed consent/assent.
- Record subject demographics.
- Review inclusion/exclusion (I/E) criteria and confirm subject eligibility.
- Record medical history.
- Record prior and/or concomitant medications and procedures/therapies.
- Have subject complete washout from any prohibited medications, if necessary.

If the subject requires washout from previous medications, the remaining activities will be performed after washout is complete as a separate Baseline Visit.

- If the washout requires longer than 45 days, re-consent/assent should occur.
- Reconfirm I/E criteria and subject eligibility.
- Perform a dermatological exam.
- Measure vital signs (including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) and height and weight (see Section 10.3.3).
- Perform a UPT for all WOCBP. The results must be negative for the subject to be enrolled.
- Perform clinical evaluations: IGA (see Section 10.1) and acne lesion counts (see Section 10.2).
- Assess LSRs (see Section 10.3.2).
- Perform standardized photography of the face (see Section 11).
- Randomize the subject and assign the subject kit according to the IWRS.
- Document Test Article Accountability. Weigh test article prior to dispensing to subject and record baseline weight.
- Demonstrate how to apply test article using the non-medicated samples provided to the site and have subject apply the non-medicated sample in the clinic under staff supervision to ensure proper application. Instruct the subject to apply the first dose on the evening of the Baseline Visit.
- Review and dispense a Subject Instruction Sheet (see Appendix 1).
- Dispense the Subject Diary and provide completion instructions (see Appendix 2).
- Review allowed skin care products per Section 8.2.
- Schedule a follow-up telephone call (Visit 2) and in clinic follow-up (Visit 3).

9.2 Visit 2 (Day 15 ± 3): Follow-Up Telephone Call

At this phone visit, the investigator or qualified designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the eCRF, as appropriate. NOTE: If severe tolerability issues or a material AE concern of any type are noted, the subject may be scheduled for an in-office visit at the investigator's discretion.
- Record any changes in the subject's concomitant medications and procedures/therapies.
- Review the Subject Diary and test article compliance.
- Remind the subject to continue to apply test article twice daily to their entire face, once in the morning and once in the evening, until the next clinic visit and to bring all bottles (used and unused) of test article with him/her to the next clinic visit.
- Confirm the next scheduled visit and remind the subject or parent/legal guardian (if applicable) not to apply test article or other products to the face within 4 hours prior to the next appointment.
- Review allowed skin care products per Section 8.2.
- Inquire if the subject has any other questions or needs; in the event the subject is having any issues with the test article or material health concerns, the investigator will determine if an unscheduled visit (see Section 9.5) or other measures are required.
- Call the day prior to the next scheduled visit to remind subjects not to apply test article or other products to the face within 4 hours of the next visit.

9.3 Visits 3 and 4 (Week 4/Day 29 ± 3 and Week 8/Day 57 ± 4): Follow-Up

At this visit, the investigator or qualified designee will:

- Query the subject about any changes in health status since the last visit. Document in the AE section of the eCRF, as appropriate.
- Record any changes in the subject's concomitant medications and procedures/therapies.
- Perform clinical evaluations: IGA (see Section 10.1) and acne lesion counts (see Section 10.2).
- Assess LSRs (see Section 10.3.2).
- Document Test Article Accountability. The subject's new and used test article will be weighed and re-dispensed as necessary.
- Collect, review, and distribute the Subject Diary as necessary.
- Review test article compliance. Test article application will be demonstrated if deemed necessary.
- Remind the subject to continue to apply test article twice daily to their entire face, once in the morning and once in the evening, until the next clinic visit and to bring all bottles (used and unused) of test article with him/her to the next clinic visit.

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- Schedule the next visit and remind the subject or parent/legal guardian (if applicable) not to apply test article or other products to the face within 4 hours prior to the next appointment.
- Review allowed skin care products per Section 8.2.
- Call the day prior to the next scheduled visit to remind subjects not to apply test article or other products to the face within 4 hours of the next visit.

9.4 Visit 5 (Week 12/Day 85 ± 4): End of Study or Early Termination

At this visit, the investigator or qualified designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the eCRF, as appropriate.
- Record any changes in the subject's concomitant medications and procedures/therapies.
- Perform a UPT for all WOCBP.
- Perform clinical evaluations: IGA (see Section 10.1) and acne lesion counts (see Section 10.2).
- Assess LSRs (see Section 10.3.2).
- Document Test Article Accountability. Weigh and collect all test articles.
- Collect and review the Subject Diary and determine test article compliance.
- The subject will exit the study.

9.5 Unscheduled Visit

An unscheduled in-office follow-up visit may be completed at the discretion of the investigator for subjects with tolerability issues or a material AE concern.

At this visit, the investigator or qualified designee will:

- Query the subject about any changes in health status or any AEs since the last visit. Document in the AE section of the eCRF, as appropriate.
- Record any changes in the subject's concomitant medications and procedures/therapies.
- Assess LSRs, if applicable (see Section 10.3.2).
- Review the Subject Diary and test article compliance.
- Remind the subject to continue to apply test article twice daily, once in the morning and once in the evening, until the next clinic visit and to bring all bottles (used and unused) of test article with him/her to the next clinic visit.
- Confirm the next scheduled visit and remind the subject or parent/legal guardian (if applicable) not to apply test article or other products to the face within 4 hours prior to the next appointment.
- Review allowed skin care products per Section 8.2.
- Call the day prior to the next scheduled visit to remind subjects not to apply test article or other products to the face within 4 hours of the next visit.

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10. CLINICAL EVALUATIONS

The following clinical evaluations will be performed according to the schedules indicated during the study. The same investigator should complete the evaluations for a given subject throughout the study. If this becomes impossible a sub-investigator with overlapping experience with the subject and the study should complete the evaluations.

10.1 Investigator's Global Assessment

The IGA score is a static evaluation of the overall severity or "average" degree of severity of a subject's disease by the investigator or qualified designee, taking into account all of the subject's facial acne lesions as the subject appears on the day of the evaluation. The investigator should NOT refer to any other assessments to assist with this evaluation and should complete the IGA score prior to performing lesion counts. This evaluation is NOT a comparison with the IGA at any other visit or a mathematical calculation based on counts of individual lesion types. Overall severity of acne will be assessed using a five-point scale from 0=Clear to 4=Severe. Subjects must have an IGA score of 2 (mild), 3 (moderate), or 4 (severe) at Baseline.

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost clear; rare non-inflammatory lesions with no more than a few small inflammatory lesions.
2	Mild severity; greater than Grade 1; some non-inflammatory 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 non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion.
4	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions.

10.2 Acne Lesion Counts

The number of non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), and nodulocystic lesions (nodules and cysts) on the face (including those present on the nose) will be counted. Subjects must have a minimum of 25 but no more than 100 non-inflammatory lesions AND a minimum of 20 but no more than 70 inflammatory lesions AND ≤ 2 nodulocystic lesions on the face at Baseline.

The entire face, vertically from the hairline to mandible rim and horizontally from ear to ear (not including any lesions on or in the ear), including the nose, will be examined for lesions defined as follows:

Non-inflammatory lesions:

- Comedones: open (blackheads) and closed (whiteheads).

Inflammatory lesions:

- Papules: raised inflammatory lesions with no visible purulent material.
- Pustules: raised inflammatory lesions with visible purulent material.

Nodulocystic lesions:

- Nodules and cysts: any circumscribed, inflammatory masses greater or equal to 5 mm in diameter with or without cystic changes.

10.3 Safety Evaluations

10.3.1 Adverse Events

All reported or observed AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any ongoing AEs. Untoward events that occur prior to the first dose of test article will be captured in the Medical History section of the eCRF unless they are related to a study-specific procedure. See Section 14 for details on Adverse Event Reporting.

10.3.2 Local Skin Reactions

At each visit, LSRs (erythema, edema, scaling/dryness, stinging/burning, pruritus, erosion, and pain) will be assessed. Erythema, edema, scaling/dryness, and erosion will be assessed by the investigator and stinging/burning, pain, and pruritus will be assessed by the subject. Assessments will be made using a 4-point ordinal scale where 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). Only LSRs that require medical intervention (e.g., prescription medication), require withholding or discontinuation of the application of the test article, or extend 2 cm beyond the Treatment Area will be documented as AEs. Any LSR that are not listed above will be recorded as an AE.

10.3.3 Vital Signs

Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured at Visit 1/Baseline. Assessments will be made after the subject has rested in a seated position for at least 5 minutes. Height and weight will also be measured at Visit 1/Baseline.

10.3.4 Urine Pregnancy Tests

A UPT will be performed at Visit 1/Baseline and at Visit 5/Week 12/EOS for WOCBP.

10.3.5 Concomitant Medications and Concurrent Procedures/Therapies

Concomitant medications and concurrent procedures/therapies will be reviewed at all visits and any changes will be recorded.

11. PHOTOGRAPHY

Photography documentation is required in this study so to participate in the study subjects must consent to photographs. Photographs taken as part of this study will be used to document the subject's baseline disease, AEs, or other findings during the study. The site will be provided with suggested guidelines to assist them in taking standardized photographs of the face in 3 views (front, right, and left [45 degrees oblique for right and left]) at Baseline. All photographs taken as part of this study are for informational purposes only and are not to assist in grading or for any other assessment. Photographs will be compiled and reviewed and may be used to evaluate investigator/grader training needs, but no formal assessments will be performed.

Note: Subjects who decline to have photographs taken during the conduct of study after Baseline may continue to participate in the study. If a subject initially consents to photographs, then declines further photography as/if required, the Sponsor may use the photographs taken under consent for the purposes noted above.

Additional details regarding photographic methods, uploading and labeling photos etc. will be provided in a Photo Manual to the site.

12. LABORATORY TESTS

12.1 Urine Pregnancy Tests

The UPTs will be performed at the study site, if the site is registered and conforms to CLIA regulations for such testing (possesses a current valid CLIA Certificate of Waiver), or at an appropriately registered reference laboratory. The investigator will report the UPT results on the eCRFs, in the subject's medical records, and in independent records maintained at the study site. The UPT used must have a minimum sensitivity of 25 mIU of β-hCG/mL.

13. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an EOS Disposition form for all completed and discontinued subjects.

13.1 Completion of the Study

Subjects who complete the 12-week course of treatment as specified in this protocol will be considered to have completed the study.

13.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- AEs
- Death
- Lack of efficacy
- Lost to follow-up
- Non-compliance with test article
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject; NOTE: if the subject decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE
- Other (e.g., any reason that may affect the outcome of the study or safety of subjects)

If a randomized subject withdraws from the study prematurely for any reason, the site should make every effort to have the subject return to the clinic to perform all of the required visit activities and to collect and reconcile all test articles (if applicable). If the randomized subject will not return to the clinic, the site should make every attempt to contact the subject; otherwise the subject will be considered lost to follow-up.

When a subject is withdrawn from the study for a test article related AE (as defined in Section 14.2), when possible, the subject should be followed until resolution or stabilization of the AE. If the subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed.

Subjects who are prematurely withdrawn or discontinued from the study will not be replaced.

13.3 Study Termination

The study may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within 5 working days.

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In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

If the study is terminated for any reason subjects should be withdrawn from the study in an orderly manner following the steps outlined in Section 13.2.

14. ADVERSE EVENT REPORTING

14.1 Adverse Event Definitions

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered test article related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation, or dose, including an overdose.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the Reference Product package insert or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB Reference Product package insert referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Reference Product package insert listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Reference Product package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

14.2 Adverse Event Details

AEs may be either spontaneously reported, observed, or elicited during questioning and examination of a subject. All AEs following the first dose of test article must be recorded on the AE eCRF. Any untoward events occurring prior to test article administration will be reported in the Medical History, unless related to a study-specific procedure. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of test article or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. AEs should be followed to resolution or stabilization (if possible) and, if they become serious, reported as serious adverse events (SAEs, see Section 14.3). If possible, the outcome of any AEs that caused permanent discontinuation or that were present at the end of the study, especially those considered by the investigator to be related to the test article, should be reported.

Information on the medical condition of subjects should begin following the subject's written informed consent/assent to participate in the study and a medical history should be taken at screening. During any wash out and baseline periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the IRB as an "unanticipated problem" in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the test article; therefore AE data should be collected from the date of the first dose of test article until the date of the final study visit. These data are considered treatment-emergent AEs.

The investigator will instruct the subject to report any AEs that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall health status since the previous visit.

The severity of each AE, as judged by the investigator, will be recorded on the appropriate AE eCRF and will be graded according to the following scale:

> **Mild** - The AE is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
>
> **Moderate** - The AE is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
>
> **Severe** - The AE interrupts usual activities of daily living or significantly affects clinical status, or may require intensive therapeutic intervention.

The investigator must determine the relationship of the AE to the test article according to the following categories:

Related – There is a strong medical evidence to suggest that the AE is related to test article usage.

Possibly Related – There is medical evidence to suggest that the AE may be related to test article usage.

Not Related – There is no medical evidence to suggest that the AE may be related to test article usage.

The investigator should categorize the outcome of the AE according to the following categories:

Fatal - Termination of life as a result of an AE.

Not Recovered/Not Resolved - AE has not improved or the subject has not recuperated.

Recovered/Resolved - AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae - subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving - AE is improving or the subject is recuperating.

Unknown - Not known, not observed, not recorded or subject refused.

14.3 Serious Adverse Event

An event that is serious must be recorded on the AE eCRF and on the TI SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered "serious" if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death; the event must be the cause of death for the SAE to meet this serious criterion.
- Life-threatening event; an event in which the subject was at risk of death at the time of the event and not an event that hypothetically might have caused death if it had been more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization (for ≥24 hours).

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- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical events; a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be SAEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen; and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

AEs classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to TI to comply with regulatory requirements. **All SAEs, whether related or unrelated to test article, must be reported as soon as possible but no later than 24 hours from when the event occurred by telephone to the Medical Monitor and, in the event that he is unavailable, to the Project Manager (see contact information below).** Written notification of all SAEs should be sent to the Project Manager by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or Reference Product package insert and must include an assessment of whether there is a reasonable possibility that the test article caused the event.

Medical Monitor:

[redacted]

In the event the Medical Monitor is unavailable, contact the Project Manager:

[redacted]

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of an SAE (regardless of its relationship to test article) that occurs within 30 days after stopping the test article, the SAE must be reported in

accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to TI, if available.

Upon receiving such notices, the investigator must review and retain the notice with the Reference Product package insert and promptly submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent/assent require revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the investigator to Health Authorities should be handled according to local regulations.

The Sponsor or designee may be required to report certain SAEs to regulatory authorities (e.g., United States FDA) within 7 calendar days of being notified about the event; therefore, it is important that investigators submit any information requested by the Sponsor or designee as soon as it becomes available.

14.4 Laboratory Test Abnormalities

There are no specific laboratory tests, other than UPT, required in this study.

14.5 Pregnancy

WOCBP (see Schedule of Events for definition of WOCBP) must have a UPT prior to study enrollment. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during the study and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent/assent (if applicable) form documenting this discussion.

WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) during the study and for 30 days after she has completed her last test article application. If a subject or investigator suspects that a subject may be pregnant at any time during the study, the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further test article and the subject must be discontinued from the study.

If following initiation of study treatment, it is subsequently discovered that a subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to TI. The investigator will also report any pregnancy associated with the study treatment as required by their IRB and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies).

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Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to TI, on the appropriate pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs or SAEs (if they fulfill the SAE criteria). Offspring should be followed for a minimum of 8 weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as an SAE with details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic, or spontaneous should be reported as an SAE. Elective abortions are generally not reported as an SAE unless an AE occurs that meets the criteria for an SAE.

15. BLINDING/UNBLINDING

This is a double-blind, randomized, placebo-controlled study. Blinding is important for the integrity of this clinical study. Test article will be packaged in identical bottles so that neither the subject, investigator nor site staff will know the identity of the contents. However, the blind may be broken in the event of a medical emergency in a subject, in which knowledge of the test article identity is critical to the subject's management. Before breaking the blind for a subject, the investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not test article related, the problem may be effectively managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind should first be discussed with the responsible Medical Monitor if possible prior to breaking the blind and the best method to do this will be determined.

A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

16. CLINICAL SUPPLIES

16.1 Test Article Information

Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, accountability, etc. of the test article is included in Appendix 3.

16.2 Supplies Provided by Therapeutics, Inc.

- eCRFs
- Source document draft templates
- Site regulatory binder
- UPT kits

- Weighing scales for test article
- Digital camera

16.3 Supplies Provided by Investigator

- Urine collection containers for UPTs

16.4 Supplies Provided by Gage Development Company, LLC

- Test article
- Samples for demonstration to subjects of test article application

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

Based on the assumption of a 40% reduction in inflammatory and non-inflammatory lesions counts for the Reference Product and a 38% reduction for GDC 268, 346 PP subjects per active arm will provide 85% probability of demonstrating therapeutic equivalence between the two active treatments at an alpha=0.05 (two one-sided tests) with 90% confidence interval bounds of the ratio of means being 0.08 and 1.25. Assuming a 25% reduction in inflammatory and non-inflammatory lesions counts for the VEH, 231 mITT subjects in the VEH arm and 462 mITT subjects in each of the active treatment arms will provide at least an 85% probability of demonstrating that each active treatment is statistically superior to vehicle treatment at a two-sided alpha of 0.05. Therefore, approximately 1200 subjects will be enrolled using a 2:2:1 randomization ratio (GDC 268: Reference Product: VEH) to obtain a total of 1155 mITT subjects and 865 PP subjects.

17.2 Endpoints

17.2.1 Efficacy Endpoints

Co-primary efficacy endpoints will include:

- Percent change from Baseline to Week 12 in the inflammatory (papules and pustules) lesion count.
- Percent change from Baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion count.

17.2.2 Safety Endpoints

Safety endpoints will include:

- Incidence (severity and causality) of any reported or observed treatment emergent AEs, whether or not they are considered to be related to the test article.

- Number of subjects with improved/same versus worsened severities compared to Baseline of the following LSRs: erythema, edema, scaling/dryness, stinging/burning, pruritus, erosion, and pain at each onsite treatment visit.

17.3 Statistical Methods

All statistical processing will be performed using SAS® Version 9.4 unless otherwise stated.

The Safety population will include all randomized subjects who applied at least one dose of test article.

The mITT population will include all randomized subjects who applied at least one dose of test article.

The PP population will include all mITT subjects who met all I/E criteria, were compliant with the assigned test articles based on the subject diaries (applied at least 75% and no more than 125% of the expected test article applications for the specified duration of the study), did not miss the scheduled test article applications for more than 3 consecutive days (i.e., 3 consecutive days with no test article application), have no other evidence of material dosing noncompliance, and completed the primary endpoint evaluation at Week 12 within the designated visit window (Day 85 ± 4 days) with no protocol violations that would affect the treatment evaluation including use of the prohibited medications.

Subject randomization will be stratified by the number of non-inflammatory lesions (≤70 / >70) present at the Baseline Visit in order to ensure balanced enrollment of subjects across the treatment groups by non-inflammatory lesion count. No subset analyses are planned based on baseline non-inflammatory lesion counts.

17.3.1 Dosing Compliance

Descriptive statistics will be used to summarize test article compliance for each analysis population. Compliant subjects are defined as those who apply at least 75% and no more than 125% of the expected test article applications, and did not miss scheduled applications for more than 3 consecutive days. The percentage of compliant subjects will be also presented.

17.3.2 Efficacy Analyses

The efficacy analyses will be conducted on the mITT and PP populations.

17.3.2.1 Primary Efficacy Analyses

For each of the co-primary endpoints (percent change from Baseline at Week 12 in the inflammatory lesion counts and in the non-inflammatory lesion counts), the 90% confidence interval of the ratio of the mean percent reduction in lesion counts between the

GDC 268 group and the Reference Product group will be assessed in the PP population. If the 90% confidence intervals are contained within the interval [0.8, 1.25] for both inflammatory and non-inflammatory lesions, bioequivalence between GDC 268 and the Reference Product will be demonstrated.

The percent change from Baseline at Week 12 in the inflammatory lesion counts and in the non-inflammatory lesion counts for each GDC 268 and Reference Product group will be compared against VEH group at an alpha=0.05 ($p<0.05$) in the mITT population using last observation carried forward (LOCF) imputation using analysis of variance (ANOVA) with factor of treatment in the statistical model using original percent change values.

If the distribution of percent change from Baseline in the lesion counts are significantly skewed, the analyses will be performed based on rank transformed data.

17.3.2.2 Exploratory Efficacy Analysis

The frequency distribution of the observed and change from Baseline IGA scores will be presented at each visit by treatment group for the mITT and PP populations.

17.3.2.3 Imputation of Missing Data

Subjects who are discontinued early from the study due to lack of treatment effect after 4 weeks of treatment will be included in the PP population analyses using LOCF. Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study will be included in the mITT and PP population analyses using LOCF. Subjects discontinued early for other reasons will be excluded from the PP population, but included in the mITT population, using LOCF.

17.3.2.4 Sensitivity Analysis

No sensitivity analyses are planned. Any additional analyses performed will be described in the final clinical study report.

17.3.2.5 Multiple Comparisons / Multiplicity

Not applicable.

17.3.3 Safety Analyses

All safety analyses will be performed in the Safety population unless otherwise stated.

17.3.3.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percent of unique subjects reporting each treatment-

emergent AE will be summarized by MedDRA system organ class (SOC), MedDRA preferred term (PT), and treatment group. AEs will also be similarly summarized by SOC, PT, maximum severity, and treatment group as well as by SOC, PT, closest relationship to test article, and treatment group. All AEs reported during the study will be listed.

17.3.3.2 Local Skin Reactions

The frequency of the individual LSRs (erythema, edema, scaling/dryness, stinging/burning, pruritus, erosion, and pain) will be tabulated by severity and treatment group at each onsite clinic visit. Subject counts for improved/same versus worsened compared to Baseline value will be also presented for the post-baseline visits.

17.4 Subgroup Analyses

No subgroup analyses are planned.

17.5 Interim Analyses

No interim analyses are planned.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent/assent (if applicable) documents, recruitment advertisements, and any amendments to these items will have IRB approval, where required, prior to study initiation. Voluntary informed consent/assent (if applicable) will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities. Contact information for each site and any clinical laboratories used in the study will be maintained up to date in a separate reference document.

18.2 Institutional Review Board and Informed Consent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent/assent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to the subject/and parent/guardian (if applicable). The investigator should also provide the IRB with a copy of the product labeling, information to be provided to the subject/and parent/guardian (if applicable) and any updates. The investigator will submit documentation of the IRB approval to TI.

The IRB-approved consent/assent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The investigator/qualified designee will explain the study to each potential subject and parent/guardian (if applicable) and the subject must indicate voluntary consent/assent by signing and dating the approved informed consent/assent (if applicable) form. The parent or legal guardian must provide written informed consent for the subject. The investigator must provide the subject and parent/guardian (if applicable) with a copy of the consent/assent (if applicable) form, in a language the subject understands.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

18.3 Protocol Compliance

The IRB-approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

18.4 Protocol Revisions

The Sponsor or designee must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to TI.

New or altered consent/assent forms required by the IRB due to a protocol change must be signed by all subjects and parent/guardians (if applicable) currently enrolled in the study and must be used for any subsequent subject enrollment.

18.5 Study Monitoring

Representatives of TI and/or the Sponsor must be allowed to visit all study sites, to review study records, and to directly compare them with source documents (including, but not limited to patient and hospital records, the source document worksheet, and any electronic medical records (i.e., access to EMRs in a HIPAA compliant manner or if that is not possible certified copies must be available from the EMR system with 10% over the shoulder review), to discuss the study conduct with the investigator and study staff, and to verify that the investigator, study staff, and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff, and facilities.

The investigator should immediately notify TI of any audits of this study by any regulatory agency and must promptly provide copies of any audit reports.

18.6 Case Report Form Requirements

The study will utilize eCRFs. Validated 21 CFR Part 11 compliant electronic data capture (EDC) software will be used to collect data. All requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change, and the reason for the change. Only individuals who have completed EDC training and are listed on the Delegation of Responsibilities Log with responsibility for eCRF completion will be provided usernames and passwords in order to access the system and make entries on the eCRF.

The investigator or physician sub-investigator must electronically sign and date each subject's eCRF. Individuals who will be providing electronic signatures must first submit documentation with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

18.7 Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

18.8 Quality Assurance Audits

Representatives from TI and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance audit of this study. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify TI in the event of a FDA site audit.

18.9 Records Retention

According to 21CFR § 312.62, an investigator is required to maintain study records for a period of 2 years following the date a marketing application is approved for the test article for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

Each site will be required to randomly select reserve samples from the shipment of test articles. Instructions on the number of kits to select and how to document the kit numbers selected as reserve samples will be included in the shipment. Each site will then store the reserve samples. In accordance with 21CFR § 320.38, each reserve sample (retain) 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 from which the reserve sample was obtained.

The investigator must contact TI or the Sponsor in writing to obtain consent prior to destroying any records or reserve samples associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to TI.

18.10 Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject or the subject's parent/guardian (if appropriate), except as necessary for monitoring by TI or the Sponsor, the FDA or other regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from TI or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

19. REFERENCES

1. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. Journal of the American Academy of Dermatology. 1998;39:S34-7.
2. Bhate K, Williams HC. Epidemiology of acne vulgaris. The British journal of dermatology. 2013;168:474-85.
3. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. Journal of the American Academy of Dermatology. 2016;74:945-73.e33.
4. FDA. Draft Guidance on Clindamycin Phosphate. Recommended Apr 2011; Revised Nov 2018.

APPENDIX 1 SAMPLE SUBJECT INSTRUCTION SHEET

Copies of the following sample subject instructions will be provided to the study site. The investigator must give each subject/parent/guardian (if applicable) a copy of this instruction sheet at Visit 1/Baseline.

SAMPLE SUBJECT INSTRUCTION SHEET FOR PROTOCOL GDC-268-001

[redacted]

CONTROLLED & CONFIDENTIAL

APPENDIX 2 SAMPLE SUBJECT DIARY

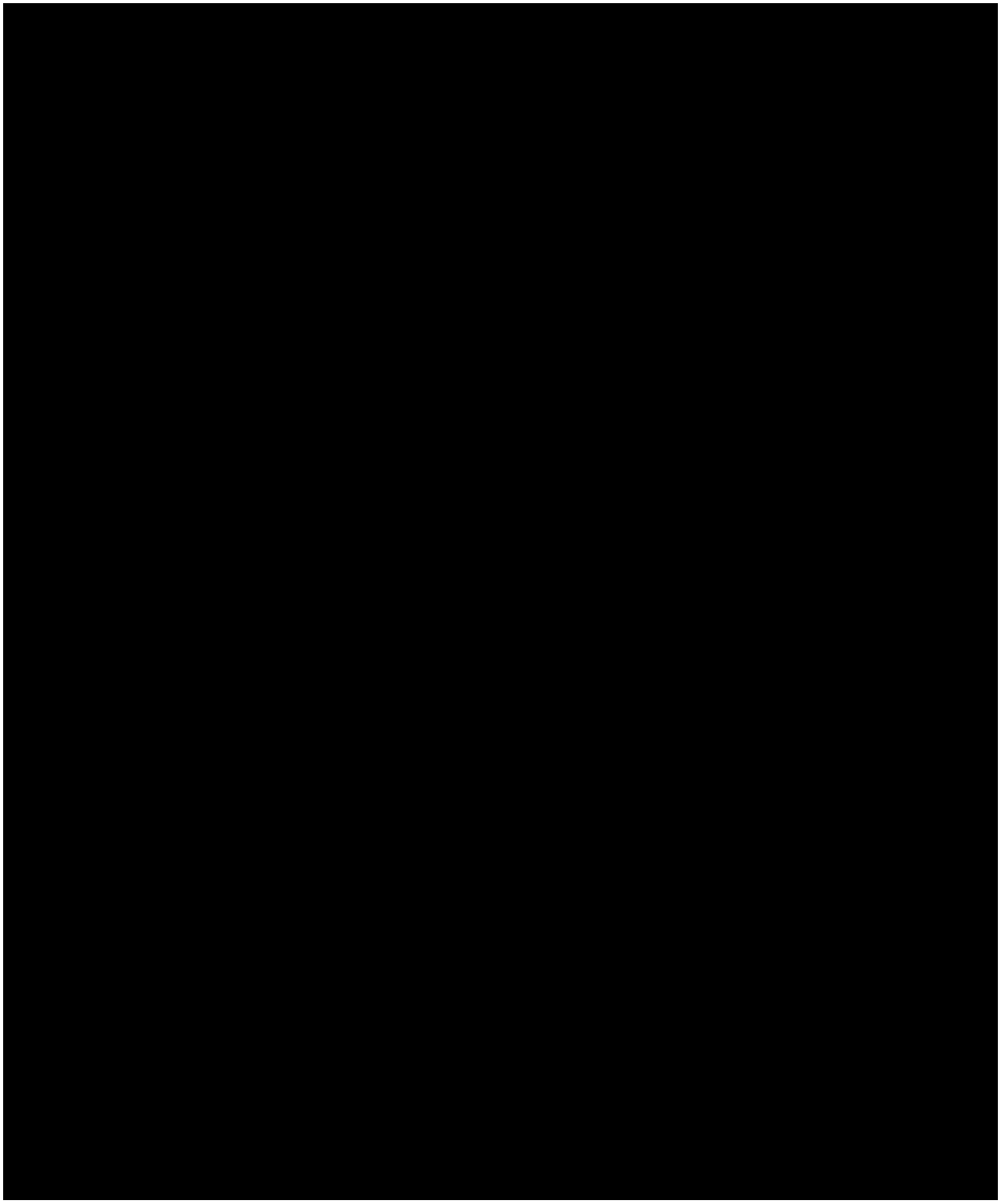
A copy of the following sample Subject Diary will be provided to the study site. The investigator must give each subject/parent/guardian (if applicable) a copy of this Subject Diary at Visit 1/Baseline and all follow-up visits, as necessary.

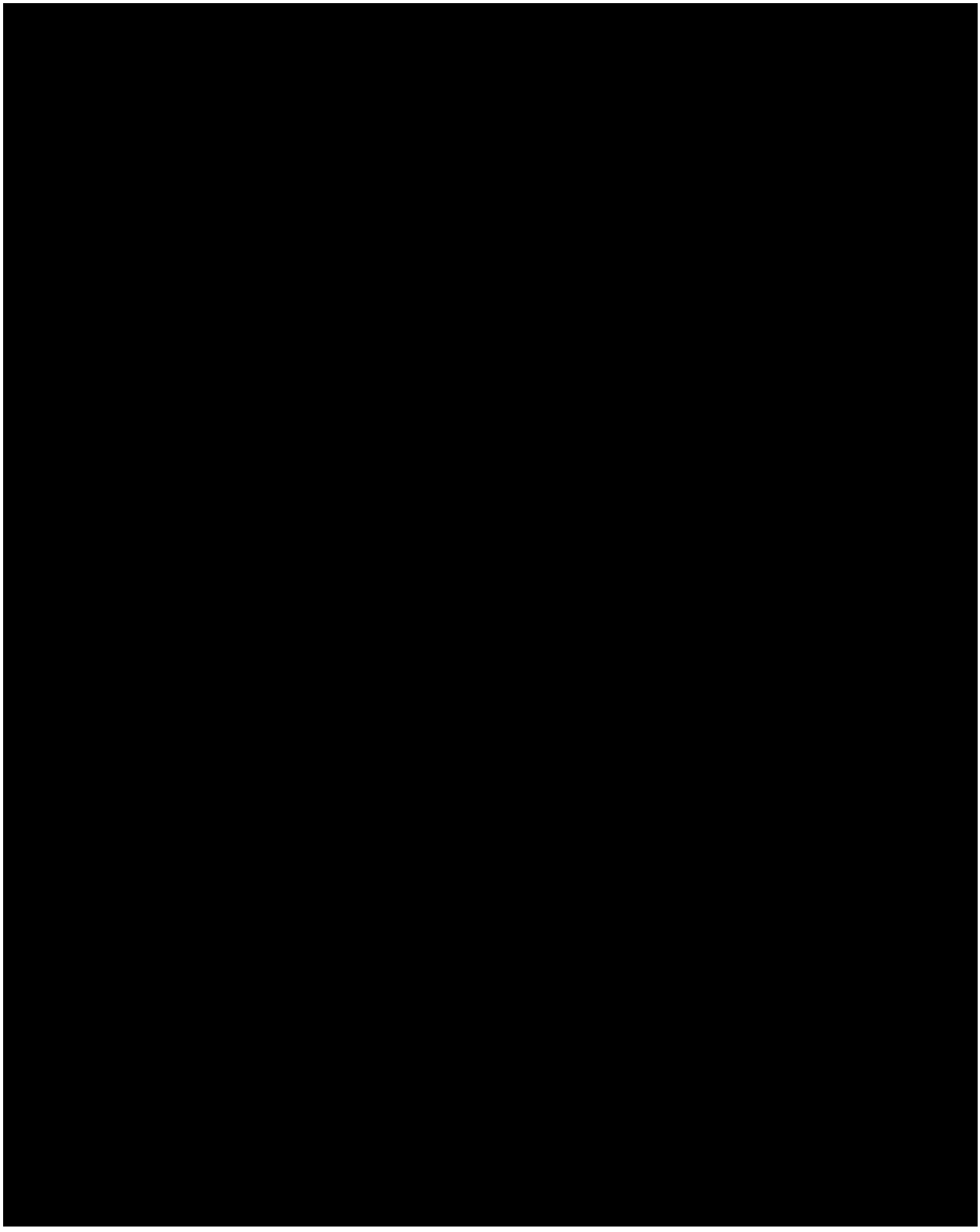
[redacted]

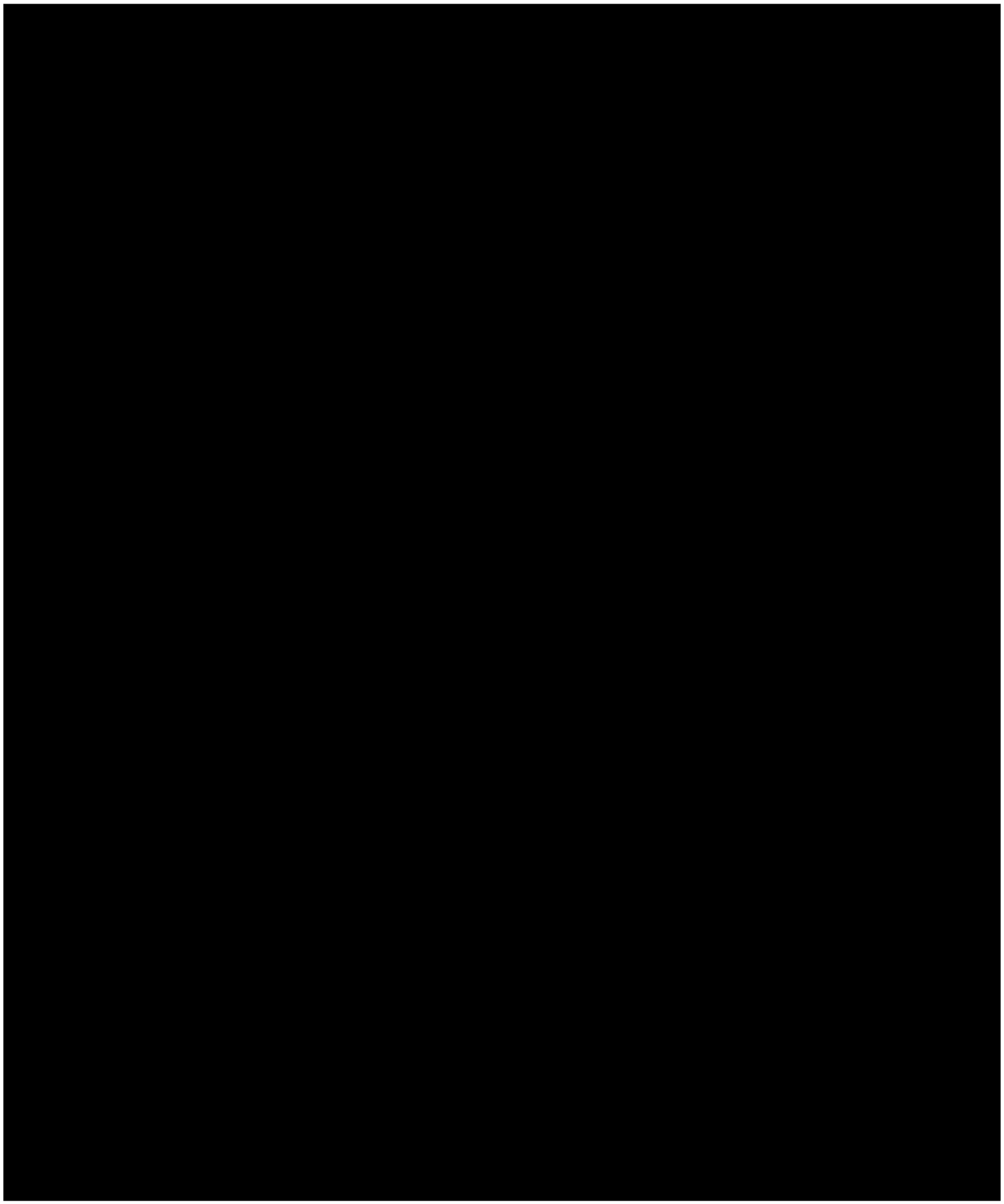
SAMPLE SUBJECT DIARY

[redacted]

APPENDIX 3 TEST ARTICLE INFORMATION







APPENDIX 4 PROTOCOL AMENDMENTS