BioPharmX

AN OPEN LABEL STUDY TO DOCUMENT THE TREATMENT EFFECT OF 1 AND 2% BPX-01 MINOCYCLINE TOPICAL GEL IN MODERATE TO SEVERE INFLAMMATORY NON-NODULAR ACNE VULGARIS

PROTOCOL # BPX-01-C04

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Medical Monitor

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SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments, and provide the necessary assurances that this trial will be conducted according to local legal and regulatory requirements and all applicable U.S. federal regulations, and ICH guidelines.

Sponsor Approval:

DocuSigned by:
AnnaMarie Daniels
FA8EDCD7C4BB4EE...

10-Aug-2017

AnnaMarie Daniels
Executive Vice President, Clinical & Regulatory Affairs
BioPharmX, Inc.

Date (DD-MMM-YYYY

INVESTIGATOR SIGNATURE PAGE

Institution Name	

Investigator Name	Signature	Date (DD-MMM-YYYY)

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) procedures, instructions from BioPharmX and their representatives, the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practices Guidelines, U.S. federal regulations, and local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
β-hCG	β-Human Chorionic Gonadotropin
BMI	Body Mass Index
bpm	Beats Per Minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CK	Creatinine Kinase
CRF	Case Report Form
CK	Creatine Kinase
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HCT	Hematocrit
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
ITT	Intent-To-Treat Population
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MIC	Minimum Inhibitory Concentration
OTC	Over-the-Counter
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
PP	Per-Protocol Population
PRO	Patient-Reported Outcome
RBC	Red Blood Cells (count)
REB	Research Ethics Board
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAF	Safety Population
TEAEs	Treatment-Emergent Adverse Events
WBC	White Blood Cells (count)

SUMMARY

Title: An Open Label Study to Document the Treatment Effect of 1 and 2% BPX-01 Minocycline Topical Gel in Moderate to Severe Inflammatory Non-nodular Acne Vulgaris (Protocol Number BPX-01-C04)

Phase: 2

Population: Up to 40 male or female subjects aged between 18 and 40 years with moderate to severe inflammatory non-nodular acne vulgaris will be included in this study.

Number of Sites: Up to 4 investigational sites will participate in this multicenter study.

Study Duration: Overall study duration is expected to be approximately 24 weeks (6 months). The study duration per subject is approximately 20-24 weeks (including 12 weeks of treatment, a screening period and the post-treatment follow-up to assess time to recurrence).

Hypothesis: BPX-01 improves disease condition in subjects with moderate to severe inflammatory non-nodular acne vulgaris.

Objectives:

Primary:

- To obtain photo-documentation of the efficacy of BPX-01 minocycline 1% or 2% topical gel in the treatment of inflammatory non-nodular acne vulgaris

Secondary:

- To evaluate the cutaneous tolerance of BPX-01 minocycline 1% or 2% topical gel

Endpoints:

Primary Efficacy Endpoint:

- Change from baseline in inflammatory lesion counts at Week 12

Secondary Efficacy Endpoint:

- Change from baseline in inflammatory lesion counts at Weeks 1, 2, 4, and 8

Exploratory Efficacy Endpoints:

- Subjects with at least a two-grade reduction in IGA at Week 12

- Percent change from baseline in inflammatory lesion counts at Weeks 1, 2, 4, 8, and 12
- Absolute change and percent change from baseline in noninflammatory lesion counts at Weeks 1, 2, 4, 8, and 12
- Absolute change and percent change from baseline in total lesion counts at Weeks 1, 2, 4, 8, and 12
- Absolute change and percent change from baseline in the Investigator's Global Assessment (IGA) at Weeks 1, 2, 4, 8, and 12
- Proportion of subjects with an IGA of clear (0) or almost clear (1) at Weeks 1, 2, 4, 8, and 12
- Proportion of subjects with at least a two-grade reduction in IGA at Weeks 2, 4, and 8
- Change from baseline in Patient Global Impression of Severity (PGI-S) at Weeks 1, 2, 4, 8, and 12
- Patient Global Impression of Improvement (PGI-I) at Weeks 1, 2, 4, 8, and 12

Safety Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Shift from baseline in clinical hematology and chemistry laboratory tests
- Change from baseline in the cutaneous tolerance score evaluated by the observer (erythema, scaling-peeling, edema)
- Change from baseline in the cutaneous tolerance score evaluated by the subject (tightness, burning, stinging, itching)
- Incidence of visual disturbances/headaches suggestive of pseudotumor cerebri and minocycline-induced skin hyperpigmentation
- Incidence of product related facial staining

Overall Study Design:

This is a 12-week, multi-center, open label, two-arm study.

Subjects will be assigned to treatment with 1% or 2% BPX-01 gel. Subjects will apply 1g of the gel as a thin film to the entire face at least 30 minutes before bedtime each night for 12 weeks. Lesion counts, IGA, and Patient-Reported Outcomes (PGI-S and PGI-I) will be performed to assess efficacy. Photographs will be taken to document treatment effect.

Safety will be assessed with the vital signs, brief physical examination, clinical laboratory tests, cutaneous tolerance score, incidence of minocycline-induced skin hyperpigmentation, incidence of visual disturbances and/or headaches suggestive of pseudotumor cerebri, incidence of product related facial staining and collection of adverse events.

Inclusion Criteria:

Subjects will be eligible if they meet all of the following criteria at the screening and baseline (Day 0) visits, unless specified otherwise:

1. Male or female subjects aged between 18 and 40 years of age, inclusive, at the time of consent.
2. Subjects do not have any medical conditions, other than acne vulgaris, that in the opinion of the investigator, put the subject at unacceptable risk or could interfere with study assessments or integrity of the data.
3. Moderate to severe inflammatory non-nodular acne vulgaris, defined as follows:
    a. IGA score of 3 (moderate) or 4 (severe) at baseline (Day 0);
    b. 20-60 inflammatory lesions on the face at baseline (Day 0);
    c. 0-100 noninflammatory lesions on the face at baseline (Day 0);
    d. Maximum of 2 nodules (≥ 5 mm) on the face at baseline (Day 0).
4. Female subjects of childbearing potential (including pre-puberty) are willing to use effective contraceptive method for at least 28 days before baseline (Day 0) and at least 28 days after the last study product administration or have a sterilized or same-sex partner for the duration of the study. Effective contraceptive methods are: systemic hormonal contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicide, or agree to sexual abstinence. Hormonal contraceptives must be on a stable dose for at least 12 weeks before baseline (Day 0). Subjects using low dose oral contraceptives must use a second form of birth control (e.g., barrier method such as condoms with spermicide).
   Note: Female subjects of nonchildbearing potential are defined as follows:
    a. Female subjects who have had surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation);
    b. Female subjects who have had a cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to the central laboratory reference range for menopausal women) or cessation of menses for at least 24 months without FSH levels confirmed;
5. Female subjects of childbearing potential must have a negative urine pregnancy test at screening and baseline (Day 0).
6. Treatment with hormonal therapy must be on a stable dose and frequency for at least 12 weeks before baseline (Day 0) and must remain stable throughout the study.
7. Subjects who use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens must have used the same product brands/types for a minimum period of 14 days prior to baseline (Day 0), must agree not to change brand/type or frequency of use throughout the study and must agree not to use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens on the clinic visit days before the visit.
8. Subjects must be capable of giving informed consent and the written informed consent must be obtained prior to any study-related procedures.

Exclusion Criteria:

Subjects will not be eligible if they meet any of the following criteria at the screening or baseline (Day 0) unless specified otherwise:

1. Female subject who is breastfeeding, pregnant or who is planning a pregnancy during the study.
2. Have acne fulminans or conglobata, or nodulocystic acne.
3. Have a history of skin disease, presence of skin condition, skin pigmentation or excessive facial hair that, in the opinion of the investigator, would interfere with the study.
4. Have a history of cancer or lymphoproliferative disease other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix.
5. Have had any prior treatment with minocycline.
6. Presence of visual disturbances and/or headaches suggestive of pseudotumor cerebri at screening or baseline (Day 0).
7. Have a clinical chemistry or hematology laboratory value that is abnormal at the screening visit and that is considered clinically significant by the investigator.
8. Has an ALT or AST at screening greater than or equal to 2 times the upper limit of normal.
9. Have used on the face an over-the-counter (OTC) topical medication for the treatment of acne vulgaris including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, salicylic acid, α-hydroxy/glycolic, antibacterial/antiseptic soap or wash within 14 days prior to baseline (Day 0). Topical acne treatments that do not have significant or measurable systemic absorption (e.g., benzoyl peroxide, salicylic acid) are allowed for treatment of acne on the back, shoulders and chest only.
10. Have used prescription topical retinoid (e.g. tretinoin, tazarotene, adapalene) or antimicrobials (e.g. clindamycin, erythromycin) or other prescription topical medications for the treatment of acne vulgaris within 28 days of baseline (Day 0). Topical antibiotics (not containing minocycline or other tetracycline-class antibiotics) may be used to treat non-acne skin lesions outside the face.
11. Have used systemic antibiotics or other systemic anti-acne drugs not mentioned in the exclusion criteria within 28 days of baseline (Day 0).
12. Have used oral, intranasal, or injectable corticosteroids within 28 days of baseline (Day 0) or require them during the study. Inhaled corticosteroids for stable medical conditions are allowed.
13. Have received an investigational therapy (including investigational drug or procedure) within 28 days of baseline (Day 0) or plan to use one during the study.
14. Have had a facial procedure (e.g. chemical peel, laser, microdermabrasion) within 8 weeks of baseline (Day 0).
15. Have excessive sun exposure, is planning a trip to a sunny climate or used tanning booths within 28 days prior to baseline (Day 0) or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.

16. Have received photodynamic therapy or phototherapy with blue or red light within 12 weeks of baseline (Day 0).
17. Have used androgen receptor blockers (such as spironolactone or flutamide) within 12 weeks of baseline (Day 0).
18. Have used drospirenone, chlormadinone acetate, and cyproterone acetate within 26 weeks of baseline (Day 0).
19. Have used oral retinoid (e.g., isotretinoin) within 52 weeks prior to baseline (Day 0) or vitamin A supplements greater than 10,000 U/d within 26 weeks of baseline (Day 0).
20. History of clinically significant drug or alcohol abuse in the last year prior to baseline (Day 0) as judged by the investigator.
21. Has known or suspected allergy to minocycline, tetracycline-class antibiotics or any component of the investigational product.

Statistical Analysis:

No statistical analysis will be performed for this small study. The low sample size will provide directional data only and no statistical significance between or within treatment groups is expected.

1 BACKGROUND

1.1 Acne Vulgaris

Acne vulgaris is the most prevalent skin disorder and it affects approximately 85% of the population at some time between the age of 12 and 24 years, and it frequently persists into adulthood.[1,2] Acne is a multifactorial chronic disease and different factors contribute to its development such as: (1) sebaceous gland hyperactivity with seborrhea, (2) abnormal keratinocyte desquamation, and (3) bacterial colonization and proliferation responsible for local inflammatory changes.[3,4] Clinically, acne is characterized by two major types of lesions that are typically located on the face, chest, and back: (1) noninflammatory open and closed comedones and (2) inflammatory papules, pustules and nodules. During puberty, surges in androgen cause over production of sebum along with abnormal desquamation of the epidermal lining of hair follicles. Formed by sebum and skin debris, the comedones provide an ideal environment for the proliferation of *Propionibacterium acnes* bacteria which are then responsible for triggering local inflammatory reactions by releasing inflammatory mediators. A wide variety of drug products, topical and systemic, are available to treat acne. The most effective acne therapies work by targeting the sebaceous gland and decreasing sebum production.

Because of their known anti-inflammatory properties, minocycline products have been particularly successful in the treatment of moderate to severe inflammatory acne vulgaris. However, there have been severe side effects associated with the oral dosage forms of minocycline. There is currently no commercially available topical dosage form of minocycline.

1.2 BPX-01 Minocycline in Acne Vulgaris

BPX-01 is a topical gel comprising minocycline hydrochloride (HCl) as the drug substance. It is a hydrophilic formulation that relies on full dissolution of the drug substance to ensure efficient and targeted delivery to the facial skin. In preclinical studies, uptake of BPX-01 has been confirmed to reach the epidermis and pilosebaceous units, with local levels above the minimum inhibitory concentration (MIC) value for *P. acnes*.[5]

Minocycline is an antibiotic currently available in multiple oral dosage forms for treating various bacterial infections. Minocycline inhibits the growth of certain species of bacteria through inhibition of protein synthesis by blocking aminoacyl-tRNA binding to the mRNA-ribosome complex. Minocycline is active against a number of gram-positive and gram-negative organisms, including *P. acnes*. The mechanism through which minocycline ameliorates acne is not fully elucidated, although reducing the bacterial count may reduce the size and quantity of lesions by reducing inflammation.[6,7,8]

BPX-01, 1% gel is intended for use in the treatment of non-nodular, moderate to severe inflammatory acne vulgaris in patients 9 years of age and older. There has been one clinical study (Phase 2a) completed with BPX-01 1% minocycline topical gel and another dose finding study (Phase 2b) completed with BPX-01 1% and 2% minocycline topical gel.

1.3 Rationale for this Study

BioPharmX is developing a new therapeutic option for patients with moderate to severe acne vulgaris. Because of an anticipated lower systemic exposure and extended half-life with BPX-01, the potential for many of the side effects seen with oral Solodyn or other oral minocycline formulations are expected to be markedly minimized or completely abrogated. The objective of this study is to document the treatment effect of 1 and 2% topical minocycline gel in subjects with moderate to severe inflammatory non-nodular acne vulgaris.

2 STUDY HYPOTHESIS AND OBJECTIVE(S)

2.1 Hypothesis

BPX-01 improves disease condition in subjects with moderate to severe inflammatory non-nodular acne vulgaris.

2.2 Objectives

Primary:

- To obtain photo-documentation of the efficacy of BPX-01 minocycline 1% or 2% topical gel in the treatment of inflammatory non-nodular acne vulgaris

Secondary:

- To evaluate the cutaneous tolerance of BPX-01 minocycline 1% or 2% topical gel

3 STUDY ENDPOINTS

3.1 Primary Endpoint

- Change from baseline in inflammatory lesion counts at Week 12

3.2 Secondary and Exploratory Endpoints

Secondary Efficacy Endpoint:

- Change from baseline in inflammatory lesion counts at Weeks 1, 2, 4, and 8

Exploratory Efficacy Endpoints:

- Subjects with at least a two-grade reduction in IGA at Week 12
- Percent change from baseline in inflammatory lesion counts at Weeks 1, 2, 4, 8, and 12
- Absolute change and percent change from baseline in noninflammatory lesion counts at Weeks 1, 2, 4, 8, and 12
- Absolute change and percent change from baseline in total lesion counts at Weeks 1, 2, 4, 8, and 12
- Absolute change and percent change from baseline in the Investigator's Global Assessment (IGA) at Weeks 1, 2, 4, 8, and 12
- Proportion of subjects with an IGA of clear (0) or almost clear (1) at Weeks 1, 2, 4, 8, and 12
- Proportion of subjects with at least a two-grade reduction in IGA at Weeks 1, 2, 4, and 8
- Change from baseline in Patient Global Impression of Severity (PGI-S) at Weeks 1, 2, 4, 8, and 12
- Patient Global Impression of Improvement (PGI-I) at Weeks 1, 2, 4, 8, and 12

Safety Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Shift from baseline in clinical hematology and chemistry laboratory tests
- Change from baseline in the cutaneous tolerance score evaluated by the observer (erythema, scaling-peeling, edema)
- Change from baseline in the cutaneous tolerance score evaluated by the subject (tightness, burning, stinging, itching)
- Incidence of visual disturbances/headaches suggestive of pseudotumor cerebri and minocycline-induced skin hyperpigmentation
- Incidence of product related facial staining

4 STUDY DESIGN

This is a 12-week, multi-center, open label, two-arm study.

Subjects will be assigned to treatment with 1% or 2 % BPX-01 gel. Subjects will apply 1g of the gel as a thin film to the entire face at least 30 minutes before bedtime each night for 12 weeks. Lesion counts, IGA, and Patient-Reported Outcomes (PGI-S and PGI-I) will be performed to assess efficacy. Photographs will be taken to document treatment effect.

Safety will be assessed with the vital signs, brief physical examination, clinical laboratory tests, cutaneous tolerance score, incidence of minocycline-induced skin hyperpigmentation, incidence of visual disturbances and/or headaches suggestive of pseudotumor cerebri, incidence of product related facial staining and collection of adverse events.

5 STUDY POPULATION

This study will include up to 40 subjects with moderate to severe inflammatory non-nodular acne vulgaris, defined as IGA score of 3 (moderate) or 4 (severe), 20-60 inflammatory lesions, 0-100 noninflammatory lesions and a maximum of 2 nodules on the face at baseline. Subjects will be male or female, aged between 18 and 40 years. Subjects who discontinue after taking the first dose of study drug will not be replaced.

5.1 Inclusion Criteria

Subjects will be eligible if they meet all of the following criteria at the screening and baseline (Day 0) visits, unless specified otherwise:

1. Male or female subjects aged between 18 and 40 years of age, inclusive, at the time of consent.
2. Subjects do not have any medical conditions, other than acne vulgaris, that in the opinion of the investigator, put the subject at unacceptable risk or could interfere with study assessments or integrity of the data.
3. Moderate to severe inflammatory non-nodular acne vulgaris, defined as follows:
    a. IGA score of 3 (moderate) or 4 (severe) at baseline (Day 0);
    b. 20-60 inflammatory lesions on the face at baseline (Day 0);
    c. 0-100 noninflammatory lesions on the face at baseline (Day 0);
    d. Maximum of 2 nodules (≥ 5 mm) on the face at baseline (Day 0).
4. Female subjects of childbearing potential (including pre-puberty) are willing to use effective contraceptive method for at least 28 days before baseline (Day 0) and at least 28 days after the last study product administration or have a sterilized or same-sex partner for the duration of the study. Effective contraceptive methods are: systemic hormonal contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicide, or agree to sexual abstinence. Hormonal contraceptives must be on a stable dose for at least 12 weeks before baseline (Day 0). Subjects using low dose oral contraceptives must use a second form of birth control (e.g., barrier method such as condoms with spermicide).
   Note: Female subjects of nonchildbearing potential are defined as follows:
    a. Female subjects who have had surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation);
    b. Female subjects who have had a cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to the central laboratory reference range for menopausal women) or cessation of menses for at least 24 months without FSH levels confirmed;
5. Female subjects of childbearing potential must have a negative urine pregnancy test at screening and baseline (Day 0).
6. Treatment with hormonal therapy must be on a stable dose and frequency for at least 12 weeks before baseline (Day 0) and must remain stable throughout the study.

7. Subjects who use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens must have used the same product brands/types for a minimum period of 14 days prior to baseline (Day 0), must agree not to change brand/type or frequency of use throughout the study and must agree not to use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens on the clinic visit days before the visit.
8. Subjects must be capable of giving informed consent and the written informed consent must be obtained prior to any study-related procedures. Subject under 18 years of age must sign an assent form, and their parent(s) or legal representative must have read and signed the informed consent form prior to any study-related procedures.

5.2 Exclusion Criteria

Subjects will not be eligible if they meet any of the following criteria at the screening or baseline (Day 0) unless specified otherwise:

1. Female subject who is breastfeeding, pregnant or who is planning a pregnancy during the study.
2. Have acne fulminans or conglobata, or nodulocystic acne.
3. Have a history of skin disease, presence of skin condition, skin pigmentation or excessive facial hair that, in the opinion of the investigator, would interfere with the study.
4. Have a history of cancer or lymphoproliferative disease other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix.
5. Have had any prior treatment with minocycline.
6. Presence of visual disturbances and/or headaches suggestive of pseudotumor cerebri at screening or baseline (Day 0).
7. Have a clinical chemistry or hematology laboratory value that is abnormal at the screening visit and that is considered clinically significant by the investigator.
8. Has an ALT or AST at screening greater than or equal to 2 times the upper limit of normal.
9. Have used on the face an over-the-counter (OTC) topical medication for the treatment of acne vulgaris including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, salicylic acid, α-hydroxy/glycolic, antibacterial/antiseptic soap or wash within 14 days prior to baseline (Day 0). Topical acne treatments that do not have significant or measurable systemic absorption (e.g., benzoyl peroxide, salicylic acid) are allowed for treatment of acne on the back, shoulders and chest only.
10. Have used prescription topical retinoid (e.g. tretinoin, tazarotene, adapalene) or antimicrobials (e.g. clindamycin, erythromycin) or other prescription topical medications for the treatment of acne vulgaris within 28 days of baseline (Day 0). Topical antibiotics (not containing minocycline or other tetracycline-class antibiotics) may be used to treat non-acne skin lesions outside the face.
11. Have used systemic antibiotics or other systemic anti-acne drugs not mentioned in the exclusion criteria within 28 days of baseline (Day 0).

12. Have used oral, intranasal, or injectable corticosteroids within 28 days of baseline (Day 0) or require them during the study. Inhaled corticosteroids for stable medical conditions are allowed.
13. Have received an investigational therapy (including investigational drug or procedure) within 28 days of baseline (Day 0) or plan to use one during the study.
14. Have had a facial procedure (e.g. chemical peel, laser, microdermabrasion) within 8 weeks of baseline (Day 0).
15. Have excessive sun exposure, is planning a trip to a sunny climate or used tanning booths within 28 days prior to baseline (Day 0) or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
16. Have received photodynamic therapy or phototherapy with blue or red light within 12 weeks of baseline (Day 0).
17. Have used androgen receptor blockers (such as spironolactone or flutamide) within 12 weeks of baseline (Day 0).
18. Have used drospirenone, chlormadinone acetate, and cyproterone acetate within 26 weeks of baseline (Day 0).
19. Have used oral retinoid (e.g., isotretinoin) within 52 weeks prior to baseline (Day 0) or vitamin A supplements greater than 10,000 U/d within 26 weeks of baseline (Day 0).
20. History of clinically significant drug or alcohol abuse in the last year prior to baseline (Day 0) as judged by the investigator.
21. Has known or suspected allergy to minocycline, tetracycline-class antibiotics or any component of the investigational product.

5.3 Discontinuations

Subjects have the right to withdraw from the study at any time for any reason without penalty. The investigator also has the right to withdraw subjects from the study if he/she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant. Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the follow-up examination.

The investigator or one of his or her staff members should contact the subject either by telephone or through a personal visit to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded. The criteria for enrollment must be followed explicitly. Subjects who discontinue the study after taking his or her first dose, but before the Week 12 visit will be asked, if they agree, to come for the last assessments listed at Week 12 (exit visit). Subjects who discontinue will not be replaced.

Reasons for discontinuation include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made

because of a serious adverse event, the study drug is to be discontinued and appropriate measures are to be taken. The investigator will notify the sponsor immediately.

- The attending physician requests that the subject be withdrawn from the study.
- The subject for any reason requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- The sponsor or regulatory authorities, for any reason, stop the study. All subjects will be discontinued from the study and notified of the reasons for the discontinuation.
- Pregnancy occurs at any time during the study.
- Presence of clinically significant symptoms suggestive of pseudotumor cerebri.
- Other: the subject may withdraw from the study for any other reason, including withdrawal of consent.

6 TREATMENT

6.1 Treatment Administered

Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. Each subject should read and sign an informed consent form prior to any screening procedures being performed. This study involves a comparison of 1% and 2% BPX-01 administered topically on a clean face at least 30 minutes before bedtime each night for a total duration of 12 weeks. Subjects will be assigned sequentially to either 1 or 2% BPX-01 in a 1:1 ratio on Day 0 (baseline) as follows:

1st 10 subjects: BPX-01 1%, 1 g topical gel once a day for 12 weeks

2nd 10 subjects: BPX-01 2%, 1 g topical gel once a day for 12 weeks

Subjects should complete their cleansing routine (e.g., washing face, bathe, shower, shaving) and have a clean face prior to study drug application and should not apply anything else to their face afterward in the evening. Every effort should be made to keep the same skin care habits throughout the study.

If an application is missed, subjects should apply the study product as soon as they remember on the same day. However, if it is the next day, the missed dose should be skipped and the next dose taken as normal. No double dose should be taken for any reason.

6.2 Study Treatment

6.2.1 Description

BPX-01 (1% and 2%) is formulated as a topical gel comprising minocycline HCl as the drug substance. The gel will be provided by BioPharmX in single-dose, aluminum tubes lined with an inert, biocompatible material. Each tube will contain 1.5 g of gel, calculated to deliver 1 g of drug product.

The investigator will be responsible for drug accountability. After verification of the drug accountability by the sponsor or designee, all study product (used and unused tubes) will be returned to the sponsor or designee after the study completion.

6.2.2 Storage Conditions

The study drug will be provided by BioPharmX to the investigator. It will be kept, on site, in a secure, temperature-controlled place at 15°C to 30°C with protection from moisture. It will only be supplied to subjects in the trial under the supervision of the investigator. Room temperature on site will be monitored and recorded. The packaging of investigational product for this clinical

study has been designed with these conditions in mind and precautions other than limiting temperature range are not required.

6.2.3 Study Drug Dispensing and Return

The study drug will be applied at home throughout the study, except for the first dose that will be applied on site at the baseline (Day 0) visit under the supervision of the study staff.

The study drug will be dispensed in a medication kit by the study site to the subjects and will be given with subject instructions for application. At baseline (Day 0) and Week 2 visits, subjects will receive one medication kit containing 18 tubes each. At Week 4 and Week 8 visits, subjects will receive two kits for a total of 36 tubes each. Single-use tubes of 1.5 g (for delivery of 1 g of gel) will be given and 1 g of gel is to be applied on the entire face once daily. Subjects are to return all tubes (used and unused) to the study site at the Week 1, 2, 4, 8, and 12 visits. The number of tubes will be counted prior to dispensing and upon return and the counts will be recorded in the source documents and eCRF. Each subject will be instructed on the importance of returning study drug at the specified visits. If a subject does not return study drug, he or she will be instructed to return it as soon as possible.

6.2.4 Drug Accountability

The investigator is responsible for maintaining accurate records of the study drug received initially, the study drug dispensed/used/returned by subjects and the study drug destroyed or returned to the sponsor or designee. All study drug accountability forms and treatment logs must be retained in the Investigator's study file. These records must be available for inspection at any time by the sponsor, its designees or by regulatory agencies.

6.2.5 Method of Assignment to Treatment

Up to 40 subjects will be assigned sequentially (1:1) to one of the two treatment groups.

6.2.6 Rationale for Selection and Timing of Doses in the Study

In preclinical studies, different BPX-01 formulations (1% and 4%) were applied as mg/cm^2 to cover approximately 5% to 15% of body surface area (BSA). Topical administration of BPX-01 once daily demonstrated rapid absorption in rats at all doses. The amount of BPX-01 1% minocycline detected in rats at the 2.5 mg/cm^2/d dose group represents the maximum amount of absorption, because rat skin is thinner than human skin. No systemic uptake of minocycline was seen in the low dose group in minipigs. The lack of minocycline in plasma with delivery of BPX-01 1% minocycline in minipigs at 2.5 mg/cm^2/d is very promising because it supports the hypothesis that targeted delivery of minocycline to the skin with limited systemic exposure is possible.[5]

The uptake of minocycline in minipig skin shows levels above the MIC value for *P. acnes*, which was found to be 0.035 µg/mL. Therefore, on the basis of these results, BPX-01 1%

minocycline at 2.5 mg/cm^2/day is the proposed first-in-human clinical dose (1 g of BPX-01, 1% minocycline applied as a thin film to the entire face) that was used in a Phase 2a study.[5] In a currently ongoing 2b dose finding study, the 1% and 2% doses are being evaluated to establish the lowest effective dose. This current open label study will provide early data on the correlation between IGA, lesion counts and photo-documentation.

6.2.7 Assessment of Treatment Compliance

Compliance to treatment with BPX-01 minocycline 1% or 2% will be monitored at each visit. Compliance to treatment will be assessed by direct questioning, review of the subject's diary, and by maintaining adequate drug dispensing and return records. The tubes containing study drug will be collected from each subject at the Week 1, 2, 4, 8, and 12 visits to further assess treatment compliance. Any deviation from the prescribed dosage regimen will be recorded in the source document and CRF.

Subjects who are significantly noncompliant to treatment will be counseled and could be discontinued from the study, at the discretion of the investigator following consultation with the sponsor. Similarly, a subject will be considered significantly noncompliant if he or she intentionally or repeatedly takes more than the prescribed amount of medication in the same time frame as judged by the investigator.

6.3 Concomitant Therapy

All medications (including OTC drugs, vitamins, and antacids) taken less than or equal to 28 days prior to screening and throughout the study must be recorded.

The investigator should assess for acceptability any concomitant procedures, medications, and dietary supplements that are not explicitly prohibited.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the dose, unit, frequency of administration, route of administration, start date, discontinuation date, and indication. If the medication is discontinued or the dosage changed, these details must be recorded.

6.3.1 Permitted Therapies

The following therapies are permitted:

- Topical acne treatments that do not have significant or measurable systemic absorption (e.g. benzoyl peroxide, salicylic acid) are allowed for treatment of acne on the back, shoulders and chest only;
- Topical antibiotics (not containing minocycline or other tetracycline-class antibiotics) may be used to treat non-acne skin lesions outside the face;

- Inhaled corticosteroids for stable medical conditions are allowed;
- Hormonal therapies (including oral contraceptives) are allowed but must be on stable dose and frequency for at least 12 weeks before baseline (Day 0) and must remain stable throughout the study (see inclusion criteria, Section 5.1, for more details);
- Subjects will be instructed that the use of make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens are permitted but they must use the same brands/types for a minimum period of 14 days prior to baseline (Day 0) and must agree not to change brand/type or frequency of use throughout the study. Subjects must also agree not to use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens on the clinic visit days before the visit;
- Subjects who choose to use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens should try to use non-comedogenic products.

6.3.2 Prohibited Therapies or Procedures

The following therapies are prohibited:

- The use of any OTC topical medications for the treatment of acne vulgaris on the face including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, salicylic acid, α-hydroxy/glycolic, antibacterial/antiseptic soap or wash within 14 days prior to baseline (Day 0) and throughout the study;
- The use of any prescription topical retinoid (e.g. tretinoin, tazarotene, adapalene) or antimicrobials (e.g. clindamycin, erythromycin) or any other prescription topical medications for the treatment of acne vulgaris within 28 days of baseline (Day 0) and throughout the study (except topical antibiotics for non-acne skin lesions as indicated in Section 6.3.1);
- The use of systemic antibiotics or other systemic anti-acne drugs not mentioned in the exclusion criteria (Section 5.2) within 28 days of baseline (Day 0) and throughout the study;
- The use of oral, intranasal, or injectable corticosteroids within 28 days of baseline (Day 0) and throughout the study;
- The use of androgen receptor blockers (e.g., spironolactone, flutamide) within 12 weeks of baseline (Day 0) and throughout the study;
- The use of an oral retinoid (e.g., isotretinoin) within 52 weeks prior to baseline (Day 0) or vitamin A supplements greater than 10,000 U/d within 26 weeks of baseline (Day 0) and throughout the study;
- Facial procedures (e.g. chemical peel, laser, microdermabrasion) within 8 weeks of baseline (Day 0) and throughout the study;
- Photodynamic therapy or phototherapy with blue or red light within 12 weeks of baseline (Day 0) and throughout the study;
- The use of drospirenone, chlormadinone acetate, and cyproterone acetate within 26 weeks of baseline (Day 0) and throughout the study;

- The use of another investigational therapy within 28 days of baseline (Day 0) and throughout the study.

7 SCHEDULE OF EVENTS

Screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the informed consent form. No treatment or trial-related procedures will be initiated before the informed consent is signed. The baseline (Day 0) visit must be performed, at the latest, 30 days after the screening visit.

Screening evaluation will be performed according to inclusion and exclusion criteria. If the individual fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1 provides a description of the procedures to be performed at each visit.

Table 1 : Schedule of Events

Procedures/ Time Points:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
	Screening	**Baseline / Day 0**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**TBD[5] Recurrence**
Visit windows	–30 to –1 d		±3 d	±3 d	±3 d	± 3 d	±3 d	n/a
Informed consent, medical history and HIPAA	X							
Demographics	X							
Collect/Record Concomitant Medications	X	X	X	X	X	X	X	X
Eligibility Assessment	X	X						
Brief Physical examination	X						X	
Vital signs[1]	X						X	
Basic Chemistry and Hematology Laboratory Panel[2]	X						X	
Urine Pregnancy Test[3]	X	X					X	
Patient global impression of severity (PGI-S)		X	X	X	X	X	X	X
Patient global impression of improvement (PGI-I)			X	X	X	X	X	X
Investigator Global Assessment (IGA)	X	X	X	X	X	X	X	X
Lesion Counts	X	X	X	X	X	X	X	X
Investigator Cutaneous Tolerance Scores[4]		X	X	X	X	X	X	

Procedures/ Time Points:	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Screening	Baseline / Day 0	Week 1	Week 2	Week 4	Week 8	Week 12	TBD[5] Recurrence
Visit windows	–30 to –1 d		±3 d	±3 d	±3 d	± 3 d	±3 d	n/a
Subject Cutaneous Tolerance Scores[4]		X	X	X	X	X	X	
Presence or absence of visual disturbances/headaches suggestive of pseudotumor cerebri			X	X	X	X	X	
Presence or absence of minocycline-induced skin hyperpigmentation			X	X	X	X	X	X
Presence or absence of minocycline-induced skin staining			X	X	X	X	X	X
Photography		X	X	X	X	X	X	X
Test Product Dispensed to Subject along with subject's instructions		X	X	X	X	X		
Subject Dairy Distribution/Collection/Review		X	X	X	X	X	X	
Collect All Study Medication Supplies / Drug Accountability			X	X	X	X	X	
Collect and Record Adverse Events		X	X	X	X	X	X	
Subject Satisfaction Questionnaire							X	

FSH = follicle-stimulating hormone; HIPAA = Health Insurance Portability and Accountability Act of 1996.

[1]Include height and weight. Height will be measured only at screening.

[2]Include FSH levels (at screening only) for female subjects who have had a cessation of menses for at least 12 months but less than 24 months.

[3]Female subjects of childbearing potential only (including pre-puberty).

[4]Cutaneous Tolerance Score

- Observer reported: erythema, scaling-peeling, edema.
- Self-Reported: tightness, burning, stinging, itching.

[5]Subjects should be instructed to call the office to schedule a visit as soon as acne recurrence is noted. Subjects should also be instructed to avoid any acne treatments until the final in office evaluation has been made.

8 STUDY ASSESSMENTS

8.1 Efficacy Assessments

Clinical evaluations of acne vulgaris will be performed by an experienced and qualified dermatologist (board certified or equivalent) or designee. To ensure consistency and reduce variability, the same assessor should perform all assessments on a given subject whenever possible.

The following points must be noted regarding to the order of the efficacy assessments:

- PROs (Patient Global Impression Questionnaires) should be completed prior to any other assessments to avoid bias in the subject's evaluation.
- The assessment of the IGA should be performed before the lesion counts.
- Acne lesion counts are to be performed after the PROs and IGA evaluations.
- Baseline assessments should be performed prior to first product administration.

The time when each assessment is performed will be documented in the source document and/or eCRF.

8.1.1 Acne Lesion Counts

The number of acne lesions on the face (papules, pustules, nodules, and open and closed comedones) will be counted at every visit, according to the following definitions. The nose is excluded for the comedone counts.

Inflammatory lesions:

Papule: A small, solid elevation 5 mm or less in diameter.

Pustule: A small, circumscribed elevation of the skin that contains yellow-white exudate.

Nodule: A circumscribed, elevated, lesion generally more than 5 mm in diameter.

Noninflammatory lesions:

Open comedone: A mass of sebaceous material that is impacted behind an open follicular orifice (blackhead)

Closed comedone: A mass of sebaceous material that is impacted behind a closed follicular orifice (whitehead)

Subjects will be examined in a well-lit room and without the aid of magnifying instruments. Total number of lesions and number of each type of lesion (papule, pustule, nodule, closed and open comedone) should be reported.

8.1.2 Investigator Global Assessment (IGA)

The Investigator's Global Assessment (IGA) of Disease Severity will be assessed at every study visit. The IGA is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity; assessment will be determined according to the following categories: 0 (clear), 1 (almost clear), 2 (mild severity), 3 (moderate severity) and 4 (severe). To be eligible, subjects must have an IGA score of 3 or 4 at the baseline (Day 0) visit. The IGA is an overall global evaluation of acne that should be performed at arm's length distance from the patient. A detailed description of IGA scores is provided in Table 2.

Table 2 : Investigator's Global Assessment Scale for Acne Vulgaris

Grade	Description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare noninflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	Severe; greater than Grade 3; up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions

Source: FDA Draft guidance on Acne Vulgaris[9]

8.1.3 Patient-Reported Outcomes (PROs)

8.1.3.1 Patient Global Impression of Severity (PGI-S)

The patient global impression of severity is a single-item question that asks the subject to rate the current severity of his or her acne. It will be assessed at baseline (Day 0), and at the Week 1, 2, 4, 8, and 12 visits.

Overall, how would you rate the severity of your acne now?

The responses are as follows[10]:

1. *Clear skin*
2. *Mild*
3. *Moderate*
4. *Severe*

8.1.3.2 Patient Global Impression of Improvement (PGI-I)

The patient global impression of improvement is a single-item question that asks the subject to rate the current symptom severity compared with how it was before taking the study medication ("Very much better" to "Very much worse"). It will be assessed at the Week 1, 2, 4, 8 and 12 visits.

Overall, how would you rate the change in severity of your acne compared with how it was before you started taking the medication in this study?

The responses are as follows[10]:

1. *Very much better*
2. *Much better*
3. *A little better*
4. *No change*
5. *A little worse*
6. *Much worse*
7. *Very much worse*

8.1.4 Photographic Documentation

Photographic documentation of changes from baseline in the disease condition will be performed at baseline, weeks 1, 2, 4, 8, 12 and at the follow-up visit. Every effort will be made to standardize lighting, facial orientation, and distance from the camera to minimize between assessment variability due to image capture.

8.2 Safety Assessments

8.2.1 Vital Signs

The following vital signs will be recorded at screening and Week 12 visits (exit visit) in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm) and body temperature (°C).

Weight (kg) and height (cm) will be recorded at the screening visit. The weight will also be recorded at the Week 12 visit (exit visit).

Any abnormal finding related to vital signs that the investigator considers to be clinically significant, must be recorded as an AE.

8.2.2 Brief Physical Examination

The following sites/systems will be included in the brief physical examination that will be performed at screening and Week 12 visits (exit visit). Each system will be scored as normal/abnormal (non-clinically significant or clinically significant). Pertinent details must be recorded for any clinically significant findings.

- General appearance
- Dermatological (except acne on the face)
- Respiratory
- Cardiovascular
- Abdominal

8.2.3 Clinical Laboratory Tests

Laboratory tests will be performed at screening and at Week 12. The tests will include hematology with differential and a standard chemistry panel (chemistry includes liver function tests). In addition, at the screening, baseline (Day 0), a urine pregnancy test will be performed for female subjects of childbearing potential (including pre-puberty) at the investigator site. The specific tests in these panels are listed in Table 3.

Table 3 Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	Basophils, Eosinophils, HCT, HGB, Lymphocytes, MCH, MCV, MCHC, Monocytes, Neutrophils, platelets, RBC, WBC
Serum chemistry	Albumin, Alkaline Phosphatase, ALT, AST, Chloride, CK, Creatinine (Enzymatic), GGT, Glucose Random, LDH, Potassium, Sodium, Total Bilirubin, Urea (BUN), Uric Acid
Urine pregnancy test	For females of childbearing potential (screening, baseline (Day 0) and Week 12 visits (exit visit))
Laboratory tests required at screening only	FSH levels for female subjects who have had a cessation of menses for at least 12 months but less than 24 months.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HCT = hematocrit; HGB = hemoglobin; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell (count); WBC = white blood cell (count).

Details about the collection and storage of clinical laboratory samples will be provided in the laboratory manual.

8.2.4 Cutaneous Tolerance Scores

Grading of local site reactions/tolerance will be performed at baseline (Day 0), and at Weeks 1, 2, 4, 8, and 12 and at the follow-up visit. At the baseline (Day 0) visit, the tolerance assessments are to be performed before the drug application.

The investigator (or qualified evaluator) will assess the presence and degree of erythema, scaling-peeling and edema at the application site using a 4-point scale, where 0=None, 1= Mild, 2= Moderate, and 3=Severe.

Erythema:

0 – None	No evidence of erythema present
1 – Mild	Slight pink coloration
2 – Moderate	Definite redness
3 – Severe	Marked erythema, bright red to dusky dark red in color

Scaling-peeling:

0 – None	No scaling
1 – Mild	Barely perceptible, fine scales present to limited areas of the face
2 – Moderate	Fine scale generalized to all areas of the face

3 – Severe	Scaling and peeling of skin over all areas of the face

Edema:

0 – None	No edema
1 – Mild	Slight edema, barely perceptible
2 – Moderate	Definite edema, raised approximately 1mm.
3 – Severe	Severe edema, raised more than 1mm and beyond exposure area

The subjects will be asked to grade their feeling of burning, stinging, tightness, and itching at the application site using a 4-point tolerability scale, where 0=None, 1= Mild, 2= Moderate, and 3=Severe.

Burning:

0 – None	No burning
1 - Mild	Slight burning sensation; not really bothersome
2 – Moderate	Definite warm, burning sensation that is somewhat bothersome
3 – Severe	Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Stinging:

0 – None	No stinging
1 – Mild	Slight stinging sensation, not really bothersome
2 – Moderate	Definite stinging sensation that is somewhat bothersome
3 – Severe	Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Tightness:

0 – None	No tightness
1 – Mild	Slight tightness sensation, not really bothersome
2 – Moderate	Definite tightness sensation that is somewhat bothersome
3 – Severe	Tightness sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Itching:

0 – None	No itching
1 – Mild	Slight itching, not really bothersome
2 – Moderate	Definite itching that is somewhat bothersome
3 – Severe	Intense itching that may interrupt daily activities and/or sleep

8.2.5 Incidence of Minocycline-Induced Skin Hyperpigmentation, Visual Disturbances/Headaches Suggestive of Pseudotumor Cerebri

Incidence of minocycline-induced skin hyperpigmentation, visual disturbances/headaches suggestive of pseudotumor cerebri will be evaluated by the investigator at Week 0, 1, 2, 4, 8 and 12 visits as follows:

1) Presence or absence of minocycline-induced skin hyperpigmentation.
2) Presence or absence of headaches suggestive of pseudotumor cerebri.
3) Presence or absence of visual disturbances suggestive of pseudotumor cerebri.

Any occurrences of these specific events will be reported as an AE.

If a subject reports headaches and/or visual disturbances suggestive of pseudotumor cerebri, the investigator should consider referral to a neurologist and must promptly contact the Medical Monitor to discuss the course of action.

8.2.6 Incidence of Product Related Facial Staining

This evaluation should occur prior to product administration at the baseline visit. Incidence of product-related skin staining will be evaluated by the investigator at Week 0, 1, 2, 4, 8 and 12 visits and recorded as presence or absence of product-related skin staining. If staining is present, photographic documentation of the stained area will be obtained. Note that care should be taken to differentiate between actual staining (yellowish discoloration that does not wash off) vs. superficial accumulation of product (washes off) or hyperpigmentation (actual purplish/blue/black discoloration of tissues).

9 ADVERSE EVENTS

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product, without regard to the possibility of a causal relationship with this treatment.

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the sponsor of any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for appropriate medical care of subjects during the study.

The investigator remains responsible for following through an appropriate health care option for adverse events that are serious or that cause the subject to discontinue before completing the study. The subject should be followed until the event is resolved or stable. Follow-up frequency is left to the discretion of the investigator.

Safety will be evaluated by collecting adverse events, recording vital signs, performing a brief physical examination, and evaluating laboratory results. The reported adverse events will be coded according to type and body system.

Prior to enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the source document and CRF. During the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

Any events occurring prior to the baseline visit will be recorded on the Medical History CRF. Events occurring after application of the 1st dose of study drug or those that increase in severity or frequency will be recorded as treatment-emergent adverse events (TEAEs) on the Adverse Event CRF. All AEs will be described in the source documents and in the CRF.

9.1 Adverse Events Causality

The investigator will establish causality of the AE to experimental treatment. The investigator should take into account the subject's history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Not related: temporal relationship of the onset of the AE, relative to the experimental treatment is not reasonable or another cause can explain the occurrence of the AE.
- Possibly related: temporal relationship of the onset of the AE, relative to the experimental treatment is possibly reasonable, follows a known response pattern to the treatment to suggest a causal relationship

- Related: temporal relationship of the onset of the AE, relative to the experimental treatment is reasonable, follows a known response pattern to the treatment, and an alternative cause is unlikely.

9.2 Adverse Events Severity

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.

- Moderate: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.

- Severe: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary.

9.3 Serious Adverse Events

If a subject experiences a serious adverse event after the first study product administration the event will be recorded as a serious adverse event in the source document and eCRF.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require

intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious*.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.3.1 SAE Reporting

BioPharmX will be in charge of the overall pharmacovigilance process for the present study. All SAEs, related or not, occurring during the course of the study must be reported to BioPharmX on an SAE form within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria).

Reporting should be done by sending the completed SAE Report Form to the following email address:

Safety Contact Information: AnnaMarie Daniels (Medical Monitor)
E-mail: amdaniels@biopharmx.com
Telephone: 310-701-2080

The Medical Monitor will evaluate all SAEs as soon as the reports are received and will assess the expectedness of each SAE to the study treatment. For each SAE received, the Medical Monitor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met. The sponsor will manage the expedited reporting of relevant safety information to concerned regulatory agencies in accordance with local laws and regulations.

9.4 Pregnancy Reporting

If a female subject becomes pregnant during the study, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female subject will be discontinued from the study. The investigator must complete a study-specific Pregnancy Form upon confirmation of a pregnancy and send it to BioPharmX within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). Post-treatment follow-up should be done to ensure subject safety. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a liveborn offspring, to 1 month of age of that infant and notify BioPharmX of the outcome as a follow-up to the initial Pregnancy Form. All pregnancies should be reported to the sponsor and ethics committee.

10 SAMPLE SIZE AND STATISTICAL METHODS

10.1 Determination of Sample Size

This small sample size is expected to provide only directional information and no statistical significance is expected for any outcome measure.

10.2 Statistical and Analytical Plans

Descriptive summaries of demographics, baseline characteristics and subject disposition will be presented. Outcomes data for each subject and each treatment group will be presented in tabular form.

10.2.1 Analysis Populations

Efficacy will be evaluated on the basis of the intent-to-treat (ITT) population. A supportive analysis will also be conducted on the per-protocol (PP) population.

All subjects who received at least one dose of the medication will be included in the ITT population. All subjects will be analyzed according to the treatment group to which they were assigned.

The per-protocol (PP) population will include all subjects who were treated with no significant protocol deviations and who provided evaluable data for the primary endpoint (absolute change from baseline in inflammatory lesions count at Week 12).

The safety population (SAF) will be defined as all subjects who received at least one dose of the medication. Analysis will be performed according to the actual treatment they received.

10.2.2 Subject Disposition

Descriptive summaries of demographic, baseline characteristics and subject disposition will be presented. The protocol deviations will be summarized by treatment and category.

10.2.3 Efficacy Analysis

10.2.3.1 Primary Analysis

Absolute change from baseline at Week 12 in inflammatory lesion count for each subject will be presented in tabular form. The mean change for each group will be compared but any conclusions are expected to be directional in nature only and not statistically significant.

10.2.3.2 Secondary and Exploratory Analyses

The secondary and exploratory efficacy endpoints will be presented in tabular form and examined for trends.

10.2.3.3 Safety Analysis

All safety data, including AEs and SAEs will be presented and tabulated according to type and body system classification. Descriptions of AEs will include the date of onset, the date the AE ended (if it resolved), the severity and seriousness of the AE, the causality of the AE to study drug, and the outcome. The focus in this protocol will be the incidence of treatment emergent adverse events (TEAEs).

Reported AEs will be summarized by the number of subjects reporting the events, as well as by System Class, severity, seriousness, and relationship to study medication. For the summary of AEs by severity, each subject will be counted only once within a System Class or type by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study medication, each subject will be counted only once within a System Class or a type by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study medication and severity, each subject will be counted only once within a System Class or a type by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim, System Class, type, start date, stop date, intensity, outcome and relationship to study drug. The AE onset will also be shown relative (in number of days) to the day of test article administration. Serious adverse events (SAEs) will be tabulated by treatment group, relationship to the test article, and a reference to the occurrence of the SAEs to the relative day of dosing.

Incidence of minocycline-induced skin hyperpigmentation, visual disturbances/headaches suggestive of pseudotumor cerebri, and product related staining will be summarized and presented descriptively by treatment group.

Concomitant medications will be listed by subject.

In addition, a list of subjects who discontinued from the study will be provided.

Shift tables describing shifts to clinically significant out of normal range will be provided for clinical laboratory results and normal-abnormal shift tables will be provided for vital signs.

Local cutaneous tolerability scores will be tabulated by treatment and visit using descriptive statistics.

10.2.4 Interim Analysis

No formal interim analysis is planned for this study.

11 DATA QUALITY ASSURANCE/SITE MONITORNG

During the study, BioPharmX or representatives will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the CRFs, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities.

The site may be audited and/or monitored by a quality assurance officer named by the sponsor and/or regulatory authorities may wish to perform on-site audits. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit, and provide assistance and documentation (including source data) as requested.

12 DATA COLLECTION AND RETENTION

Subject data will be entered by site personnel using paper CRFs.

The investigator must maintain source documents for each subject in the study to support any information or evaluations that are not performed solely for the study and are not recorded directly into the study CRFs.

13 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that the subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents, including photographs, submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrolment log relating codes with the names of subjects. The investigator should maintain documents not for submission to BioPharmX (e.g., subjects' written consent forms) in strict confidence.

14 INVESTIGATOR'S FILES AND RETENTION OF DOCUMENTS

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: investigator study file and subject clinical source documents.

The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Trial Agreement (CTA), whichever is longer.

15 ETHICS

15.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2008) and that are consistent with "Good Clinical Practice" ICH Tripartite Guideline (July 2002) and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

15.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by a research ethics board/ institutional review board (REB/IRB). This board must operate in accordance with the current federal regulations. For sites with local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

15.3 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

If new safety information results in significant changes in the risk/benefit assessment or any new information that may affect willingness to continue to participate, the consent form should if necessary be reviewed and updated by the (REB/IRB). All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and asked to give their consent to continue in the study.

16 PUBLICATION POLICY

The publication policy will be addressed in the Research and Financial agreement, and all details outlined in the agreement will apply to this protocol.

17 REFERENCES

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4. Weiss JS. Acne: evolving concepts of pathogenesis need to guide therapeutic developments. J Drugs Dermatol. 2013; 12: s66.
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