CLINICAL STUDY PROTOCOL

Study Title:	**A Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of BTX 1503 in Patients with Moderate to Severe Acne Vulgaris**
Protocol Number:	BTX.2018.001
Version:	2.4
Phase:	2
Sponsor:	Botanix Pharmaceuticals Ltd 68 Aberdeen Street Northbridge WA 6003 Australia
Final Approval Date:	07-June-2018

NCT03573518

PROTOCOL SIGNATURE PAGE – SPONSOR

Study Title: **A Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of BTX 1503 in Patients with Moderate to Severe Acne Vulgaris**

Protocol Number: BTX.2018.001

Version: 2.4

Signature:

The undersigned acknowledges that he/she has received and read Protocol BTX.2018.001, Version 2.4, dated 07-June-2018.

Sponsor Representative	Signature	Date
VP, Clinical and Regulatory Affairs		07 June 2018

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

Study Title: **A Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of BTX 1503 in Patients with Moderate to Severe Acne Vulgaris**

Protocol Number: BTX.2018.001

Version: 2.4

Signature:

The undersigned acknowledges that he/she has received and read Protocol BTX.2018.001, Version 2.4, dated 07-June-2018.

Principal Investigator	Signature	Date

By signing this protocol, the investigator has agreed to conduct this study in accordance with the requirements of this clinical protocol and in accordance with established principles of current Good Clinical Practice (GCP), Title 21 of the Code of Federal Regulations sections 50, 56, and 312 as applicable, and the ethical principles that have their origin in the Declaration of Helsinki.

DOCUMENT REVISION HISTORY		
	Date	Summary of changes
Version 1.0	12-FEB-2018	Original document
Version 2.0	18-April-2018	• Protocol was modified from a 28-day to 84-day treatment. All sections wherein the length of treatment was specified have been updated. Note: No changes were made to the definitions for the IGA assessment or the cutaneous tolerability assessments. • A 2.5% daily dosing arm was added and randomization has been updated to 2:2:2:1:1 with 90 subjects in each active group and 45 subjects in each vehicle group for a total sample size of 360 subjects. • Pediatric and adolescents were added for new age range of 9 – 40 years with appropriate language for consent/assent requirements updated. • The primary and secondary endpoints have been changed from Day 28 to Day 84. • Exploratory endpoints of IGA and lesions counts on Day 14, Day 28, and Day 56 have been added. • Handling of missing data has been changed to use of last observation carried forward (LOCF) as the primary method with mixed model as sensitivity analysis. • Background and potential risks/benefits sections updated with data on 90-day minipig study, 28-day oral rat study, and 28-day clinical study in subjects with acne vulgaris. • Update of eligibility criteria: o Inclusion #9 and #10 clarification on concomitant use of moisturizers, sunscreens and makeup on the face, o Inclusion criterion #11, #13, and #14 to extend the use of contraception to 30 days after final study drug application, o Exclusion #6 clarification to exclude medications known to induce or exacerbate acne, o Exclusion #13 for use of testosterone, and o Exclusion #30 to clarify exclusion for drug screen findings.

		• Section 6.1 and Section 10.1.6 changed for distribution of study drug from Pharmaceuticals Packaging Professionals (PPP) in Melbourne, Australia to The Coghlan Group (TCG) in Bastrop, Texas, USA. • Section 6.1.2 updated for new mode of delivery or study drug including weighing of study drug for compliance. • Section 7.1 added definition of comedones, papules, and pustules. • Section 7.3 moved IGA assessment prior to lesion counts. Section 7.4 and 7.5 added clarification on concomitant use of moisturizers, sunscreens and makeup on the face.
Version 2.1	10-May-2018	• Section 5.1 Inclusion #14 updated criteria that subjects shall refrain from sperm donation from 60 days to 90 days after the trial. • Section 6.1.1 added TCG will provide study drug to the US sites and Pharmaceutical Packaging Professionals (PPP) will provide to the Australian sites. • Section 6.1.2 update to volume of study drug in each pump. 30mL changed to approximately 39mL for BID dosing and 20mL to approximately 21mL for QD dosing. Each kit will contain 4 pumps instead of 5. • Section 6.1.2 Label: update to study label to include investigational use only and Keep Out of Reach of Small Children. • Section 6.1.2 update to include bottle number on label and removal of back-up pump being dispensed as part of a kit. • Section 6.1.2 update from 50 mL bottle to 60mL bottle. • Section 6.1.2 Label – changed batch number to bottle number. • Section 6.1.3 removal of retest date included on the carton label. • Section 7.2.1 removal of culture from urinalysis. • Section 7.3.2 included weigh and dispense study drug. • Section 9.6.1 change of week number to bottle number on study label and update to fills on study drug pumps for each group, 30mL changed to approximately 39mL for BID dosing and 20mL to approximately 21mL for QD dosing. • 9.4.3 updated that total lesion counts will be presented as total and not just separate inflammatory and non-inflammatory, as

		well as IGA scores and the frequency and percent distribution of the dichotomized IGA.
Version 2.2 AUS	22-May-2018	Version 2.2 AUS is reserved for the protocol that is being conducted in Australia and tailored for local IRB requirements.
Version 2.3	27-May-2018	• Section 5.1, #14 increased sperm donation restriction from 60 days to 90 days after final study drug administration. • Section 5.1, #11 increased birth control requirements for males from 30 days to 90 days. • Section 6.1.2 Label: removed "Small" to state Keep Out of Reach of Children.
Version 2.4	07-June-2018	• Removal of children 9-11 years of age from population being studied.

1. PROTOCOL SUMMARY

Title:	A Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of BTX 1503 in Patients with Moderate to Severe Acne Vulgaris
Study Phase:	2
Dose and Treatment Duration:	There will be five dose groups. All subjects will apply study drug for 84 days. • BTX 1503 5% twice daily (BID), • BTX 1503 5% once daily (QD), • BTX 1503 2.5% once daily (QD), • Vehicle BID, or • Vehicle QD.
Study Duration:	The study will be a total of up to 17 weeks in duration; screening period up to 35 days (5 weeks) and 84 days (12 weeks) of treatment.
Investigational Product:	BTX 1503 5.0% (w/w) liquid formulation, or BTX 1503 2.5% (w/w) liquid formulation
Concurrent Control:	Vehicle without active ingredient
Administration Route and Form:	BTX 1503 or Vehicle will be applied topically to the entire face.
Objective:	The objective of this study is to assess safety and efficacy of various doses of BTX 1503 in subjects with moderate to severe acne vulgaris of the face.
Study Design:	This will be a multi-center, randomized, double-blinded, vehicle-controlled, parallel group, dose-finding study in pediatrics, adolescents and adults (aged 12 to 40 years).

Outcome Measurements:	The efficacy outcome measures are: <u>Primary endpoint:</u> The primary efficacy endpoint for the study is: • Absolute change from Baseline in inflammatory lesion counts at Day 84. <u>Secondary endpoints</u>: The secondary endpoints for the study are: • Absolute change from Baseline in non-inflammatory lesion counts at Day 84, • The percent change from Baseline in the inflammatory lesion counts at Day 84, • The percent change from Baseline in the non-inflammatory lesion counts at Day 84, • The proportion of subjects with at least a 2-grade reduction from the Baseline IGA score at Day 84, • The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 84, and • The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 84 and at least a 2-grade reduction from the Baseline IGA score. <u>Exploratory endpoints</u>: The exploratory endpoints are: • The change from Baseline in the total lesion count at Day 84, • The percent change from Baseline in the total lesion count at Day 84, • The change from Baseline in the IGA scores at Day 84, • The absolute and percent change from Baseline in inflammatory, non-inflammatory and total lesion counts at Day 14, Day 28 and Day 56, • The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 14, Day 28 and Day 56,

	• The proportion of subjects with at least a 2-grade reduction from the Baseline IGA score at Day 14, Day 28 and Day 56, and • The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 14, Day 28 and Day 56 and at least a 2-grade reduction from the Baseline IGA score. • The change from Baseline in the Acne-QoL at Day 84, and • Subject's assessment of the change in their acne from Baseline to Day 84 (Patient Reported Outcome [PRO]). The safety outcome measures to be assessed are: • Adverse events (AEs) reported from time of consent/assent through the end of the study. • Complete blood count (CBC), chemistry, and urinalysis conducted at Baseline and at Day 84. Cutaneous tolerability (erythema, scaling, dryness, pruritus, and burning/stinging) will be assessed at the Baseline, Day 14, Day 28, Day 56 and Day 84 Visits. Cutaneous tolerability will be graded using the following scale: 0, None; 1, Slight; 2, Moderate; 3, Severe. Pregnancy testing will be conducted for women of child-bearing potential (WOCBP) at the Screening Visit, the Baseline Visit (if > 7 days from Screening Visit) and at the Day 28, Day 56 and Day 84 Visits.
Total Sample Size:	Subjects will be randomized 2:2:2:1:1 (BTX 1503 5% BID:BTX 1503 5% QD:BTX 1503 2.5% QD:Vehicle BID:Vehicle QD) with 90 subjects in each BTX 1503 group and 45 subjects in each vehicle group for a total of 360 subjects.
Methods:	Subjects will begin screening to determine eligibility to participate in the study. At the Screening Visit, informed consent/assent, medical history/review of systems, demographics, height and weight, tobacco/alcohol history, concomitant medications, and a urine pregnancy test (UPT) for WOCBP will be obtained. A urine drug screen (UDS) will be performed. In addition, lesion counts on the face (inflammatory and non-inflammatory lesions counted separately) and an IGA will be conducted to assess subject eligibility. Subjects will be 12 to 40 years of age with moderate to severe acne vulgaris of the face

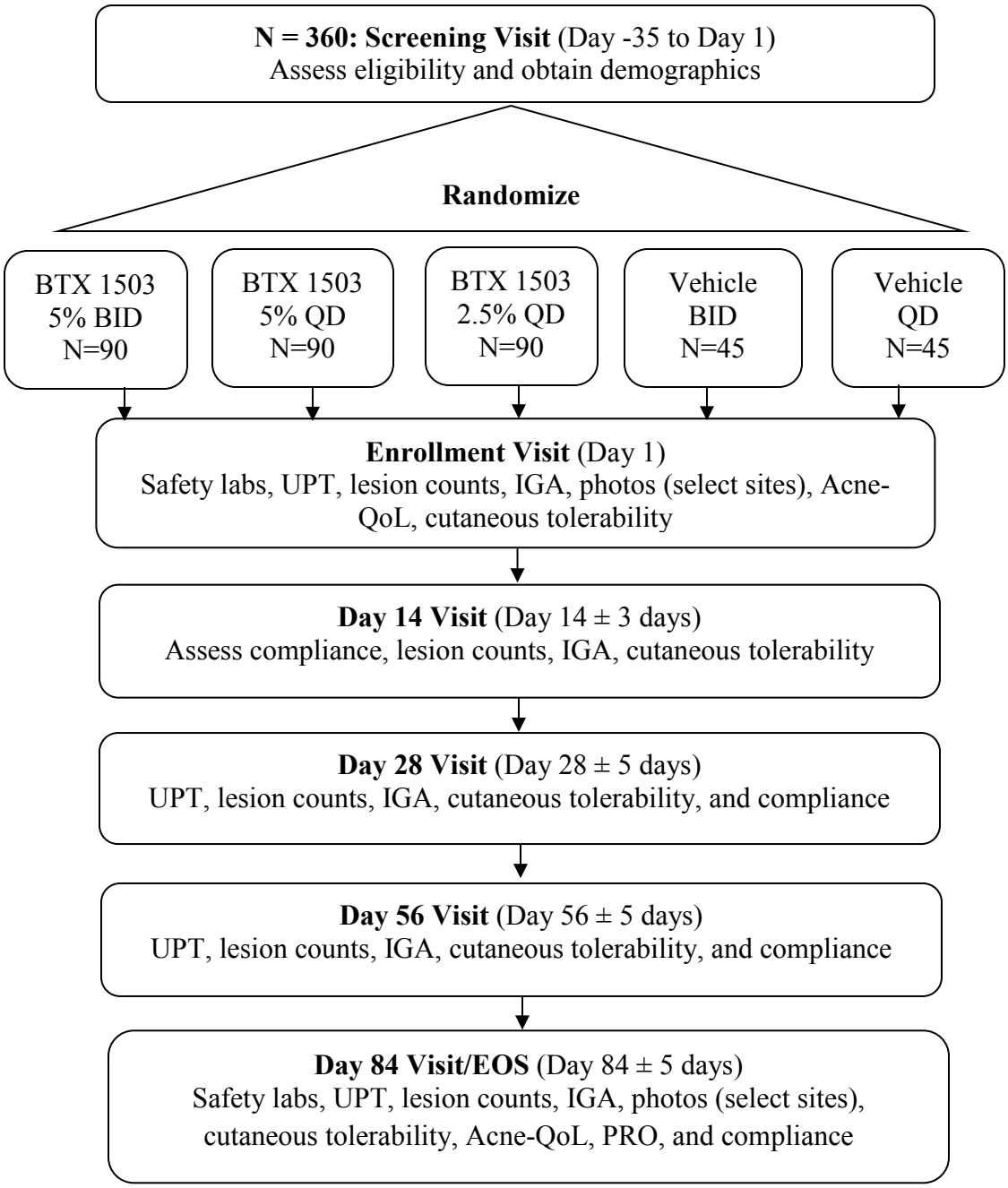
	(20 to 50 inflammatory lesions, 20 to 100 non-inflammatory lesions, and an IGA score of 3 or 4). If a subject is deemed eligible, they may be enrolled and begin Baseline assessments (within 35 days after the Screening Visit). Assessments for safety (CBC, chemistry, and urinalysis) will be obtained at the Baseline Visit (Day 1). If the Screening and Baseline Visits are not conducted on the same day, lesion counts, IGA, UDS, and a review of concomitant medications will be repeated. A UPT for WOCBP will be repeated if greater than 7 days from the Screening Visit. Baseline photographs of the face (selected sites) will be obtained. The Acne-QoL will be administered. Clinical site staff will apply the first dose of study drug. Cutaneous tolerability assessments will be conducted prior to and approximately 15 minutes after the first application. Subjects will be given a diary and sufficient study drug to last until their Day 28 Visit and instructed in the proper application to cover their entire face. Subjects will return to the clinic on Day 14 for a review of their diary to ensure compliance with study drug applications. Lesion counts, IGA and cutaneous tolerability assessments will be conducted. In addition, the subject will apply study drug during the visit for the clinical site to confirm correct application techniques. AEs and concomitant medications will be reviewed. Subjects will return to the clinic on Day 28 and Day 56 for cutaneous tolerability assessments, UPT, lesion counts and IGA. Subjects will also be queried for AEs and changes in concomitant medications. Diaries and study drug will be returned and reviewed for compliance. In addition, the subject will apply study drug during the visit for the clinical site to confirm correct application techniques. Study drug will be dispensed along with the diary for the next 28 days of study drug treatment. Subjects will return to the clinic for their final visit on Day 84 for safety, tolerability and efficacy assessments, including lesion counts and IGA scoring of facial acne. Safety labs (CBC, chemistry, and urinalysis) and a UPT for WOCBP will be obtained. Photographs of the face will be obtained at selected sites. Cutaneous tolerability assessments will be conducted, and concomitant medications and AEs will be reviewed. The Acne-QoL and a patient reported outcome (PRO) will be administered at Day 84, assessing the subject's perception of the change

	in their acne relative to Baseline. See Table 3 for full Schedule of Assessments.
Statistical Methods	***Analysis Sets:*** This study will be evaluated using 3 analysis sets: intent-to-treat (ITT), per protocol (PP), and safety. Efficacy conclusions will be drawn from the ITT analysis set. The PP analysis set will be used to support the efficacy findings in the ITT analyses. Safety conclusions will be drawn from the safety analysis set. Demographics will be summarized using the safety analysis dataset by age, gender, race, ethnicity, height and weight. The primary efficacy analysis will be conducted on the ITT population using last observation carried forward (LOCF) for missing data. For continuous variables, the mean, standard deviation (SD), median, and range will be presented along with the 95% confidence interval (CI). Categorical variables will be summarized by proportions along with the 95% CI. Vehicle QD and Vehicle BID groups may be combined for analyses. ***Handling of Missing Data:*** The primary method of handling missing efficacy data in the ITT analysis set will be based on LOCF. Other imputation methods (e.g., mixed model for repeated measurement [MMRM]) may be used as a sensitivity analysis. All safety analyses will be conducted using the safety analysis set. No imputations will be made for missing safety data. ***Efficacy Analyses:*** The efficacy analyses will be performed using the ITT (primary) and PP (supportive) analysis sets. The efficacy variables include the IGA and lesion counts (inflammatory and non-inflammatory) collected at Screening/Baseline and all subsequent study visits. The primary efficacy endpoint is the absolute change in inflammatory lesion count at Day 84. Absolute and percent changes in lesion counts from Baseline will be calculated for each subject at Day 14, Day 28, Day 56 and Day 84. The IGA will be dichotomized into “success” and “failure” at study Day 14, Day 28, Day 56, and Day 84 with a subject considered a “success” at each individual visit if the IGA at that visit is Clear (“0”) or Almost

	Clear ("1") and at least 2 grades less than the Baseline score. Exploratory efficacy assessments also include the Acne-QoL which will be scored according to the author's scoring system (Martin 2001), and the subject's assessment of improvement (PRO) using proportions by category. Descriptive statistics (including mean, median, standard deviation [SD], minimum, and maximum, unless otherwise stated) will be presented for the following parameters by study group using both the ITT and PP analysis sets: • Inflammatory, non-inflammatory, and total lesion counts at Baseline, Day 14, Day 28, Day 56, and Day 84, • Absolute and percent change from Baseline in inflammatory, non-inflammatory, and total lesion counts at study Day 14, Day 28, Day 56, and Day 84, • IGA scores and frequency and percent distribution of the dichotomized IGA at study Day 14, Day 28, Day 56, and Day 84. This Phase 2 study is designed to identify the response to two different dosing frequencies and two concentrations of BTX 1503. Statistical tests applied to the outcomes will be exploratory. No adjustments for Type 1 error will occur. The change from Baseline in lesion counts (inflammatory and non-inflammatory; separate and combined, and total) at Days 14, 28, 56, and 84 will be analyzed using ANCOVA with Baseline lesion count and treatment as covariates. Success on IGA defined as a score of clear or almost clear and/or at least a 2-grade improvement from Baseline at Day 14, Day 28, Day 56, and Day 84 will be analyzed using logistic regression, adjusting for Baseline IGA. ***Safety Analyses***: All subjects who receive at least one confirmed dose of study drug and have at least one post-Baseline assessment will be included in the safety analyses. Safety analyses will include summaries of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and changes in laboratory assessments. TEAEs and SAEs will be summarized by treatment group, the number of subjects reporting events, system organ class, preferred term, severity, relationship to study drug, and

	seriousness. A list of subjects who prematurely discontinue from the study due to an AE and the reason for discontinuation will be provided. The number and percentage of subjects reporting each medication will be summarized. Medications taken by each subject will be listed. ***Cutaneous Tolerability:*** Cutaneous tolerability (erythema, scaling, dryness, pruritus, and burning/stinging) will be summarized by treatment group at the Baseline, Day 14, Day 28, Day 56, and Day 84 Visits. Cutaneous tolerability will be graded using the following scale: 0, None; 1, Slight; 2, Moderate; 3, Severe. **Sample Size:** The sample size for this study is based on clinical considerations only. Subjects will be randomized 2:2:2:1:1 with 90 subjects in each active treatment group and 45 in each vehicle group for a total 360 subjects. This is considered adequate to evaluate the safety and tolerability of BTX 1503 in the treatment of acne vulgaris.

1.1. SCHEMATIC OF STUDY DESIGN



AEs and concomitant medications collected at each visit.

TABLE OF CONTENTS

2. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Background Information

Botanix Pharmaceuticals' BTX 1503 containing the active pharmaceutical ingredient, cannabidiol (CBD; *2-[(1R,6R)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol*) in a topical liquid formulation, is being developed for the treatment of acne vulgaris. CBD is a member of a broader family of compounds known as cannabinoids, a class of compounds originally derived from the *cannabis sativa* plant.[1] CBD is chemically synthesized under Good Manufacture Practices (GMP) for use in this study.

Synthetic CBD is not psychoactive and clinical trials have demonstrated that CBD may successfully treat epilepsy, arthritis, pain, and even Fragile X Syndrome.[2] Interest in CBD-based therapeutics has increased significantly in recent years, as published data has highlighted the potential efficacy and safety benefits of this compound.[3] There are now more than 100 human clinical trials that have been completed, are underway, or pending recruitment around the world that are studying CBD in a range of diseases.[4]

No known well-controlled, human clinical studies have ever been conducted using CBD to treat skin disease, and no CBD containing pharmaceuticals have been approved to treat skin disease. Researchers have found that CBD may play a beneficial role in regulating the cutaneous endocannabinoid system by decreasing unwanted skin cell growth, sebum production and skin inflammation associated with many human skin diseases.[1]

2.2. Rationale

2.2.1. Mechanism of Action

This study is intended to establish preliminary safety and tolerability in subjects with acne vulgaris treated with BTX 1503. The rationale for the use of BTX 1503 in acne is provided herein.

Acne is the most common skin disease in the world and is characterized by partial obstruction of the pores and associated local skin lesions that can appear on the face, chest or back.[5,6] Obstructed pores can become enlarged and inflamed as sebum and its breakdown products accumulate, resulting in visible lesions that can be unsightly and cause permanent scarring.[5,6] Acne usually begins in puberty and affects many adolescents and young adults, but it can occur at any stage of life. Approximately 85 percent of people between the ages of 12 and 24 experience at least minor acne.[7] Acne often causes significant physical and psychological problems such as permanent scarring, poor self-image, depression and anxiety.[8]

Acne lesions are believed to result from an interaction of four primary pathogenic factors:

- the excessive production of sebum or lipids by sebaceous glands in the skin;
- hyper-proliferation of keratinocytes that contribute to clogging of pores through which sebum is normally released to the skin surface;

- colonization of the area in and around the sebaceous gland by bacteria; and
- inflammation, often associated with colonization by bacteria and their breakdown of sebum into irritating breakdown products.[1]

For many years, treatment of acne has been dominated by the same four prescription pharmaceutical product classes:

i. Antimicrobials. Antimicrobials for acne treatment target bacterial colonization and inflammation and are widely used topically and, in more severe disease, orally.[8] While antimicrobials have been shown to be effective, there is a growing interest in limiting the use of antibiotics in acne, because of concerns regarding bacterial resistance.[9,10,6]

ii. Retinoids. Topical retinoids address some of the changes in skin cells that contribute to clogging of the pores and are among the most commonly used prescription acne medications. Their limitations include skin irritation, photosensitization, and relatively modest efficacy in comparison with systemic therapies.[10]

iii. Isotretinoin. Oral isotretinoin (marketed initially as Accutane or Roaccutane) operates to significantly reduce sebum production and is indicated for the treatment of severe recalcitrant nodular acne. Even in the case of very severe disease, the efficacy of oral isotretinoin can be significant, with large proportions of patients achieving partial or complete clearance, after one course of therapy.[8,11] However, oral isotretinoin is associated with significant systemic toxicity, including liver damage and severe birth defects, which largely limit its use as second line treatment in patients with severe disease who enroll in a monitoring program intended to restrict distribution of the drug. Mood disorders, depression, suicidal ideation and suicides have been reported in patients taking oral isotretinoin, but a causal relationship has not been established.[8,12,13,14,15]

iv. Hormonal therapies. Oral agents that reduce the activity of sex hormones (called androgens) are also highly effective, as these treatments also reduce sebum production.[16] Hormonal therapies have well-known systemic side effects, such as mood disturbance, loss of muscle mass and reduced sexual desire, that are related to their effects on sex hormones (they are most often used in the form of contraceptives). As such, they are not widely used in men or in women not seeking contraception.[17]

No topical treatments are currently available which target all the above pathogenic factors.[18] Acne treatment guidelines recommend that acne treatment be directed toward as many of the four primary pathogenic factors as possible.[19] Accordingly, patients are often treated with combination regimens that incorporate multiple agents with complementary mechanisms of action targeting different pathogenic factors.[20] While systemic therapies (such as isotretinoin) may inhibit sebum production, their use is limited by significant systemic side effects. An unmet need remains for effective therapies that are not associated with antibiotic resistance or treatment-limiting side effects, particularly therapies with novel mechanisms of action.[9]

BTX 1503 is focused on modulating the body's endocannabinoid system of receptors which regulate skin function, growth and renewal.[21] It is understood that CBD may play a significant role in normalizing unwanted skin growth, reducing excessive production of oils and reducing inflammation and infection, amongst other functions.[1] Botanix Pharmaceuticals is exploring whether endocannabinoid modulating drugs (such as synthetic CBD) can be exploited in the management of acne.

BTX 1503 is a formulation of active synthetic CBD and inactive excipients designed to deliver a consistent dose of CBD to directly treat patients with acne. It is considered that CBD may:

- normalize excessive lipid synthesis of human sebocytes
- decrease proliferation (but not the viability) of these human sebocytes;
- inhibit hyperproliferation of keratinocytes;
- exert anti-inflammatory actions; and
- have anti-bacterial effects.[1,22]

2.2.2. Nonclinical and Clinical Data

Nonclinical information on the safety pharmacology, pharmacokinetics and metabolism, and toxicology profiles of CBD has been extensively reported in the scientific literature. The clinical safety of CBD has also been established and reviewed in the published scientific literature. Clinical investigations with CBD have been reported in both normal subjects and patients, including treatment of individuals with oral doses of up to 300 mg/day (5 mg/kg/day or 185 mg/m^2/day, for an individual with an average body weight of 60 kg). Higher oral doses of up to 1,500 mg/day (25 mg/kg/day or 925 mg/m^2/day) have been reported to be well tolerated. CBD formulated as a topical gel (Zynerba Pharmaceuticals) for treatment of epilepsy has also been shown to be safe and well-tolerated with only mild, transient application site AEs observed.

Botanix Pharmaceuticals has conducted a Phase 1a single and multiple-ascending dose study (BTX 2017.001) of BTX 1503 in normal healthy volunteers in Australia involving 20 subjects. This study demonstrated that daily topical treatment with up to 3.75 mg/kg/day (225 mg CBD/day or 0.398 mg/cm^2/day[1]) applied as 3 mL of BTX 1503 5% (w/w) BID for 14 days was safe and well-tolerated. Forty-two (42) AEs were reported in 18 of the 20 participants. All AEs were reported as mild except one moderate vasovagal reaction to cannula insertion for blood draws (unrelated). Facial dryness and itchiness were the most frequently reported related AEs. One subject reported application site stinging, and one subject reported stinging in the eyes after accidental transfer of BTX 1503 into the eyes.

In a subsequent Australian Phase1b open-label study (BTX.2017.002) of BTX 1503 in subjects with moderate to severe acne involving 21 subjects, daily topical treatment with up to 3.75

[1] Area of application assumed to be 565 cm^2 (*i.e.*, on the face), which is reported by the European Union Scientific Committee on Consumer Safety (SCCS) to be half of the surface area for a female head (SCCS Notes of Guidance for the Testing of Cosmetic Substances and Their Safety Evaluation, 8th edition, 2012; Table 2). Available at: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf.

mg/kg/day (225 mg CBD/day or 0.398 mg/cm^2/day) applied as 3 mL of BTX 1503 5% (w/w) BID for 28 days was shown to be safe and well-tolerated. There was only 1 AE associated with the study drug treatment; application site pain (sore eyes). Slight to moderate erythema was reported most frequently in cutaneous tolerability assessments. However, most subjects that reported erythema pre or post-study drug application had erythema at Baseline and treatment with BTX 1503 did not exacerbate the erythema. Only 1 subject had increased erythema from Baseline and this was reported at Day 35, seven days after their final application of study drug. Slight scaling was reported in 2 subjects (9.5%), slight dryness was reported in 4 subjects (19.0%) and slight burning/stinging was reported in 5 subjects (23.4%). Only 1 positive cutaneous tolerability assessment (slight dryness) was reported at more than a single visit.

In support of this planned Phase 2 clinical study, dermal toxicology studies of 90 days in duration in minipigs with BTX 1503 have not revealed any clinically significant toxicities or laboratory abnormalities. Details on the results of these studies are provided in the Investigator's Brochure.

The published literature has suggested that CBD may be an inhibitor of human cytochrome P450 CYP1A1 at concentrations that are 9.7-fold of observed maximum plasma concentrations (C_{max}) in clinical studies with BTX 1503.

The testes was the only target organ for toxicity identified in published studies in rats and monkeys: effects on sperm maturation were observed in a 25-day inhalation study in male rats [no-observed-adverse-effect level (NOAEL) of less than 0.6 mg CBD/kg/day (< 3.6 mg/m^2/day) and lower testis weights and inhibition of spermatogenesis were observed at a daily oral dose of 300 mg/kg CBD/kg/day (3,600 mg/m^2/day) in male monkeys. However, there were no changes in testis weight nor microscopic findings in the testes following 28 days of oral dosing in male rats at doses up to 400 mg/kg/day with the CBD to be used in the BTX 1503 formulations. The Area Under the Concentration (AUC) exposures are over 1000-fold higher than reported in clinical studies involving BID dosing with BTX 1503. In addition, there were no changes in testis weight nor microscopic correlates in the testes following 90 days of dermal dosing in minipigs using BTX 1503 at doses up to 150 mg/kg/day (AUC exposures in males at least 24-fold higher then observed in clinical studies with BTX 1503).

2.3. Rationale for Study

This study is designed to investigate the efficacy, safety and tolerability of BTX 1503 in subjects with moderate to severe acne. In this study, BTX 1503 will be applied at 3 different dosage regimens and compared against a Vehicle control. The treatment period will be 12 weeks to coincide with the FDA's recommended minimum treatment duration to demonstrate efficacy.

2.4. Potential Risks and Benefits

2.4.1. Known Potential Risks

Based on studies conducted by Botanix Pharmaceuticals, the potential risks associated with BTX 1503 include:

- Ocular irritation
- Local application site AE's
- Cutaneous reactions which may include erythema, dryness, scaling, and burning/stinging.

Facial dryness and facial itchiness were reported as possible effects of study drug treatment in Botanix Pharmaceuticals' healthy volunteer study (BTX.2017.001). In the current study, subjects will be allowed to use their usual moisturizers. Subjects in this study will be given instructions on what to do if BTX 1503 liquid accidentally gets into the eyes.

In the BTX.2017.002 study, slight to moderate erythema was reported most frequently in cutaneous tolerability assessments. However, most subjects that reported erythema pre-or post-study drug application had erythema at Baseline and treatment with BTX 1503 did not exacerbate the erythema. Only 1 subject had increased erythema from Baseline and this was reported at Day 35, seven days after their final application of study drug. Slight scaling was reported in 2 subjects (9.5%), slight dryness was reported in 4 subjects (19.0%) and slight burning/stinging was reported in 5 subjects (23.4%). Only one positive cutaneous tolerability assessment (slight dryness) was reported at more than a single visit.

In the published scientific literature, the only target organ for toxicity that has been identified was the testes in rat and monkey studies. It is uncertain if the reduction in spermatogenesis noted in these animal studies has a clinical correlate. In addition, this finding was not observed in the 28-day oral rat study or in a 90-day dermal minipig study conducted with Botanix Pharmaceuticals' BTX 1503.

The other aspect of systemic exposure to CBD reported in the published scientific literature was the potential for competitive binding to CYP450 isozymes, indicating a potential for drug-drug interactions. Given the limited systemic exposure observed in Botanix Pharmaceuticals' healthy volunteer study, the potential for a drug-drug interaction is considered to be minimal.

2.4.2. Known Potential Benefits

Non-clinical data suggests BTX 1503 may target pathways relevant in pathogenesis of acne. Activity of BTX 1503 was observed in the BTX.2017.002 study in subject with moderate to severe acne. Statistically significant improvements from Baseline in inflammatory and non-inflammatory lesion counts were observed. Improvements were also observed in the IGA and in the PRO. Although improvements in acne were observed in this 28-day treatment study, the benefit of BTX 1503 in patients with 12 weeks of treatment is unknown.

3. OBJECTIVE

The objective of this study is to assess safety and efficacy of various doses of BTX 1503 liquid formulation in subjects with moderate to severe acne vulgaris of the face.

4. STUDY DESIGN AND ENDPOINTS

4.1. Description of the Study Design

This is multi-center, randomized, double-blind, vehicle-controlled, parallel group, dose-finding study. Approximately 360 subjects will be enrolled.

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint

The primary endpoint for the study is the absolute change from Baseline in inflammatory lesion counts at Day 84.

4.2.2. Secondary Endpoints

The secondary endpoints for the study are:

- Absolute change from Baseline in non-inflammatory lesion counts at Day 84,
- The percent change from Baseline in the inflammatory lesion counts at Day 84,
- The percent change from Baseline in the non-inflammatory lesion counts at Day 84,
- The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 84,
- The proportion of subjects with at least a 2-grade reduction from the Baseline IGA score at Day 84, and
- The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 84 and at least a 2-grade reduction from the Baseline IGA score.

4.2.3. Exploratory Endpoints

The exploratory endpoints for the study are:

- The change from Baseline in the total lesion count at Day 84,
- The percent change from Baseline in the total lesion count at Day 84,
- The change from baseline in the IGA scores and Day 84,
- The absolute and percent change from Baseline in inflammatory, non-inflammatory and total lesion counts at Day 14, Day 28 and Day 56.
- The proportion of subjects with at least a 2-grade reduction from the Baseline IGA score at Day 14, Day 28 and Day 56,
- The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 14, Day 28 and Day 56,

- The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 14, Day 28 and Day 56 and at least a 2-grade reduction from the Baseline IGA score.
- The change from Baseline in the Acne-QoL at Day 84, and
- Subject's assessment of the change in their acne from Baseline to Day 84 (PRO).

4.2.4. Safety Endpoints

Safety for this study will be assessed by:

- Collection of reported adverse events throughout the study,
- Safety labs conducted at Baseline and Day 84,
- Monitoring of concomitant medications throughout the study,
- All women of childbearing potential (WOCBP) will have a urine pregnancy test (UPT) performed at the Baseline, Day 28, Day 56, and Day 84 Visits.

4.2.5. Cutaneous Tolerability

Cutaneous tolerability will be assessed at Baseline and each subsequent visit using a 4-point tolerability scale (0-3). Erythema, scaling, and dryness will be assessed by the investigator at Baseline and at each visit. Subjects will also be asked to rate symptoms of itching and burning/stinging over the preceding 24 hours at Baseline and subsequent visits using a 4-point (0-3) scale (see Table 1).

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Inclusion Criteria

To be included in the study, subjects with acne vulgaris must meet the following inclusion criteria.

1. Subject (or legal guardian) has the ability and willingness to sign a written informed consent/assent.
2. Subject is of either gender and 12 to 40 years of age.
3. Subject is in good general health without clinically significant haematological, cardiac, respiratory, renal, endocrine, gastrointestinal, psychiatric, hepatic, or malignant disease, as determined by the investigator.
4. Subject has suitable venous access for blood sampling.
5. Subject is able and willing to complete the study and to comply with all study instructions and attend the necessary visits.
6. Subject has acne vulgaris of the face defined as:
    a. 20 to 50 (inclusive) inflammatory lesions on the face
    b. 20 to 100 (inclusive) non-inflammatory lesions on the face
    c. An Investigator's Global Assessment (IGA) score for acne severity of 3 or 4 (moderate or severe) assessed on the face.
7. Subject has ≤ 2 nodular/cystic acne lesions (>5 mm in diameter).
8. Subject must refrain from the use of other treatments for acne during the study.
9. Subject must agree to not wash or shave their face, swim or otherwise get their face wet for at least 1 hour after application of study medication.
10. Subject must agree to maintain their regular use of sunscreens, moisturizers, shaving cream, and facial make up throughout the entire course of the study.
11. Male subjects and their partners must agree and commit to use a barrier method of contraception during the study and for 90 days after last study drug application.
12. A negative UPT result for all WOCBP at the Screening Visit and Baseline Visit, if applicable. A WOCBP is one who is not permanently sterilized or is not postmenopausal. Postmenopausal is defined as 24 months with no menses without an alternative medical cause.

13. Sexually active women must agree to use the following throughout the study and for 30 days after last study drug application:
    a. One of these highly effective contraception methods
        i. Intrauterine device (IUD); hormonal (injections, implants, transdermal patch, vaginal ring; tubal ligation; partner vasectomy, OR
    b. Oral contraceptives WITH a barrier method (listed below), OR
    c. Two barrier forms of contraception (listed below)
        i. Male or female condom; diaphragm; cervical cap.
14. Male subjects must refrain from sperm donation during the study treatment period until 90 days after final study drug administration.
15. Male subjects must agree to keep their face clean shaven (no moustache or goatee; short sideburns acceptable) throughout the study and use the same method for shaving as was used for the 4 weeks prior to the Screening Visit.

5.2. Exclusion Criteria

If a subject meets any of the following exclusion criteria, they may not participate in the study.

1. People who would otherwise qualify for the study but are living in the same household as a study subject, are not allowed to participate in the study.
2. Female subject who is breast feeding, pregnant, or planning to become pregnant any time during the course of the study.
3. Subject with history of known or suspected intolerance to the drug product excipients.
4. Subject has known HIV infection.
5. Subject has acne conglobata, acne fulminans, secondary acne (chloracne), pseudo-folliculitis, severe acne requiring systemic treatment, or is taking a medication known to induce or exacerbate acne.
6. Subject has severe truncal acne.
7. Subject has excessive facial hair that would interfere with the evaluation of safety or with the diagnosis or assessment of acne vulgaris.
8. Subject has sunburns, unevenness in skin tones, tattoos, scars, excessive hair, freckles, birthmarks, moles, or other skin damage or abnormality that would result in the inability to evaluate the skin of the face.
9. Subject has any skin condition of the face other than acne vulgaris.
10. Subject has used oral retinoid (e.g. isotretinoin) within 6 months (180 days) prior to the Baseline Visit.

11. Subject has used Vitamin A supplements greater than 10,000 units/day within 6 months (180 days) prior to the Baseline Visit.
12. Subject has used androgen receptor blockers (such as spironolactone or flutamide) within 3 months (90 days) prior to the Baseline Visit.
13. Subject has initiated treatment with hormonal therapy or changed dosing with hormonal therapy within 3 months (90 days) prior to the Baseline Visit. Note: Dose and frequency of any hormonal therapy started more than 3 months (90 days) prior to the Baseline Visit must remain unchanged throughout the study. Hormonal therapies include, but are not limited to, anabolic steroids and birth control pills. Subjects taking testosterone therapy are excluded from participation.
14. Subject has had facial procedures (chemical or laser peel, microdermabrasion, etc.) within 8 weeks (56 days) prior to the Baseline Visit.
15. Subject has had treatment with systemic antibiotics within 4 weeks (28 days) prior to the Baseline Visit.
16. Subject has had treatment with systemic anti-acne drugs within 4 weeks (28 days) prior to the Baseline Visit.
17. Subject has had treatment with systemic anti-inflammatory drugs within 4 weeks (28 days) prior to the Baseline Visit.

    Note: Occasional non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin use on an as-needed basis, and if not used consecutively for >14 days prior to the Baseline Visit, is acceptable and does not require washout. Subjects receiving intranasal and inhaled corticosteroids may participate. Low dose (81mg) aspirin taken daily is acceptable.
18. Subject has had treatment with systemic (oral) corticosteroids other immunosuppressive medications within 4 weeks (28 days) prior to the Baseline Visit.
19. Subject has had treatment with prescription topical retinoid use on the face (e.g. tretinoin, tazarotene) within 4 weeks (28 days) prior to the Baseline Visit.
20. Subject has had treatment with topical prescription antibiotics (e.g. dapsone, clindamycin, erythromycin, or sulfacetamide) or combination products that include a topical antibiotic within 2 weeks (14 days) prior to the Baseline Visit.
21. Subject has had treatment with over-the-counter (OTC) topical medications for the treatment of acne vulgaris including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, adapalene, α-hydroxy/glycolic acid on the face within 2 weeks (14 days) prior to the Baseline Visit.
22. Subject is currently using any medication that, in the opinion of the investigator, may affect the evaluation of the study product or place the subject at undue risk.
23. Subject has had photodynamic therapy within 8 weeks (56 days) prior to the Baseline Visit.

24. Subject has used a tanning bed within 2 weeks (14 days) prior to the Baseline Visit.
25. Subject has used home-based light treatment within 2 weeks (14 days) prior to the Baseline Visit.

NOTE: Use of the treatments listed in Exclusion Criteria 10 through 25 above are not permitted throughout the study.

26. Subject has an underlying disease that requires the use of interfering topical or systemic therapy.
27. Subject has other dermatological conditions that require the use of interfering topical or systemic therapy or that might interfere with study assessments such as, but not limited to, atopic dermatitis, psoriasis, perioral dermatitis, or rosacea.
28. Subject has had excessive sun exposure (in the opinion of the investigator) within one week prior to the Baseline Visit and an unwillingness to refrain from excessive sun exposure during the study.
29. Subject has a clinically relevant history or currently suffering from any disease or condition that, in the opinion of the investigator, may affect the evaluation of the study product or place the subject at undue risk. This may include respiratory (including chronic asthma requiring repetitive drug interventions), gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, or connective tissue diseases or disorders.
30. Subject has a clinically relevant history of, or current evidence of, abuse of alcohol or other drugs. Subjects may be deemed eligible if the UDS identifies subject-reported, prescribed drugs or appropriate levels of alcohol, as determined by the investigator.
31. Subject has participated in another investigational drug or device research study within 4 weeks (28 days) of the Baseline Visit or five half-lives of the drug, whichever is longer.
32. Any other reason that would make the subject, in the opinion of the investigator or sponsor, unsuitable for the study.

5.3. Subject Withdrawal or Termination

5.3.1. Reasons for Withdrawal or Termination

If a subject is withdrawn from the study, the subject's enrollment in the study will terminate and study drug application will be discontinued. Efforts will be made to perform all assessments scheduled for the Day 84 Visit prior to subject withdrawal. The Day 84 Visit should be scheduled for day 84 (±5 days), if possible.

A subject may be withdrawn from further study participation under the following circumstances:

- At the subject's request.

- Noncompliance with protocol by the subject as determined by the study site staff and investigator.
- Adverse Event (decision to be removed from study made by either the investigator or subject). The investigator must notify the sponsor immediately if a subject is withdrawn because of an AE.
- Pregnancy.
- Decision by the investigator or sponsor that termination is in the subject's best medical interest or for an administrative decision for a reason other than that of an AE.
- Lost to follow-up, as determined by failure to respond to at least 2 telephone calls followed by certified letter sent to the subject's last known address. All attempts to contact the subject must be documented in the subject's source documents.
- Sponsor decision to halt the entire study.

5.3.2. Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator. If the study is prematurely terminated or suspended by the sponsor, the PI will promptly inform the Institutional Review Board (IRB) or Ethics Committee (EC) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects,
- Insufficient compliance to protocol requirements,
- Data that are not sufficiently complete and/or evaluable.

The study may resume once concerns about safety, protocol compliance, or data quality are addressed and satisfy the sponsor and IRB/EC.

6. STUDY DRUG

6.1. Study Drug

6.1.1. Acquisition

Study drug will be provided to the US study sites by The Coghlan Group (TCG) in Bastrop, Texas, USA and to the Australian sites by Pharmaceutical Packaging Professionals (PPP) in Port Melbourne, Victoria, Australia. Initial shipments will be made to supply the study sites prior to enrollment of the first subject. Additional supplies will be made available as needed based on subject enrollment.

6.1.2. Formulations, Appearance, Packaging, and Labeling

Botanix Pharmaceuticals' BTX 1503 contains the active pharmaceutical ingredient, cannabidiol (CBD). CBD is a member of a broader family of compounds known as cannabinoids, a class of compounds originally derived from the *cannabis sativa* plant.[1] CBD is chemically synthesized under Good Manufacturing Practices (GMP) for use in this study.

The active study product is a clear to light yellow, slightly viscous liquid with a 2.5% or 5% (w/w) concentration of CBD in a formulation of excipients which have been used extensively in other topical products. The liquid spreads easily and quickly evaporates, leaving the CBD and a small amount of excipients on the skin. The Vehicle liquid is identical in appearance to the BTX 1503 liquid.

Each milliliter of the BTX 1503 5% liquid formulation contains 37.5 mg of CBD. Each milliliter of the BTX 1503 2.5% liquid formulation contains 18.75 mg of CBD. All subjects will apply 2.0 mL, 4 pump actuations, of BTX 1503 BID or QD or Vehicle BID or QD based on their randomized treatment group. Subjects will receive the following daily exposure to CBD.

- Subjects randomized to BTX 1503 5% BID will apply 150.0 mg of CBD daily,
- Subjects randomized to BTX 1503 5% QD will apply 75.0 mg of CBD daily,
- Subjects randomized to BTX 1503 2.5% QD will apply 37.5 mg of CBD daily.

Study drug will be supplied in 60 mL multi-dose, metered pumps delivering 0.5 mL per actuation. Each pump for BID dosing will contain approximately 39 mL of study drug and each pump for QD dosing will contain approximately 21 mL of study drug. This will provide dosing for 7 days for all subjects. Pumps for all groups will be labeled identically, except for kit number and bottle number, to maintain the blind.

Study drug will be pumped into the palm of one hand and applied to the face using fingertips of the other hand. Study drug will be applied to the entire face, regardless of location of acne lesions.

Study drug will be provided in kits. Each kit will contain adequate study drug for 4 weeks of daily applications (28 days). Prior to distribution, pumps will be weighed by clinical site staff and the weights recorded in the source documents and the eCRF. Each kit will contain 4 pumps, one for

each week of dosing. When a subject is enrolled, the site will access the IWRS to receive a kit number for the first 28 days of dosing based on the IWRS randomization. At the Day 28 and Day 56 Visits, the site will access the IWRS to obtain the kit number for the following 28 days of dosing. All distributed pumps will be returned by the subject at the Day 28, Day 56, and Day 84 Visits and weighed to monitor compliance and document doses delivered.

The study drug bottle may include the following information:

Caution: New Drug--Limited by Federal (or United States) law to investigational use only.
KEEP OUT OF REACH OF CHILDREN
Drug Ingredient: BTX 1503 or Vehicle
Directions: Use in accordance with study drug application instructions.
FOR TOPICAL APPLICATION ONLY.
Protocol # BTX.2018.001
Flammable. Store between 15-30^{o}C.
Bottle #
Kit #
Sponsor: Botanix Pharmaceuticals Ltd

6.1.3. Product Storage and Stability

The study drug will be stored at a controlled room temperature of 15°C to 30°C and should not be refrigerated. Prior to dispensing to the subject, the study drug will be stored in a secured location with access only by authorized study personnel. Study drug has been tested to ensure that there is adequate stability for the duration of the study. Retest dates may be included on the carton labeling.

6.1.4. Preparation

No preparation of the study drug is required.

6.1.5. Dosing and Administration

Subjects will receive their initial application of study drug on Day 1 at the clinical sites administered by the clinical site staff. When the subject is ready for study drug application, a pump is selected from the assigned study kit. The clinical site staff will remove the cap and apply the first dose of the study drug to the subject's entire face. All subsequent applications will be completed by the subject. To ensure that the entire face is covered, the study drug should be applied in a consistent manner for each application.

Subjects will be instructed in how to apply study drug. After their first application in the clinic subjects will apply their study drug at home. Each application of study drug will occur at the approximately the same time in the morning with the second application (for BID dosing groups) approximately 8 to 12 hours later. Subjects will apply study drug at the clinical site during the Day 14, Day 28, Day 56 and Day 84 Visits (final dose). A diary will be maintained documenting

compliance with the self-administered applications. All study drug bottles (used and unused) will be returned to the clinical site on the Day 28, Day 56, and Day 84 Visits.

Study drug should not be applied to the eyes or mouth. Subjects are to thoroughly wash their hands after study drug application. The study drug must not be handled by a family member or caregiver for study drug application.

6.1.6. Starting Dose

The dose for all subjects will be 2.0 mL, 4 pump actuations, of study drug applied to the entire face. No escalation of dose will occur.

6.1.7. Dose Adjustments/Modifications/Delays

There are no pre-planned dose adjustments, modifications, or delays.

6.1.8. Duration of Therapy

Subjects will apply study drug for 84 days with a final application on Day 84. Subjects receiving BID dosing will apply 167 doses and subjects receiving QD dosing will apply 84 doses.

6.1.9. Tracking of Dose

All subjects will be required to maintain a diary documenting each application of study drug. The subject will record that they applied each study dose. Subjects will return the study drug bottles (used and unused) at each visit. The clinical site staff will review the diary and count used/unused bottles to ensure subject compliance with dosing.

6.2. Study Drug Accountability Procedures

At each study visit the clinical site will weigh each pump dispensed to the subject and returned from the subject to calculate the amount (grams) of study drug used. The investigator will keep a current and accurate inventory of all clinical supplies received. These records will be reviewed at each monitoring visit performed by the CRA per SOPs.

7. STUDY PROCEDURES AND SCHEDULE

7.1. Study Specific Procedures/Evaluations

At the Screening Visit (Visit 1), all subjects/legal guardians will review and sign an informed consent/assent form attesting to their knowledge of the study requirements, risks, and benefits. The following study specific procedures will occur for all subjects at the Screening Visit:

- Demographics, height, weight, and a medical history, including alcohol and tobacco use, will be obtained,
- A review of systems will be conducted by the principal investigator or designee,
- All WOCBP will have a UPT conducted. The test must be negative for the subject to be enrolled,
- A urine drug screen will be conducted to ensure that the subject is not taking drugs of abuse,
- A count of inflammatory and non-inflammatory lesions on the face and an IGA will be collected,
- The subjects will be queried for concomitant medications that they are currently taking. Concomitant medications include all prescribed and over the counter (OTC) medications and any supplements, and
- Eligibility criteria will be reviewed to determine if subjects may proceed to study enrollment.

If subjects are eligible upon screening, they may be enrolled into the study on the same day.

At various visits throughout the study, the following will occur for all subjects to monitor the safety of the study drug treatment:

- Blood draws will be conducted for CBC and chemistry analysis,
- Collection of urine will occur for a urinalysis,
- Cutaneous tolerability assessments will be conducted by the principal investigator or an appropriately trained designee. Cutaneous tolerability will be graded using the following scale: 0, None; 1, Slight; 2, Moderate; 3, Severe. Evaluation for, and grading of, the following will be done at each evaluation:
    - Erythema (investigator assessed),
    - Scaling (investigator assessed),
    - Dryness (investigator assessed),
    - Pruritus in last 24 hours (subject reported), and
    - Burning/Stinging in last 24 hours (subject reported).

The definition for each level of grading for each tolerability assessment is provided in Table 1.

Table 1. Cutaneous Tolerability Assessments Scale for Acne Vulgaris

Tolerability Assessment	Severity			
	None = 0	Mild = 1	Moderate = 2	Severe = 3
Erythema	No erythema	Slight pinkness present	Definite redness, easily recognized	Intense redness
Scaling	No scaling	Barely perceptible shedding, noticeable only on light scratching or rubbing	Obvious but no profuse shedding	Heavy scale production
Dryness	No dryness	Slight but definite roughness	Moderate roughness	Marked roughness
Pruritus (in last 24 hours)	No itching	Only aware of itching at times; only present when relaxing; not present when focused on other activities	Often aware of itching; annoying; sometimes disturbs sleep and daytime activities	Constant itching; distressing; frequent sleep disturbance; interferes with activities
Burning/Stinging (in last 24 hours)	No Burning/Stinging	Slight warm, tingling/stinging sensation; not really bothersome	Definite warm, tingling/stinging sensation that is somewhat bothersome	Hot, tingling/stinging sensation that has caused definite discomfort

- Subjects will be queried to report any AEs that have occurred since the last visit.
- Subjects will be queried to report any new medications or changes in current medications.

For all subjects, assessment of compliance with study drug application will be conducted through collection of a study diary on which subjects will record their daily administration. Subjects will be required to bring all used and unused study drug to each visit where the study site will assess compliance. At each study visit the clinical site will weigh each pump dispensed to the subject and returned from the subject to calculate the amount (grams) of study drug used.

The following efficacy assessments will be performed at the Screening, Baseline, Day 14, Day 28, Day 56, and Day 84 Visits:

- Counting of inflammatory and non-inflammatory lesions of the face by the principal investigator (PI) or appropriately trained designee. Thorough, documented, training will be provided to the PI and/or designee in the method for identifying and counting lesions.
- Administration of the IGA by the PI or appropriately trained designee. The IGA will be graded based on the scale provided in Table 2.

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

Grade		Description
0	Clear	No evidence of facial acne vulgaris
1	Almost Clear	Few non-inflammatory lesions (comedones) are present; a few non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red) may be present
2	Mild	Several to many non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present; no nodulo-cystic lesions
3	Moderate	Many non-inflammatory (comedones) and inflammatory (papules/pustules) are present; there may or may not be one small nodulo-cystic lesion
4	Severe	Significant degree of inflammatory disease; papules/pustules are a predominant feature; a few nodulo-cystic lesions may be present; many comedones may be present.

- Photographs of the subject's face will be obtained at selected sites at the Baseline Visit and the Day 84 Visit. Details on the methods for photography are provided in the Photography Manual.
- At Baseline and at Day 84, the Acne-QoL will be administered.

- On Day 84, the subject will be asked to complete the Patient Reported Outcome (PRO) to assess the perception of their acne relative to their baseline. The subject will complete the assessment to answer the following question: "Compared to the beginning of treatment, my acne is?" with a response of "Much better", "Slightly better", "The same", "Slightly Worse", or "Much worse".

For purposes of conducting IGA scoring, the following definitions will apply:

- Open comedo - a widely dilated follicle, plugged with sebum and keratin (blackhead)
- Closed comedo - a small, flesh-colored closed follicle, filled with sebum and firm to palpation
- Papule - a small solid, inflamed, elevated lesion less than 5 mm in diameter
- Pustule - a circumscribed, erythematous raised skin lesion containing white exudate or pus, less than 5 mm in diameter
- Nodule - an erythematous, raised, firm, deep-seated papule equal to or greater than 5 mm in diameter

7.2. Laboratory Procedures/Evaluations

7.2.1. Clinical Laboratory Evaluations

For all subjects, a CBC, chemistry, and urinalysis will be conducted at the Baseline and Day 84 Visits. Details are provided in the Laboratory Manual. Blood samples will be taken per standard venipuncture techniques. The following will be assessed:

CBC: White blood cell (WBC) count (with automated differential for absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, haemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and platelet count;

Chemistry: Glucose, albumin, total protein, calcium, sodium, potassium, chloride, CO_2 (bicarbonate), blood urea nitrogen (BUN), creatinine, alkaline phosphatase, alanine amino transferase (ALT), aspartate amine transferase (AST), and total bilirubin;

Urinalysis: Color, clarity, specific gravity, pH, protein, glucose, and leukocyte esterase. If the results are abnormal or further analysis is requested by the site, the sample will undergo microscopic analysis for red blood cells, white blood cells, and squamous epithelial cells.

For all WOCBP, a UPT will be conducted at the Screening Visit, Baseline Visit (if > 7 days from Screening Visit), and the Day 28, Day 56, and Day 84 Visits. Details for collecting and testing urine for the UPT are provided in the Laboratory Manual.

7.2.2. Specimen Preparation, Handling, Shipment, and Storage

Specimen preparation, handling, shipment, and storage for the CBC, chemistry and urinalysis are described in the Laboratory Manual.

7.3. Study Schedule

7.3.1. Screening Visit

At the Screening Visit (Day -35 to Day 1), the following will be conducted:

- Obtain written informed consent/assent
- Conduct medical history and review of systems
- Obtain subject demographics
- Obtain subject's height and weight
- Obtain smoking and alcohol history and current use
- Conduct UPT for all WOCBP
- Collect urine sample to test for drugs of abuse
- Perform IGA
- Count inflammatory and non-inflammatory lesions (separately) on the face
- Review eligibility criteria
- Query subject for concomitant medications

If the subject is found to be eligible for participation in the study, the Baseline Visit procedures may then be conducted. If the subject requires any washout period, this period must be completed within 35 days prior to the Baseline Visit. Subjects found to be ineligible will be screen failed and the reason for screen failure will be recorded.

7.3.2. Baseline Visit

If the subject is deemed eligible and proceeds to enrollment on the same day as the Screening Visit, in addition to the screening assessments the following will be conducted:

- Collect blood sample for CBC and chemistry
- Collect urine sample for urinalysis
- Take photographs of face (selected sites)
- Administer Acne-QoL prior to first application of study drug
- Assess cutaneous tolerability prior to application of study drug
- Apply study drug on subject's face (see Section 6.1.5)
- Assess cutaneous tolerability approximately 15 minutes after the application of study drug
- Monitor subject for adverse events
- Train subject in proper application of study drug. Dispense study drug
- Dispense study diary and train the subject in diary completion
- Weigh and dispense study drug

If the subject is not enrolled on the same day as the Screening Visit, the following will be conducted at the Baseline Visit:

- Review eligibility criteria
- Query subject for changes in concomitant medications
- Collect blood sample for CBC and chemistry
- Collect urine sample for urinalysis
- Conduct UPT (WOCBP only) (if > 7 days from Screening Visit)
- Collect urine sample to test for drugs of abuse
- Perform IGA
- Count inflammatory and non-inflammatory lesions (separately) on the face
- Take photographs of face (selected sites)
- Administer Acne-QoL prior to first application of study drug
- Assess cutaneous tolerability prior to application of study drug
- Apply study drug on subject's face (see Section 6.1.5)
- Assess cutaneous tolerability approximately 15 minutes after the application of study drug
- Monitor subject for adverse events
- Train subject in proper application of study drug.
- Weigh and dispense study drug
- Dispense study diary and train the subject in diary completion

7.3.3. Study Drug Application Period

At the Day 1 Visit, subjects will receive their first study drug application at the clinical site during the visit. Subjects will be trained in the correct application of the study drug. Application of study drug should occur at approximately the same time each day. For subjects receiving BID dosing, the evening application should take place approximately 8 to 12 hours after the morning application. A diary will be maintained documenting compliance with the self-administered applications. At the Baseline, Day 28, and Day 56 Visits, the subject will be provided an ample supply of study drug to complete dosing for the next 28 days. Study drug will be applied at the clinical site during the Day 14, Day 28, Day 56 and Day 84 Visits (final dose) to ensure compliance with application instructions. Subjects will be instructed to not apply their study drug prior to the study visit.

7.3.4. Day 14 Visit

At the Day 14 Visit ± 3 days, the following will be conducted.

- Query subject for changes in concomitant medications since the Baseline Visit
- Query subject for adverse events that occurred since the Baseline Visit
- Review subject dosing diary and the number of used/unused bottles to ensure compliance
- Perform IGA

- Count facial inflammatory and non-inflammatory lesions (separately) on the face
- Assess cutaneous tolerability prior to application of study drug
- Study drug application by the subject
- Assess cutaneous tolerability approximately 15 minutes after the application of study drug

7.3.5. Day 28 and Day 56 Visits

At the Day 28 Visit ± 5 days and the Day 56 Visit ± 5 days, the following will be conducted.

- Query subject for changes in concomitant medications
- Query subject for adverse events that occurred since the previous visit
- Conduct UPT for WOCBP
- Perform IGA
- Count inflammatory and non-inflammatory lesions (separately) on the face
- Collect and weigh study drug
- Collect study diary and dispense new diary for next 28 days
- Assess for cutaneous tolerability prior to application of the study drug
- Subject will apply dose of study drug in front of clinical site staff
- Assess cutaneous tolerability approximately 15 minutes after application of the study drug
- Weigh and dispense study drug for next 28 days of dosing

7.3.6. Day 84/ End of Study Visit

The final application of study drug will occur during the Day 84 Visit. Subjects will be instructed to not apply their final application of study drug until they are seen in the clinic. At the Day 84 Visit (Day 84 ± 5 days) the following will be conducted.

- Query subject for changes in concomitant medications
- Query subject for adverse events that occurred since the Day 56 Visit
- Conduct UPT for WOCBP
- Collect blood sample for CBC and chemistry
- Collect urine sample for urinalysis
- Perform IGA
- Count inflammatory and non-inflammatory lesions (separately) on the face
- Take photography of face (selected sites)
- Administer Acne-QoL
- Administer PRO
- Collect and weigh study drug
- Collect study diary
- Assess for cutaneous tolerability prior application of the final dose
- Subject will apply final dose of study drug in front of clinical site staff
- Assess cutaneous tolerability approximately 15 minutes after application of the final dose

- Discharge subject from study

7.3.7. Early Termination Visit

If a subject terminates the study early for reasons other than an AE, attempts will be made to complete the assessments required for the Day 84 Visit on Day 84 (± 5 days), if possible.

7.3.8. Schedule of Events Table – Subjects with Acne Vulgaris

The Schedule of Events is provided in Table 3.

Table 3: Time and Events Schedule

Parameter	Screening Visit (-35 to Day 1)	Baseline Visit (Day 1)[a]	Day 14 Visit (Day 14 ±3 days)	Day 28 Visit (Day 28 ±5 days)	Day 56 Visit (Day 56 ±5 days)	Day 84 Visit[c] (Day 84 ±5 days)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Written informed consent/assent	X					
Medical history/ review of systems	X					
Demographics with Height and Weight	X					
Tobacco and Alcohol History	X					
Urine pregnancy test (WOCBP only)	X	X		X	X	X
Eligibility criteria review	X	X				
Safety Laboratory (CBC, chemistry and urinalysis)		X				X
Urine drug screening	X	X				
Investigator's Global Assessment	X	X	X	X	X	X
Inflammatory and non-inflammatory lesion count	X	X	X	X	X	X
Photography of Face (selected sites)		X				X
Administer Acne-QoL		X				X
Administer PRO						X
Ensure compliance with study drug administration			X	X	X	X
Study drug administration by site personnel (am)		X				
Study drug administration by subject		Day 1 pm to Day 84[d]; Day 14, 28, 56, and 84 doses applied in clinic				
Concomitant medications	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Cutaneous tolerability assessments[b]		X	X	X	X	X
Dispense study drug and diary		X		X	X	
Collect diary and study drug				X	X	X

[a] Screening and Baseline Visit may occur on the same day.

[b] Assess cutaneous tolerability prior to and approximately 15 min after initial dose on Day 1 and the subject applications on Day 14, Day 28. Day 56, and Day 84

[c] If subject discontinues treatment early, Day 84 evaluations will be performed when possible.

[d] Subjects randomized to BID dosing will apply study drug in the morning and evening, 8 to 12 hours apart.

7.4. Concomitant Medications, Treatment and Procedures

All concomitant medications taken during study participation will be recorded on the case report forms (eCRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, OTC medications, and non-prescription medications. In addition, vitamins, supplements and other non-pharmaceuticals products that are taken orally are to be reported in the eCRF. Any use of marijuana products will be reported.

Subjects will use their normal facial cleansers throughout the study. The face will be washed daily with these cleansers. Subjects will be instructed to wash their face prior to the Baseline, Day 14, Day 28, Day 56, and Day 84 Visits. The face will not be washed within 5 minutes prior to, or within 1 hour after application of study drug. Subjects must agree to maintain their regular use of sunscreens, moisturizers, and facial makeup throughout the entire course of the study. Sunscreens, moisturizers and makeup may be applied to the face after study drug has adequate time to dry. Detailed dosing instruction will be provided to the subjects.

7.5. Prohibited Medication, Treatment, and Procedures

The following medications, treatments, and procedures are prohibited for all subjects during the study.

- Use of topical acne treatments or other topical medication on the face
- Shaving cream and cleansers cannot be used within 5 minutes prior to, or for 1 hour after application of study medication
- Participation in a clinical study of any investigational product or procedure
- Use of any medications, other than the study drug, for treatment of acne vulgaris
- Use of any medication that, in the opinion of the investigator, may affect the evaluation of the study product (e.g., tetracycline or macrolide for > 7 days for URI) or place the subject at undue risk
- Use of oral retinoids (e.g., isotretinoin) or high dose (> 10,000 IU) Vitamin D
- Use of systemic corticosteroids (inhaled or intranasal corticosteroid ≤ 1000 µg daily dose is acceptable), oral antibiotics, or anti-inflammatory drugs (occasional NSAIDs to treat ailments other than acne are permitted)
- Use of hormonal therapy solely for the control of acne
- Use of an androgen receptor blocker (e.g., spironolactone)
- Facial procedures (e.g., microdermabrasion, chemical or laser peel)
- Photodynamic therapy
- Use of home-based light therapies
- Use of tanning beds

Subjects should avoid swimming and heavy exercise for 1 hour after application of study drug.

Subjects are to avoid contact of their face with other persons (e.g. kissing and hugging) for 1 hour after application of study drug.

Subjects will wash their hands directly after application of study drug.

7.6. Rescue Medication, Treatments and Procedures

This section is not applicable.

7.7. Subject Access to Study Agent at Study Closure

Subjects will not have access to the study drug after completion of their participation until the product is available commercially.

8. ASSESSMENT OF SAFETY

8.1. Specification of Safety Parameters

8.1.1. Definition of Adverse Events (AE)

An AE is defined as any untoward medical occurrence in a study subject which does not necessarily have to have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug treatment, whether or not considered related to the study drug.

Any events involving illnesses or injuries with onset during the study or any events involving exacerbations of pre-existing illnesses should be recorded. All clearly related signs and symptoms should be grouped together and recorded as a single diagnosis in the eCRF. A pre-existing condition will not be reported as an AE unless the condition worsens during the trial. The condition, however, must be reported in the Medical History section of the eCRF. Scheduled or planned diagnostic and therapeutic procedures such as surgery will not be reported as AEs.

8.1.2. Definition of Serious Adverse Events (SAE)

Each AE will be independently judged by the investigator in terms of seriousness**.** A serious AE (SAE) is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,

  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.

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in permanent impairment of a body function or permanent damage to a body structure,
- Is a congenital anomaly/birth defect,
- Necessitates medical or surgical intervention to preclude any one of the outcomes listed in this definition.

8.2. Classification of Adverse Events

8.2.1. Relationship to Study Drug

The investigator will review each event and assess its relationship (unrelated, unlikely, possibly, probably, definitely) to drug treatment. The following definitions will be used for these causality assessments.

Unrelated	• The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions. • Definitely not related to drug. • Temporal sequence of an AE onset relative to administration of drug not reasonable. • Another obvious cause of an AE.
Unlikely	• Time sequence is unreasonable. • There is another more likely cause for an AE.
Possibly	• Corresponds to what is known about the drug. • Time sequence is reasonable. • Could have been due to another equally, likely cause.
Probably	• Is a known effect of the drug. • Time sequence from taking drug is reasonable. • Ceases on stopping the drug. • Cannot be reasonably explained by the known characteristics of the subject's clinical state.
Definitely	• Is a known effect of the drug (e.g., listed in Investigator's Brochure). • Time sequence from taking drug is reasonable. • Event stops upon stopping drug, event returns upon restarting drug. NOTE: Re-challenge will only be considered after consultation with the medical monitor and the sponsor.

8.2.2. Severity of Event

Each sign or symptom reported will be graded on a 5-point severity scale (Grade 1, 2, 3, 4 and 5).

The following definitions for rating maximum severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living.** Note**:** An experience may be severe but may not be serious, (e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Note: A semi-colon indicates 'or' within the description of the grade.

*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.2.3. Expectedness

For this study, all AEs will be recorded.

The safety and tolerability of BTX 1503 5% was evaluated in a Phase 1a study in healthy volunteers and in a Phase 1b study in subjects with moderate to severe acne vulgaris. These studies demonstrated that BTX 1503 5% was safe and well tolerated with up to 3 mL applied BID (225 mg CBD daily) for up to 28 days. Adverse events reported as related to study drug treatment were facial dryness and itchiness. Mild cutaneous reactions included erythema, dryness, scaling, and burning/stinging.

Studies of the active ingredient (CBD) administered orally in multiple therapeutic settings has described no consistent findings for systemic AEs. Based on findings in a cumulative irritation study of the BTX 1503 vehicle, mild skin irritation may occur.

8.3. Time Period and Frequency for Event Assessment and Follow-up

All AEs occurring after signing of the consent/assent form through completion of the Day 84 Visit will be recorded. AEs arising after the time of initiation of first treatment with study drug will be

considered treatment emergent AEs (TEAEs). At each contact with the subject, the investigator or designee will seek information on AEs by non-leading specific questioning and, as appropriate, by examination. All observed or volunteered AEs, regardless of suspected causal relationship to study drug, must be recorded on the AE page of the eCRF.

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions will be recorded. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to resolution or considered stable by the investigator.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.4. Reporting Procedures

8.4.1. Adverse Events Reporting

All AEs will be recorded on the AE eCRF. For each AE, the name of the event, date of onset, relationship to study drug, severity, seriousness (Y/N), whether a medication was used to treat the event, date of resolution (or ongoing), and outcome (fatal, recovered/resolved, recovered/resolved with sequelae, ongoing) will be noted.

8.4.2. Serious Adverse Event Reporting

Each AE will be independently judged by the investigator in terms of seriousness**.** A SAE is defined in Section 8.1.2.

All SAEs will be reported to the sponsor via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and Bioavailability/Bioequivalence, dated December 2012. The IRB/EC will be notified of the Alert Reports.

All AEs will be followed until resolution or until the investigator determines that the subject's status has returned to normal or has stabilized.

8.4.3. Reporting of Pregnancy

As part of the eligibility criteria, WOCBP must agree to use appropriate contraception methods to avoid pregnancy during the study. If a subject does become pregnant, or is suspected of being

pregnant, the subject will be immediately withdrawn from any further treatment with the study drug. The pregnancy, or suspected pregnancy will be immediately reported to the medical monitor.

Any subject that becomes pregnant during the study will be followed to term to collect pregnancy outcomes pending acquisition of the subject's permission.

8.5. Safety Oversight

Oversight of the safety of the study will be the responsibility of the medical monitor. Safety data will be regularly reviewed (monthly at a minimum). If unexpected safety signals are observed, the medical monitor and the sponsor will determine if the enrollment or the study should be discontinued, or the protocol amended to include additional safety monitoring.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical and Analytical Plans

A separate Statistical Analysis Plan (SAP) will be prepared for this study. The statistical approaches to analysis of the data are described in this protocol. Further detail on the structure of tables, listings, and figures is provided in the SAP.

9.2. Statistical Hypotheses

The purpose of this Phase 2 study is to describe the safety and efficacy of treatment with the BTX 1503 5% liquid formulation or 2.5% liquid formulation vs Vehicle liquid formulation with QD or BID dosing in subjects with acne vulgaris. P-values for selected variables will be presented to assist in evaluating the outcome of the study. Failure to achieve a statistically significant result does not imply a failed study; results from this study will be used to inform statistical approaches for registration studies.

The primary efficacy endpoint of the study is the change from Baseline in inflammatory lesion counts. The study will evaluate the superiority of active study drug over vehicle based on the following hypotheses:

H_0: $\mu_{active} - \mu_{vehicle} = 0$

H_1: $\mu_{active} - \mu_{vehicle} > 0$.

Where H_0 is the null hypothesis, H_1 the alternative hypotheses, μ_{active} is the absolute change in the number of inflammatory lesions counts from Baseline to Day 84, and $\mu_{vehicle}$ is the absolute change in the number of inflammatory lesions counts from Baseline to Day 84.

Secondary and exploratory endpoints do not have a priori hypotheses but will be evaluated using appropriate statistical methods to inform statistical approaches for future studies.

9.3. Analysis Datasets

This study will be evaluated using 3 analysis sets: intent-to-treat (ITT), per protocol (PP), and safety. Efficacy conclusions will be drawn from the ITT analysis set. The PP analysis set will be used to support the efficacy findings in the ITT analyses. Safety conclusions will be drawn from the safety analysis set.

The ITT analysis set includes all subjects who are randomized and is based on randomized study group, regardless of study drug received. The safety analysis set includes all subjects who are randomized, receive at least 1 confirmed dose of study drug, and have at least 1 post-Baseline assessment. The safety analysis set will be assessed based on study drug received, regardless of group to which subject was randomized. The PP analysis set includes all subjects in the ITT analysis set who complete the Day 84 visit without noteworthy study protocol violations, including compliance with study drug application, Day 84 visit window, and completion of efficacy

evaluations on Day 84. The full definition of the PP population is given in the SAP which will be approved prior to database lock.

Subjects who have a documented lack of treatment effect or who are discontinued from the study due to an AE that was considered by the investigator to be study drug related will be included in the PP analysis set. Specific criteria for identifying the PP analysis set will be determined prior to breaking the blind.

Vehicle QD and Vehicle BID groups may be combined for analyses.

9.4. Description of Statistical Methods

9.4.1. General Approach

All statistical processing will be performed using SAS® 9.3 or higher. Demographics will be summarized by age, gender, race, ethnicity, height and weight. Summary statistics will be presented for change from Baseline in lesion counts (inflammatory and non-inflammatory separate and combined) and IGA. For continuous variables, the mean, standard deviation (SD), median, and range will be presented. Categorical variables will be summarized by frequency counts and percentages.

9.4.2. Safety Analyses

All subjects who receive at least one confirmed dose of study drug and have at least one post-Baseline assessment will be included in the safety analyses.

All treatment-emergent adverse events (TEAEs) reported during the study will be recorded and classified based on MedDRA terminology. Treatment-emergent adverse events are those AEs with an onset on or after the first application of study medication. All reported TEAEs will be summarized by treatment group, the number of subjects reporting events, system organ class, preferred term, severity, relationship to study drug, and seriousness. When summarizing events by causality and severity, each subject will be counted only once within a system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification.

Serious adverse events (SAEs) will be summarized by cohort, system organ class, preferred term, severity, outcome and relationship to study drug; and all SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinue from the study due to an AE and the reason for discontinuation will be provided.

Concomitant medication will be mapped to ATC Level 2 using the WHODrug dictionary. The number and percentage of subjects reporting each medication will be summarized. Medications taken by each subject will be listed.

Changes from Baseline in safety laboratory assessments (CBC, chemistry and urinalysis) at Day 84 will be summarized using shift tables. Abnormal values will be summarized. Laboratory values will be listed by subject.

Cutaneous tolerability will be assessed at the Baseline, Day 14, Day 28, Day 56 and Day 84 Visits. Summaries will present frequencies and percentages for the grading of each of the signs/symptoms that was performed at each scheduled visit/time point combination. The summary of cutaneous tolerability assessment scores table will present summary statistics for the scores ('None'=0, 'Slight'=1, 'Moderate'=2 and 'Severe'=3) and the change from Baseline values at each scheduled post-Baseline visits/time point for each of the signs/symptoms. Listings will be provided by subject.

9.4.3. Efficacy Analyses

The efficacy analyses will be performed using the ITT (primary) and PP (supportive) analysis sets. The efficacy variables include the IGA and lesion counts (inflammatory and non-inflammatory) collected at Screening/Baseline and the Day 14, Day 28, Day 56, and Day 84 Visits. Absolute and percent changes in lesion counts from Baseline will be calculated for each subject. The IGA will be dichotomized into "success" and "failure", with a subject considered a "success" at each individual visit if the IGA at that visit is Clear ("0") or Almost Clear ("1") and at least 2 grades less than the Baseline score. Efficacy variables also include the Acne-QoL assessed at Baseline and Day 84 which will be scored according to the author's scoring system (Martin 2001), and the subject's assessment of improvement (PRO) using proportions by category.

Descriptive statistics (including mean, median, standard deviation [SD], minimum, and maximum, unless otherwise stated) will be presented for the following parameters by study group using both the ITT and PP analysis sets:

- Inflammatory, non-inflammatory, and total lesion counts at Baseline and study Day 14, Day 28, Day 56, and Day 84,
- Absolute and percent change from Baseline in inflammatory, non-inflammatory, and total lesion counts at study Day 14, Day 28, Day 56, and Day 84, and
- IGA scores and frequency and percent distribution of the dichotomized IGA at study Day 14, Day 28, Day 56, and Day 84.

<u>Primary endpoint:</u>

The primary efficacy endpoint for the study is:

- Absolute change from Baseline in inflammatory lesion counts at Day 84.

<u>Secondary endpoints</u>:

The secondary endpoints for the study are:

- Absolute change from Baseline in non-inflammatory lesion count at Day 84,

- The percent change from Baseline in the inflammatory lesion count at Day 84,
- The percent change from Baseline in the non-inflammatory lesion count at Day 84,
- The proportion of subjects with at least a 2-grade reduction from the Baseline IGA score at Day 84,
- The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 84, and
- The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 84 and at least a 2-grade reduction from the Baseline IGA score.

Exploratory endpoints:

The exploratory endpoints are:

- The change from Baseline in the total lesion count at Day 84,
- The percent change from Baseline in the total lesion count at Day 84,
- The change from baseline in the IGA scores and Day 84,
- The absolute and percent change from Baseline in inflammatory, non-inflammatory and total lesion counts at Day 14, Day 28 and Day 56.
- The proportion of subjects with at least a 2-grade reduction from the Baseline IGA score at Day 14, Day 28 and Day 56, and
- The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 14, Day 28 and Day 56,
- The proportion of subjects with an IGA score of "clear" or "almost clear" at Day 14, Day 28 and Day 56 and at least a 2-grade reduction from the Baseline IGA score.
- The change from Baseline in the Acne-QoL at Day 84, and
- Subject's assessment of the change in their acne from baseline to Day 84 (PRO).

Tests of superiority for the primary and secondary endpoints of absolute change from Baseline in lesion counts will be based on either parametric or nonparametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on an ANCOVA with factors of treatment and the respective Baseline lesion count as covariates, or on ranked data submitted to an ANCOVA with factors of treatment, analysis center, and the respective Baseline lesion count as a covariate.

Data will be reviewed for skewedness (details in the SAP). If a parametric analysis is indicated, the results of the parametric analysis will be considered the primary analysis. If a nonparametric analysis is indicated, the absolute or percent changes in inflammatory lesion counts will be rank-transformed prior to submitting them to the ANCOVA. Results of the rank-transformed analyses

will then be considered the primary analysis; results of the nonrank-transformed analyses will be also presented.

The dichotomized IGA will be analyzed with logistic regression, adjusting for baseline IGA and site. Pairwise tests will be conducted comparing the treated groups to vehicle. The lesion count and IGA analyses employ the methods for handling missing data described in Section 9.4.9.

9.4.4. Subset analyses

Subset analyses will be conducted for the primary efficacy endpoint. These analyses will be summarized using descriptive statistics. The specific subsets within the ITT analysis set that will be evaluated include: Baseline lesion counts, Baseline IGA, sex, age, ethnicity, race, and for the group less than the median age and greater than or equal to the median age.

9.4.5. Adherence and Retention Analyses

Compliance with study drug administration will be summarised based on dosing information from the clinical sites along with diary information obtained from subjects self-administering the study drug. Subjects who drop-out from the study for any reason will be summarised.

9.4.6. Baseline Descriptive Statistics

Demographics will be summarised by age, gender, race, ethnicity, height, and weight. Alcohol and tobacco history will be summarised,

9.4.7. Planned Interim Analyses

No interim analysis is planned.

9.4.8. Multiple Comparison/Multiplicity

This Phase 2 study is designed to identify the response to two different concentrations and dosing frequencies of BTX 1503. Statistical tests applied to the outcomes will be exploratory for establishing the dose and sample size for Phase 3 studies. No adjustments for Type 1 error will occur.

9.4.9. Handling of Missing Data

All efforts will be made to minimize the occurrence of missing data. It is not expected that dropout rates will differ between groups. Therefore, the primary method of handling missing efficacy data in the ITT analysis set will be based on last observation carried forward (LOCF).

Other imputation methods (e.g., MMRM) may be used as a sensitivity analysis to the LOCF method.

All safety analyses will be conducted using the safety analysis set. No imputations will be made for missing safety data.

Additional details on imputation and sensitivity analyses are provided in the SAP.

9.4.10. Tabulation of Individual Response Data

Individual response data will be presented in data listings.

9.5. Sample Size

The sample size for this study is based on clinical considerations only. Subjects will be randomized 2:2:2:1:1 with 90 subjects in each active treatment group and 45 subjects in each vehicle group for a total 360 subjects. This is considered adequate to evaluate the safety and tolerability of BTX 1503 in the treatment of acne vulgaris.

9.6. Measures to Minimize Bias

9.6.1. Enrollment/Randomization/Masking Procedures

A randomization code will be prepared by an unblinded statistician at the CRO. This statistician will be the only person aware of the randomization code. Randomization will be 2:2:2:1:1 (90 subjects in each active group and 45 in each vehicle group) and done by site. Once a subject is deemed eligible to enroll, randomization will occur. The site will contact the IVRS/IWRS to receive the kit number to be used for that subject throughout the study.

Study drug, active or vehicle, will be labelled identically except for the kit number and bottle number. Study drug pumps will contain approximately 39 mL for BID dosing groups and approximately 21 mL for QD dosing groups. There is no double-dummy in this study for BID vs QD dosing, so knowledge of volumes (during study drug accountability) will not unmask treatment groups (active vs vehicle). The vehicle study drug is indistinguishable from the active study drug.

9.6.2. Evaluation of Success of Blinding

For this Phase 2 study, no analyses to evaluate the success of the blinding will be conducted. Subjects known to have been unblinded during the study will be addressed in the final analysis as described in the SAP.

9.6.3. Breaking the Study Blind/Subject Code

During the study, the randomization code will not be broken except in the case of a safety concern, either for an individual subject or for the entire study.

If a subject has an adverse event that may necessitate unblinding of the randomization code, the site will contact the CRO and sponsor to discuss if there are options other than unblinding. If the site and sponsor agree that unblinding is in the best interests of the subject, the unblinded statistician will be contacted to conduct the unblinding. For circumstances where the CRO or

sponsor cannot be contacted, and the subject is in imminent danger without knowledge of their treatment, unblinding can be done through the IVRS/IWRS system.

At the completion of the study, the blind will be broken only after all data on all subjects has been entered into the database and the database is locked. Database lock procedures will follow the CRO's SOPs.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

This research will be carried out in accordance with the protocol, the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, June 1996), the National Statement on Ethical Conduct in Human Research (updated May 2015), and the ethical principles set forth in the Declaration of Helsinki.

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Informed Consent/Assent Process

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent/assent from each subject 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. In states or institutions where permission is required from a legal guardian and the child is required to assent to participate, the appropriate assent-permission process will be followed according to the relevant local and/or state laws. Appropriate IRB/EC-approved forms for obtaining written informed consent/assent will be provided by the investigator or by the sponsor or its designee.

The case report forms for this study contain a section for documenting informed consent/assent and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent/assent form will be reviewed and updated if necessary. All subjects (including those already being treated) will be informed of the new information, given a copy of the revised form and be re-consented/assented to continue in the study.

10.1.2. Institutional Review Board (IRB)/Ethics Committee (EC)

This protocol, the informed consent/assent form and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent/assent) as well as any advertising or compensation given to the subject, will be reviewed by the IRB/EC, and the study will not start until the IRB/EC has approved the protocol or a modification thereof. The IRB/EC is constituted and operates in accordance with the principles and requirements described in 21 CFR 56, ICH E6, and the National Statement on Ethical Conduct in Human Research (updated May 2015).

Protocol modifications to this study must be made only after consultation between an appropriate representative of the sponsor and the investigator. Protocol amendments must be prepared and approved by the sponsor and reviewed and approved by the IRB/EC prior to implementation.

10.1.3. Subject and Data Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples

in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB/EC may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location as described in Section 10.1.9.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the CRO. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the clinical sites' research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the CRO and ultimately with the sponsor.

10.1.4. Research Use of Stored Human Samples, Specimens or Data

Samples and data collected under this protocol will be used to study the safety of the study drug, BTX 1503 liquid formulation. No genetic testing will be performed. Samples and data will be stored using codes assigned by the clinical study site, the CROs, and/or the laboratories assessing the samples. Data will be kept in password-protected computers. Only those entities participating in the study will have access to the samples and data.

The study involves taking digital photographs of the subject's face at selected sites. The subject or subject's parent/guardian will consent/assent, in advance of any photographs being taken, to the taking, copyright, publication, and use of their photographs. The subject's eyes will be masked to conceal their identity. The photographs will be part of the study record and will be sent to the sponsor and regulatory agencies. The photographs will only be linked to the subject's study code and not the subject's name.

10.1.5. Future Use of Stored Specimens

All blood and urine samples used for assessment or study drug safety will be destroyed after analysis. No specimens will be stored for future use.

10.1.6. Key Roles and Study Administration

The sponsor of this study is Botanix Pharmaceuticals Ltd (Botanix). Botanix has engaged Premier Research (Durham, North Carolina, US) to oversee the conduct of the study. Premier will conduct

the data management, clinical monitoring and statistical management of the study. The medical monitor for this study will be provided by Premier. His/her responsibility will be to oversee the safety of subjects in the study.

The IRB/EC, which protects the rights and welfare of subjects, will be either local or centralized based on the study site. Central IRBs will be preferentially used when possible. Clinical sites outside of the US, will have IRB/EC oversight based on local and national requirements.

Photography of facial acne at selected sites will be performed utilizing equipment from a photography vendor. The vendor will provide a Photography Manual describing correct techniques for photographing subjects. Photographs from the study are the property of Botanix and will become part of the study record.

Study drug will be manufactured in the United States. The Coghlan Group (TCG; Bastrop, Texas, USA) is responsible for packaging, labeling, and distribution of the study drug.

A qualified vendor will act as the central lab for analysis of the blood and urine samples. Results will be provided to the sites for their subject management and to Premier for data analysis.

There will be no DSMB for this study. Blinded safety data will be reviewed in real-time by the medical monitor to assure subject safety.

10.1.7. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a CRO contracted by the sponsor to conduct this activity.

On-site monitoring will occur for initial site assessment and training throughout the study and at a frequency adequate to assess the above based on the number of subjects enrolled at each site and the time from enrollment of the subjects. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the Case Report Form. The investigator (or his/her designee) agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

A site visit monitoring report will be prepared for each visit. Details of clinical site monitoring are documented in the Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the preparation and distribution of monitoring reports.

Independent audits may be conducted by auditors from the sponsor or its designee or regulatory agencies.

10.1.8. Quality Assurance and Quality Control

Each clinical site, CRO, and laboratory participating in this study will have SOPs for quality management that describe:

- How data will be evaluated for compliance with the protocol, ethical standards, regulatory compliance, and accuracy in relation to source documents.
- The documents to be reviewed (e.g., eCRFs, clinic notes, product accountability records, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.
- Who will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with protocol) and QC issues (e.g., correcting errors in data entry).
- Staff training methods and how such training will be tracked.
- If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra-and inter-examiner agreement.

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the clinical study monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9. Data Handling and Record Keeping

The investigator shall supply the sponsor or its designee on request with any required background data from the study documentation or clinic records. This is particularly important when data on the electronic Case Report Forms requires clarification. In case of special problems/and or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

All source data forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out with a single line, but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate.

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the sponsor or its designees or to health authority inspectors after appropriate notification. The verification of the eCRF Data must be by direct inspection of source documents.

For each subject enrolled, an eCRF must be completed by an authorized delegate from the study staff and signed by the principal investigator. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome. The investigator should ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the eCRF's and in all required reports.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of subjects.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinic and office charts, laboratory notes, memoranda, subjects' memory aids or evaluation checklists, subject diaries, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Source documents will be maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject's official study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the electronic data capture (EDC) system, a 21 CFR Part 11-compliant data capture system provided by the CRO. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source 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 (1) Investigator's Study File, and (2) Subject clinical source documents. The Investigator's Study File will contain the protocol/amendments, Case Report and Query Forms, IRB/EC and governmental approval (as appropriate) with correspondence, sample informed consent/assent, study drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence. All records defined in 21 CFR 312.57 will be kept on file.

The investigator must keep these two categories of documents on file for at least 2 years after the latest of the following: completion, discontinuation of the study, or the regulatory submission for which the study is being performed is no longer under review. After that, the documents may be destroyed, subject to local regulations.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in a sealed container(s) off-site so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when data on the eCRFs requires clarification. In case of special problems/and or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, ensuring that subject confidentiality is protected.

10.1.10. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or other study requirements (e.g., SOPs, Laboratory Manuals, etc). The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the clinical study monitor or to the CRO. Protocol deviations must be sent to the IRB/EC per their guidelines. The site investigator/study staff is responsible for knowing and adhering to their IRB/EC requirements.

It is not anticipated that waivers of eligibility requirements will be granted for any subjects. However, if eligibility requirements are waived in special circumstances, waivers must be approved by the medical monitor and the sponsor before a subject may be enrolled. Documentation of granted waivers will be maintained in the investigator's and sponsor's files.

10.1.11. Publication and Data Sharing Policy

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to Botanix Pharmaceuticals at least 30 days prior to submission. This allows Botanix Pharmaceuticals to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Botanix Pharmaceuticals will generally support publication of multicenter trials in their entirety. In this case, a coordinating investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement.

10.2. Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.3. List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BID	Twice Daily
CBC	Complete Blood Count
CBD	Cannabidiol
CFR	Code of Federal Regulations
CI	Confidence Interval
CMP	Clinical Monitoring Plan
CRA	Clinical Research Assistant / Associate
CRO	Clinical Research Organization
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food & Drug Administration

GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-Steroidal Anti-inflammatory Drug
OTC	Over the Counter
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
UDS	Urine Drug Screen
UPT	Urine Pregnancy Test
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

11. REFERENCES

1. Olah A, Toth B, Borbiro I, et al, Cannabidiol exerts sebostatic and anti-inflammatory effects on human sebocytes, *J Clin Invest* 2014; 124(9); 3713-3724
2. Fernandez-Ruiz J, Sagredo O, Pazos M, et al, Cannabidiol for Neurodegenerative Disorders: Important New Clinical Applications for this Phytocannabinoid? *Br J Clin Pharmacol* 2012: 75(2); 323-333
3. Volkow N, The Biology and Potential Therapeutic Effects of Cannabidiol: "Cannabidiol: Barriers to Research and Potential Medical Benefits" Presentation to NIDA June 24, 2015
4. Search of Clinical Trials database (ClinicalTrials.gov) in December 2017
5. Katsambas A, Papakonstantinou A. Acne: systemic treatment. *Clinics in Dermatology* 2004;22:412-8.
6. Bhate K, Williams HC. What's new in acne? An analysis of systematic reviews published in 2011-2012. *Clinical and Experimental Dermatology* 2014;39:273-7; quiz 7-8.
7. Bhate K, Williams HC. Epidemiology of acne vulgaris. The British Journal of Dermatology 2013; 168: 474-85.
8. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC et al. Guidelines of care for acne vulgaris management. *Journal of the American Academy of Dermatology* 2007;56:651-6
9. Dreno B, Thiboutot, D, Gollnick H, et al, Antibiotic stewardship in dermatology: limiting antibiotic use in acne. *Eur J Dermatol*. 2014; 24(3): 330-344
10. Rolewski S. Clinical Review: Topical Retinoids. *Dermatology Nursing* 2003; 15(5) Online
11. Peck GL, Olsen TG, Butkus D, Pandya M, Arnaud-Battandier J, Gross EG et al. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. *Journal of the American Academy of Dermatology*1982;6:735-45.
12. Kaymak Y, Taner E, Taner Y. Comparison of depression, anxiety and life quality in acne vulgaris patients who were treated with either isotretinoin or topical agents. *International Journal of Dermatology* 2009;48:41-6.
13. Hahm BJ, Min SU, Yoon MY, Shin YW, Kim JS, Jung JY et al. Changes of psychiatric parameters and their relationships by oral isotretinoin in acne patients. *The Journal of Dermatology* 2009;36:255-61.
14. Magin P, Pond D, Smith W. Isotretinoin, depression and suicide: a review of the evidence. *The British Journal of general Practice: the Journal of the Royal College of General Practitioners* 2005;55:134-8.
15. Janiczek-Dolphin N, Cook J, Thiboutot D, Harness J, and Clucas A, Can sebum production predict acne outcome? Br J Derm 2010; 163: 683-688

16. Salvaggio H, Zaenglein A, Examining the use of oral contraceptives in the management of acne *International Journal of Women's Health* 2010:2 69–76

17. Ebede T, Arch E, Berson D, Hormonal Treatment of Acne in Women, *J Clin and Aesthetic Derm* 2009; 2(12): 16-22

18. Berson D, Stein Gold L, Koo J, and Zane L, contemporary Treatment Approaches to Acne and Psoriasis, Skin and Allergy News (Supp) from March 18-24, 2005 Hawaii Dermatology Meeting

19. European Dermatology Forum: Guideline on the Treatment of Acne Published 2001

20. Simonart T. Newer approaches to the treatment of acne vulgaris. *American Journal of Clinical Dermatology* 2012;13:357-64.

21. Biro T, Toth B, Hasko G, et al, The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities *Trends Pharmacol Sci*. 2009; 30(8): 411–420.

22. van Klingeren B, ten Ham M, Antibacterial activity of Δ9-tetrahydrocannabionol and cannabidiol *Antoine van Leeuwenhoek* 1976; 42: 9-12