CLINICAL STUDY PROTOCOL

Study Title:	**A Randomized, Double-Blind, Vehicle-Controlled Study of the Safety, Tolerability and Efficacy of BTX 1204 in Patients with Moderate Atopic Dermatitis**
Protocol Number:	BTX.2018.003
Version:	1.0
Phase:	2a
Sponsor:	Botanix Pharmaceuticals Ltd 68 Aberdeen Street Northbridge, WA 6003 Australia
Final Approval Date:	21-AUG-2018

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PROTOCOL SIGNATURE PAGE – SPONSOR

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Signature:

The undersigned acknowledges that he/she has received and read Protocol BTX.2018.003, Version 1.0, dated 21-AUG-2018.

Sponsor Representative	Signature	Date
Mark Davis VP, Clinical and Regulatory Affairs		21 August 2018

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

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Version: 1.0 DRAFT v0.9

Signature:

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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 812 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	21-AUG-2018	Original document

LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
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
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food & Drug Administration
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
IND	Investigational New Drug
IGA	Investigator's Global Assessment
IFN	Interferon
IL	Interleukin
IRB	Institutional Review Board
ITF	Investigator's Trial File
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the Counter
PK	Pharmacokinetics
p.m.	Post Meridiem
PPG	Polypropyleneglycol
PPP	Pharmaceutical Packaging Professionals

QA	Quality Assurance
QC	Quality Control
QD	Once Daily
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
TMF	Trial Master File
UDS	Urine Drug Screen
UPT	Urine Pregnancy Test
vIGA-AD	Validated Investigator Global Assessment scale for Atopic Dermatitis
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

PROTOCOL SUMMARY

Title:	**A Randomized, Double-Blind, Vehicle-Controlled Study of the Safety, Tolerability and Efficacy of BTX 1204 in Patients with Moderate Atopic Dermatitis**
Study Phase:	2a
Dose and Treatment Duration:	There will be two dose groups. All subjects will apply study drug for 84 days. • BTX 1204 4% twice daily (BID), or • Vehicle BID
Study Duration:	There will be a total of up to 112 days; screening period (up to 28 days), and 84 days of treatment.
Investigational Product:	BTX 1204 Liquid Formulation
Concurrent Control:	BTX 1204 Vehicle
Administration Route and Form:	BTX 1204 4% (w/w) or Vehicle applied topically
Objective:	To determine the safety, tolerability and efficacy of BTX 1204 in subjects 12 to 70 years of age with moderate atopic dermatitis (AD).
Study Design:	This is a multi-center, randomized, double-blind, vehicle-controlled, parallel-group study.
Outcome Measures:	The efficacy of BTX 1204 4% (w/w) will be evaluated using the Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD™; heretofore – IGA), Body Surface Area (BSA) of AD, Signs of AD (erythema, exudation, excoriation, induration/papulation, and lichenification), and Eczema Area Severity Index (EASI) Scores completed by the treating dermatologist along with Itching-Numerical Rating Score (I-NRS) and Worst Itching NRS (WI-NRS) scores reported by subjects. At selected sites, a target lesion will be identified, photographed and scored with the Signs of AD.

	The efficacy outcome measures are: Primary endpoint: The primary efficacy endpoint for the study is the proportion of subjects with IGA success defined as an IGA score of "Clear" (0) or "Almost Clear" (1) with at least a 2-grade improvement from Baseline at Day 85. Secondary endpoints: The secondary endpoints for the study are: • The proportion of subjects with an EASI 75 score at Day 85, • The proportion of subjects with an EASI 50 score at Day 85, • The change from Baseline in the Signs of AD score at Day 85, • The proportion of subjects with an IGA of Clear or Almost Clear at Day 85, • The proportion of subjects with at least a 2-grade improvement in ISGA from Baseline at Day 85, • The change from Baseline in the percent of BSA affected by AD at Day 85, • The time to achieve IGA success, and • The change from Baseline to Day 85 in the I-NRS Exploratory endpoints: The exploratory endpoints are: • The change from Baseline in the Signs of AD score at Day 15, Day 29, and Day 57, • The change from Baseline in the percent of BSA affected by AD at Day 15, Day 29, and Day 57, • The proportion of subjects with IGA success defined as an IGA score of "Clear" (0) or "Almost Clear" (1) with at least a 2-grade improvement from Baseline at Day 15, Day 29, and Day 57, • The percent change from Baseline in the EASI Score at Day 85,

	• Change from Baseline in the subject's reports of pruritus obtained daily on a Patient Diary. • Time to improvement of pruritus (change of ≥ 4 in the Worst Itch Numerical Rating Score [WI-NRS, 0 – 10 score]), • Subject's assessment of the change in their AD from Baseline to Day 85 (Patient Reported Outcome [PRO]), and • The change from Baseline to Day 29, and Day 57, and Day 85 in the Signs of AD score for the target lesion (at selected sites only). The safety outcome measures to be assessed are: • Reported adverse events (AEs) including treatment-emergent (TEAE) monitored from time of consent through the end of study; • Changes in clinical labs including complete blood count (CBC), chemistry, and urinalysis between Baseline and Day 85, • Subject's reports of burning/stinging obtained during visits on Day 1, Day 15, Day 29, Day 57, and Day 85. 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 29, Day 57 and Day 85 Visits.
Total Sample Size:	Approximately 200 subjects randomized 1:1 (100 subjects to BTX 1204 4% and 100 subjects to Vehicle) will be enrolled.
Methods:	Subjects will begin screening to determine eligibility to participate in the study. Informed consent/assent, medical history/review of systems, demographics, height and weight will be obtained. Urine pregnancy testing (UPT) will be conducted for WOCBP and a urine drug screen (UDS) will occur. Measurement of the total body surface area (BSA) of AD involvement and IGA will be assessed at Screening. At selected photography sites, a target lesion will be identified. Within 28 days after the Screening Visit, Baseline assessments for safety (CBC, chemistry, and urinalysis) will be obtained on Day 1. If the subject is eligible to participate, Screening and Baseline may occur at the same visit. If the Screening Visit and Baseline Visit are not concurrent, IGA, UPT, UDS, and BSA of AD, will be repeated at the

	Baseline Visit. Review of eligibility criteria will be repeated. Signs of AD and the EASI scores will be obtained. Subjects will be asked to rate their pruritus using the itch numeric rating score (I-NRS) which is an average level of itch over the past 24 hours on a scale of 0 (no itch) to 10 (worst imaginable itch). At selected sites, photographs and Signs of AD scoring of the target lesion will be obtained. Subjects will be randomized 1:1 using an Interactive Web-based Response System (IWRS) to receive active BTX 1204 4% or Vehicle. Subjects will receive their first dose of study drug applied by the site staff and will be observed in the clinic for approximately 15 minutes after the initial application. Subjects will be given 4 weeks of study drug and instructed in the proper application for twice daily (BID) applications to cover their AD lesions, except on the scalp and groin. Subjects will be provided with a diary to record their daily pruritus score using the worst itch numeric rating score (WI-NRS). Subjects will record the WI-NRS over the past 24 hours each day prior to their morning application. Subject will also record on the diary the time of their morning and evening applications of study drug. Subjects will return to the clinic on Day 15. Subjects will be queried for adverse events and changes in concomitant medications since their previous visit. Returned study drug will be weighed and diaries will be reviewed for compliance. The site will obtain IGA, BSA of AD, Signs of AD score, EASI score. Subjects will be asked to rate their pruritus using the I-NRS. The subject will then apply their dose of study drug during the visit for the clinical site to confirm correct application techniques. Subjects will return to the clinic on Day 29 and Day 57. Subjects will be queried for adverse events and changes in concomitant medications since their previous visit. A UPT will be done on WOCBP. Returned study drug will be weighed and diaries will be reviewed for compliance. The site will obtain IGA, BSA of AD, Signs of AD, and EASI Score. Subjects will be asked to rate their pruritus using the I-NRS. At selected sites, the target lesion will be photographed and scored with the Signs of AD score. The subject will then apply their dose of study drug during the visit for the clinical site to confirm correct application techniques. Another four weeks of study drug will be dispensed along with a new diary.

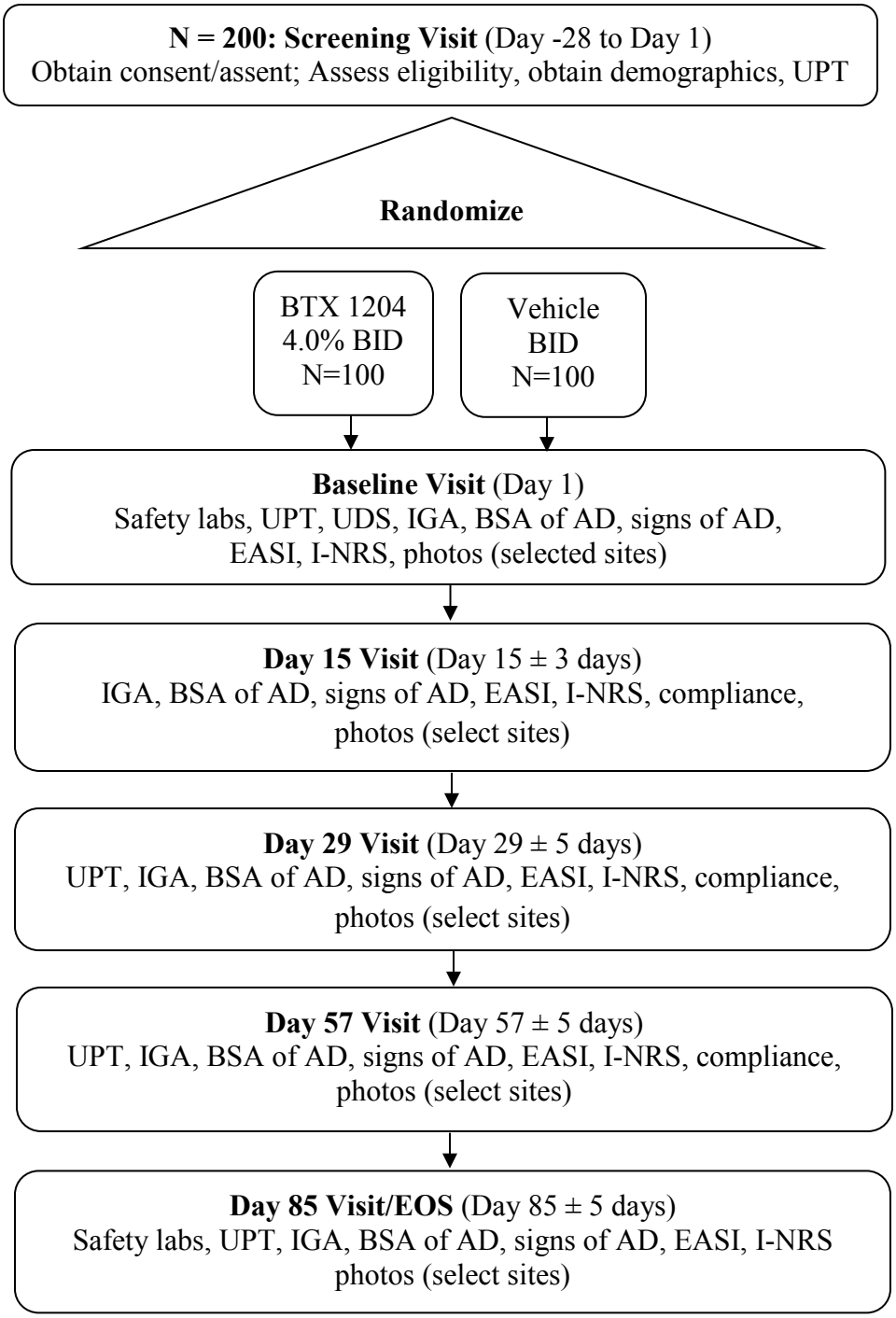
	The final study drug application will be applied in the evening prior to the Day 85 Visit. Subjects will return to the clinic for their final visit on Day 85 for safety assessments; blood samples for CBC and chemistry, and urine samples for urinalysis. A UPT will be conducted for WOCBP. Subjects will be queried for adverse events and changes in concomitant medications since their previous visit. Returned study drug will be weighed and diaries will be reviewed for compliance. The site will obtain IGA, BSA of AD, Signs of AD score, and EASI Score. Subjects will be asked to rate their pruritus using the I-NRS. At selected sites, the target lesion will be photographed and scored with the Signs of AD score. If a subject discontinues from the study early, all Day 85 assessments will be completed. After completion of study assessments, the subject will be discharged from the study.
Statistical Methods	All statistical processing will be performed using SAS® unless otherwise stated. ***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 ITT analysis set will consist of all randomized subjects with at least one post-baseline efficacy assessment and will be based on randomized study group, regardless of study drug received. The PP analysis set will be used to support the efficacy findings in the ITT analyses and will include subjects with no major protocol deviations. Safety conclusions will be drawn from the safety analysis set. The safety analysis set will include all subjects that received at least one application of study drug and had at least one post-baseline safety assessment with treatment based on study drug received regardless of randomization group. Demographics will be summarized using the safety analysis set by baseline age, gender, race, ethnicity, height, weight, and BMI. The primary efficacy analysis will be conducted on the ITT population. 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. ***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, BSA of AD, Signs of AD score, and EASI score collected at Screening and/or Baseline and all subsequent study visits. The primary efficacy endpoint for the study is the proportion of subjects with IGA success defined as an IGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline at Day 85. The IGA will be dichotomized into "success" and "failure" at study Day 15, Day 29, Day 57, and Day 85. This Phase 2a study is designed to identify the response to BTX 1204 relative to vehicle. Statistical tests applied to the outcomes will be exploratory. No adjustments for Type 1 error will occur. Success on IGA defined as a score of Clear (0) or Almost Clear (1) and at least a 2-grade improvement from Baseline at Day 15, Day 29, Day 57, and Day 85 will be analyzed using logistic regression, adjusting for Baseline IGA. The change from Baseline in BSA of AD at Day 15, Day 29, Day 57 and Day 85 will be analyzed used ANCOVA with Baseline BSA of AD and treatment as covariates. Summary statistics will be presented for the change from Baseline in each of the Signs of AD (erythema, exudation, excoriation, induration/papulation, and lichenification) at each timepoint (Day 15, Day 29, Day 57 and Day 85). A total score will be calculated based on the sum of each of the Signs of AD (0, 1, 2, or 3; max score of 15) and the change from Baseline will be summarized for each timepoint. The change from Baseline in Signs of AD at Day 15, Day 29, Day 57, and

	Day 85 will be analyzed using ANCOVA with Baseline Signs of AD score and treatment as covariates. Summary statistics will be prepared for the change from Baseline in the EASI Score and I-NRS at each timepoint (Day 15, Day 29, Day 57 and Day 85). Summary statistics will also be prepared for the change from Baseline in the Signs of AD score for the target lesion (selected sites) at each timepoint (Day 15, Day 29, Day 57 and Day 85). Summaries of the pruritus scores reported by the subjects in the daily Patient Diary will be presented using daily means by treatment and with graphic presentations. ***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 AEs, TEAEs, serious AEs (SAEs), and changes in laboratory assessments. AEs, TEAEs and SAEs will be coded using the MedDRA dictionary and 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. Changes in laboratory parameters from Baseline to Day 85 will be summarized using shift tables to evaluate for trends. Abnormal laboratory findings will be summarized and listed by subject. Concomitant medications 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. **Sample Size:** The sample size for this study is based on clinical considerations only. Subjects will be randomized 1:1 with 100 subjects in each treatment group for a total 200 subjects. This is considered adequate to evaluate the safety and tolerability and preliminary information on efficacy of

	twice daily BTX 1204 4% in the treatment of moderate atopic dermatitis in subjects aged 12-70.

SCHEMATIC OF STUDY DESIGN



Adverse events and concomitant medications monitored throughout the study

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TABLES

1. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

1.1. Background Information

Botanix Pharmaceuticals' BTX 1204 contains the active pharmaceutical ingredient, cannabidiol (CBD; *2-[(1R,6R)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol*). CBD is a member of a broader family of compounds known as cannabinoids, a class of compounds originally derived from the *cannabis sativa* plant. [Olah 2014] CBD is chemically synthesized under Good Manufacture Practices (GMP) for use in this study.

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. [Volkow 2015] CBD is not psychoactive and clinical trials have demonstrated that CBD may successfully treat epilepsy, arthritis, pain, and even Fragile X Syndrome. [Fernandez-Ruiz 2012] There are now more than 150 human clinical trials that have been completed, are underway, or pending recruitment around the world that are studying CBD in a range of diseases. [ClinicalTrials.gov Aug 2018]

Botanix Pharmaceuticals is developing a number of topical formulations aimed at exploiting the potential immune regulatory and anti-inflammatory effects of CBD that have reported in the literature. Initial clinical development of these topical formulations has focused on establishing the safety and local cutaneous tolerability when applied to the skin of healthy volunteers either as a single dose or as multiple doses. Subsequent clinical studies have again focused on establishing safety and local cutaneous tolerability in the disease state under investigation. To date, Botanix Pharmaceuticals has completed 3 Phase 1 clinical studies with formulations containing concentrations of CBD up to 5% (w/w) with once (QD) or twice daily (BID) dosage regimens for up to 28 days. These formulations have been well-tolerated on normal skin and on skin displaying the underlying pathology of acne or atopic dermatitis (AD). In the most recent study, 37 subjects with mild to moderate AD were treated with either vehicle or BTX 1204 4% (w/w) BID for 28 consecutive days. Evidence of a potential therapeutic benefit of BTX 1204 over vehicle was observed through at reduction in the Signs of AD scores from Baseline.

This study is intended to establish safety, tolerability and efficacy in subjects with moderate AD treated BID with BTX 1204 4% (w/w) Liquid Formulation compared to subjects treated with Vehicle for 12 weeks.

1.2. Rationale

1.2.1. Pathogenesis of Atopic Dermatitis

Atopic dermatitis is an inflammatory cutaneous disease which may co-exist with other immunoglobulin E (IgE)-dependent atopic diseases such as allergic rhinitis, bronchial asthma, and food allergy. [Nowicki 2015] The disease is a skin disorder which presents itself as itchy, inflamed, red, and possibly lichenified (*i.e.* thickened) skin with affected areas potentially distributed widely over the body. [National Eczema Organization, 2017] The pathogenesis of the disease is thought

to involve an acute T-helper 2 (Th2) cell response followed by a chronic response involving additional T-helper populations; although more recent research suggests that Th2 cells and a more generalized T-cell response are present during both acute and chronic phases. [Gandhi 2017] The importance of Th2 cells and interleukin (IL)-4 and IL-13 signaling in the disease is supported by the effectiveness of dupilumab, a human monoclonal antibody specific to IL-4Rα that can block IL-4 and IL-13 signaling, to improve many symptoms of AD including pruritus, and reduction in AD area and severity. [Gandhi 2017]

The classical steps of AD pathogenesis are the following (Figure 1):

- A skin barrier defect or entry of a skin irritant triggers the release of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) from keratinocytes, which activate dendritic cells (antigen-presenting cells in the skin) and Langerhans cells.

- During the "acute phase" of onset, dendritic cells cause excessive Th2, T-helper 22 (Th22), and T-helper 17 (Th17) cell activation (note that these changes continue into the "chronic phase" of the disease).

    - Th2 cells produce IL-4, IL-13, and IL-31, which then induce changes in keratinocyte gene expression, disrupt skin barrier function, and trigger itch symptoms. IL-4 and IL-14 can increase additional TSLP release from keratinocytes, which causes further Th2 cell activation.

    - Activated Th22 cells release IL-22 which promotes keratinocyte hyperplasia, downregulates keratinocyte differentiation, and synergizes with IL-17 to induce pro-inflammatory S100 genes.

    - Activated Th17 cells release IL-17 which can regulate S100 protein and gene expression.

- During the chronic stage (day 3 onward), dendritic cells recruit T-helper 1 (Th1) cell populations *via* IL-12 and continue to recruit Th22 and Th17 cells. Th1 cells release interferon-γ (IFN-γ), which may decrease the role of Th2 cells in the disease. Th1, Th22, and Th17 cells induce responses that continue to attract additional immune cells to the epidermis, alter keratinocyte differentiation, and induce epidermal thickening.

Figure 1 Pathogenesis of Atopic Dermatitis

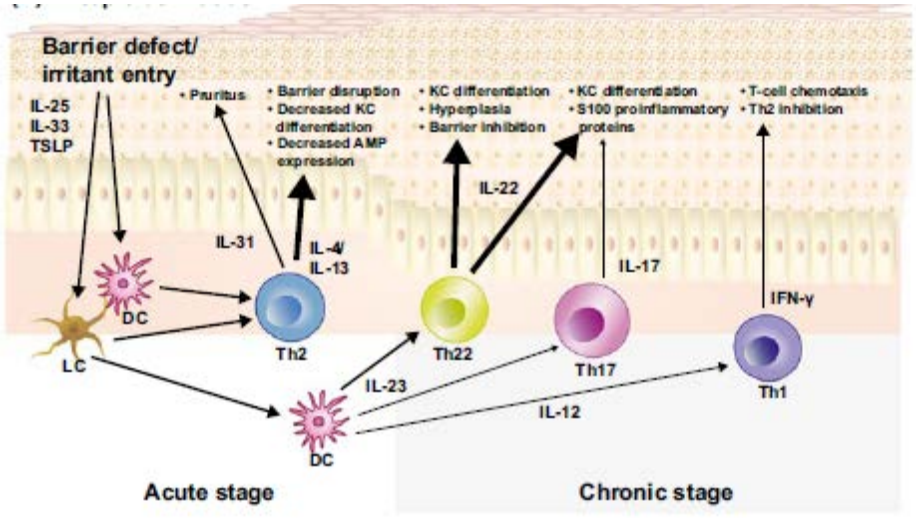

Figure 1 provides the various pathways involved in atopic dermatitis (from Guttman-Yassky 2017). DC = dendritic cell; IFN-γ = interferon-γ; IL = interleukin; KC = keratinocyte; LC = Langerhans cell; Th = T-helper; TSLP = thymic stromal lymphopoietin

It is estimated that Th2 cell response is dominant in ~80% of AD cases (extrinsic AD), but in other instances (intrinsic AD), there is a shift to a more pronounced Th22 and Th17 response. [D'Erme 2017] A recent study suggests that IL-17 may have a more dominant role in AD than proposed in classical models [Tan 2017]:

- Compared to healthy children, IL-17 protein levels were elevated in AD skin lesions, but not in the serum of children with AD, indicating that IL-17 acts locally.

- The effects of 2,4-dinitrochlorobenzene (DNCB; used to induce a model of AD in mice) were evaluated in IL-17 knockout and in wild-type C57Bl/6 mice. DNCB was able to induce AD-like lesions in both types of mice; however, epidermal and dermal thickness of the lesions in the IL-17 knockout mice were significantly decreased compared to what was observed in wild-type mice.

- Skin mRNA levels of the Th2 cytokines IL-4 and IL-13 were decreased in IL-17 knockout mice compared to wild-type mice; however, there was no difference in skin mRNA expression levels of IFN-γ. Splenocytes isolated from naïve IL-17 knockout mice released less IL-4 following concanavalin A (ConA) stimulation (a model of T-cell activation) compared to splenocytes from treated wild-type mice.

IL-17 has been shown to trigger a pro-inflammatory response in an immortalized human keratinocyte cell line (HaCaT cells). The addition of IL-17 increased the release of pro-inflammatory IL-6 and IL-8, but not IL-1β. This suggests that IL-17 may play a key role in the immune response associated with AD.

1.2.2. Rationale for the Development of BTX 1204 for the Treatment of Atopic Dermatitis

The published literature suggests that CBD can potentially address the underlying immunological pathways and inflammatory response associated with AD. CBD has been shown to alter gene expression of antigen-primed T-cells to induce a state of anergy *via* the Erg2 pathway and induce gene expression changes that leads to decreased antigen recognition in B-cells in an autoimmune disease model with a predominant Th17 response. [Kozela 2015] This suggests that CBD was able to decrease primed T-cell activity and also inhibit subsequent B-cell response. CBD also altered gene expression in gingival stem cells to reduce antigen expression, thereby decreasing the potential for these cells to initiate an autoimmune response (Libro 2016), which could also provide a rationale for the use of CBD as a possible therapy for GvHD. [Yeshurun 2015a, Yeshurun 2015b] CBD was also shown to suppress multiple T-cell populations and inhibit general T-cell activation. [Faubert Kaplan 2003, Ignatowska-Jankowska 2009] Numerous experimental models have indicated that CBD can decrease concentrations of pro-inflammatory mediators and also increase the release of anti-inflammatory cytokines (such as IL-10). CBD has also been shown to directly inhibit inflammatory responses due to the addition of IL-17A or IFN-γ. [De Filippis 2011, Harvey 2014] The potential for CBD to inhibit the effects of IFN-γ and/or decreasing IFN-γ levels could serve a dual purpose; lower levels of IFN-γ could translate to a decreased inflammatory response and improve skin barrier function by reducing IFN-γ-mediated inhibition of long-chain fatty acid ceramide production in the skin. [Tawada 2014]

Importantly, the literature indicates that CBD can inhibit the migration, proliferation and cell maturation processes involved in Th17, Th1, and Th2 immune responses. [Kozela 2015, Kozela 2016, Lee 2016] These are considered critical immune pathways involved in the pathophysiology of AD. [Guttman-Yassky 2017] CBD may have beneficial effects on AD due to direct antioxidant effects, and ability to improve antioxidant status in models of inflammation and autoimmune disease. [Ben Shabat 2006, Booz 2011, De Filippis 2011, Fouad 2011, Mukhopadhyay 2011, Fouad 2012, Giacoppo 2015, Lee 2016] Finally, CBD may also provide a therapeutic benefit for the treatment of AD by modulating the inflammatory response regulated by keratinocytes. CBD inhibited the production of monocyte chemotactic protein-2 (MCP-2), IL-6, IL-8, and tumor necrosis factor-α in polyinosinic-polycytidylic acid stimulated human keratinocyte (HaCaT) cells. [Petrosino 2018] CBD has also been shown to directly inhibit the proliferation of keratinocytes. [Wilkinson 2007]. The potential mechanisms for CBD activity in AD are listed in **Table 1**.

Table 1 Potential Mechanisms of Cannabidiol as a Treatment for Atopic Dermatitis

Atopic Dermatitis
• Decrease differentiation and proliferation and activity of t-helper 1, 2, and 17 cells. • Decrease interferon-γ and IL-17 levels and downstream effects. • Decrease interferon-γ, which may have an inflammatory effect and improve ceramide production in the skin. The latter may prevent deterioration of skin barrier function. • Decrease monocyte chemotactic protein-2 (MCP-2), IL-6, IL-8, and tumor necrosis factor-α. • Decrease keratinocyte proliferation. • Increase intracellular expression of antioxidants and decrease reactive oxygen species.

It should be noted that there were no publications evaluating the effects of CBD on AD in the clinic or in animal models of this disease. Additionally, there were no publications identified that explored the effects of CBD on the Th22 cell pathway.

While CBD did appear to have a consistent anti-inflammatory and autoimmune inhibitory effect in the identified publications, some caution is warranted when trying to evaluate the potential effects of CBD for AD based on data from different autoimmune inflammatory disease models, as the underlying cause of the diseases models could differ. For example, CBD had definitive effects on inhibiting IL17 release, decreasing Th17 cell activity and gene expression activity in an *in vitro* model of autoimmune encephalitis; however, CBD did not have any effects on antigen-mediated TNF-α or INF-γ release in this same model. [Kozela 2013, Kozela 2015, Kozela 2016] Similarly, in a murine model of type 1 diabetes, CBD was reported to inhibit Th1-mediated autoimmunity, but shift an immune response towards Th2 immunity, which was considered beneficial for the disease. [Weiss 2008] It is unclear whether CBD would induce a shift in T-cell populations in AD. Although there were subtle differences in how specific pathways were affected by CBD in these models, overall, CBD did demonstrate notable effects on inhibiting autoimmune responses in the test systems evaluated.

An additional consideration needs to be given to a specific mechanism of action for CBD. While not thoroughly investigated in each case, many of these studies showed that the reported effects of CBD are likely to be independent of cannabinoid receptors (CB_1 or CB_2). Additional receptors that could be involved with CBDs effects on immune response and inflammation could be peroxisome proliferator-activated receptors (PPARs), adenosine A_2 receptors, or the transient receptor potential cation channel subfamily V1 (TRPV1). [De Filippis 2011, Esposito 2011, Hegde 2011, Ribeiro 2012, Petrosino 2018] However, the involvement of specific receptors is likely different for each model of autoimmune inflammation.

1.2.3. BTX 1204 Nonclinical and Clinical Data

The safety of BTX 1204 is supported by information from the published literature and studies conducted by Botanix Pharmaceuticals. Botanix Pharmaceuticals has conducted nonclinical and clinical studies with CBD and with CBD formulated in an almost identical siloxane-based formulation known as BTX 1503. The only difference between these formulations is that BTX 1503 contains a very small amount of polydimethylsiloxane (dimethicone) at 1.0% (w/w). Comparative *in vitro* biopharmaceutic studies have shown both formulations have comparable transdermal permeation rates and equivalent deposition into the epidermal and dermal skin layers.

To date, Botanix Pharmaceuticals has performed a full battery of genotoxicity studies, an ocular irritation study, a single dose pharmacokinetic (PK) study in minipigs, a 28-day repeat-dose oral toxicology study in rats, 28-and 90-day dermal toxicology studies in minipigs, and a local lymph node assay (LLNA) that support the safety of BTX 1204. In addition, nonclinical information on systemic exposure to CBD obtained from the published scientific literature on the efficacy and safety pharmacology, on PK and metabolism, and on toxicity support the safety of CBD.

The results from these studies along with a comprehensive review of the scientific literature has established the safety profile of CBD and supports the proposed clinical investigation (BTX.2018.003) with topical application of CBD to patients with AD. Details on the observations from Botanix Pharmaceuticals' studies and the extensive literature review can be found in the IB.

In addition, to the nonclinical data, the safety and tolerability of BTX 1204 4% (w/w) was evaluated in subjects with mild to moderate AD (BTX.2017.004). In this study, BTX 1204 4% (w/w) Solution or Vehicle was applied to a target AD lesion and surrounding skin BID (180 mg CBD/day) for 28 consecutive days.

Safety was assessed through collection of AEs, laboratory findings (CBC, chemistry, and urinalysis), urine drug tests conducted to detect the presence of THC, signs of AD score on the target lesion (erythema, exudation, excoriation, induration/papulation, and lichenification), and cutaneous tolerability assessments.

This study demonstrated that daily topical treatment of BTX 1204 4% (w/w) Solution BID was safe and well tolerated. No early discontinuations occurred as a result of an AE. There were no SAEs reported and the most common AEs were general disorders and administration site conditions including application site erythema, application site pruritus, and application site pain.

In studies conducted with BTX 1503, a formulation similar to BTX 1204 but with a drug load of 5% (w/w), facial dryness and facial itchiness were reported as possible effects of the study drug treatment in a healthy volunteer study (BTX.2017.001). In an acne study (BTX.2017.002), 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.

There is adequate support for evaluating the use of BTX 1204 4% (w/w) Liquid Formulation in this clinical study based on the findings observed in nonclinical and clinical studies conducted by Botanix Pharmaceuticals and its active ingredient CBD along with the extensive published literature on the use of CBD in multiple settings.

1.3. Potential Risks and Benefits

1.3.1. Known Potential Risks

Based on studies conducted by Botanix Pharmaceuticals with BTX 1204 4% and similar CBD products, the potential risks associated with BTX 1204 include:

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

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 1204 liquid accidentally gets into the eyes via a provided "patient instruction" video.

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 the 28- or 90-day dermal minipig studies 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.

1.3.2. Known Potential Benefits

This study is the second study in evaluating the use of BTX 1204 4% (w/w) in subjects with AD.

The preliminary efficacy of BTX 1204 4% (w/w) was evaluated in a Phase 1b, randomized, double-blind, vehicle-controlled study. After only 4 weeks of treatment, subjects receiving BTX 1204 4% (w/w) had improvements in the Signs of AD score compared to treatment with Vehicle. A total of 34.8% of subjects receiving BTX 1204 had a $\geq$ 4-point improvement in the Signs of AD score compared to 18.2% of subjects receiving vehicle. Improvement was observed primarily in erythema, exudation and lichenification.

Based on the non-clinical and accumulating clinical data, there is evidence that treatment with BTX 1204 4% (w/w) in subjects with AD may lead to decreased inflammation which may lead to a decrease in the signs and symptoms associated with AD. As with any new form of treatment, potential benefits are not guaranteed. Results from this study will provide guidance for additional safety and efficacy studies in AD and potentially other target patient populations.

2. OBJECTIVE

The objective of this study is to determine the safety, tolerability and efficacy of BTX 1204 4% (w/w) in subjects with moderate atopic dermatitis.

3. STUDY DESIGN AND ENDPOINTS

3.1. Description of the Study Design

This is a randomized, double-blind, vehicle-controlled, Phase 2a study in subjects with moderate AD. Eligible subjects will be enrolled and randomized to treatment with BTX 1204 4% (w/w) or Vehicle for 84 days. Approximately two hundred (200) subjects randomized 1:1 (100 active: 100 vehicle) will be enrolled.

3.2. Study Endpoints

The primary endpoint for the study is the proportion of subjects with an Investigator's Global Assessment (IGA) success defined as an IGA score of "Clear" (0) or "Almost Clear" (1) with at least a 2-grade improvement from Baseline at Day 85.

The secondary endpoints for the study are:

- The proportion of subjects with an EASI 75 score at Day 85,
- The proportion of subjects with an EASI 50 score at Day 85,
- The change from Baseline in the Signs of AD score at Day 85,
- The proportion of subjects with an IGA of Clear or Almost Clear at Day 85,
- The proportion of subjects with at least a 2-grade improvement in ISGA from Baseline at Day 85,
- The change from Baseline in the percent of body surface area (BSA) affected by AD at Day 85,
- The time to achieve IGA success, and
- The change from Baseline to Day 85 in the Itch-Numerical Rating Scale (I-NRS)

Exploratory analyses will be conducted for:

- The change from Baseline in the Signs of Atopic Dermatitis score at Day 15, Day 29, and Day 57,
- The change from Baseline in the percent of body surface area (BSA) affected by AD at Day 15, Day 29, and Day 57,
- The proportion of subjects with IGA success defined as an IGA score of "Clear" (0) or "Almost Clear" (1) with at least a 2-grade improvement from Baseline at Day 15, Day 29, and Day 57,
- The absolute and percent change from Baseline in the Eczema Area Severity Index (EASI) score at Day 15, Day 29, Day 57, and Day 85,

- Change from Baseline in the subject's reports of pruritus obtained daily on a Patient Diary,
- Time to improvement of pruritus (change of ≥ 4 in the Worst Itch Numerical Rating Score [WI-NRS, 0 – 10 score]),
- Subject's assessment of the change in their AD from Baseline to Day 85 (Patient Reported Outcome [PRO]), and
- The change from Baseline to Day 29, and Day 57, and Day 85 in the Signs of AD score for the target lesion (selected sites).

Safety outcome measures to be assessed are:

- Reported adverse events (AEs) including treatment-emergent (TEAE) monitored from time of consent through the end of study,
- Changes in clinical labs including complete blood count (CBC), chemistry, and urinalysis between Baseline and Day 85, and
- Subject's reports of burning/stinging obtained during visits on Day 1, Day 15, Day 29, Day 57, and Day 85.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Inclusion Criteria

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

1. Subject is of either gender between 12 and 70 years of age, inclusive.
2. Subject (or parent/legal guardian) has the ability and willingness to sign a written informed consent.
3. Subject has a diagnosis of chronic (≥1 year), stable atopic dermatitis (AD) according to Hanifin and Rajka [Hannifin 1980]
4. Subject has ≥ 5% and ≤ 30% body surface area (BSA) of AD involvement excluding the scalp and groin.
5. Subject has an Investigator's Global Assessment (IGA) score of moderate (3) atopic dermatitis on the 5-point IGA (0-4) scale.
6. For selected photography sites, subject has a target lesion 25 to 200 cm^2 in surface area on the trunk, upper extremities or lower extremities with a Baseline Signs of AD score of ≥ 6 and ≤ 12.
7. Subject is in good general health without clinically significant hematological, cardiac, respiratory, renal, endocrine, gastrointestinal, psychiatric, hepatic, or malignant disease, as determined by the investigator.
8. Subject has suitable venous access for blood sampling.
9. Subject is able and willing to complete the study and to comply with all study instructions and attend the necessary visits.
10. Male subjects and their partners must agree and commit to use a barrier method of contraception throughout the study and for 90 days after last study drug application.
11. A negative urine pregnancy test (UPT) result for all WOCBP at the Screening Visit and Baseline Visit. A WOCBP is one who is not permanently sterilized or not postmenopausal. Postmenopausal is defined as 12 months with no menses without an alternative medical cause.
12. Sexually active women must agree to use the following throughout the study and for 30 days after last study drug application. WOCBP who are not sexually active at Baseline and become sexually active must identify a plan for contraception.
    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; contraceptive sponge.
13. Males subjects must refrain from sperm donation during the study treatment period and until 90 days after last study drug application.

4.2. Exclusion Criteria

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

1. Female subject who is breast feeding, pregnant, or planning to become pregnant.
2. Subject who has an IGA score of 2 (mild) or 4 (severe).
3. Subject with history of known or suspected intolerance to the drug product excipients (hexamethyldisiloxane, polypropylene glycol (PPG) 15 stearyl ether, silicone gum, and isopropyl alcohol).
4. Subject has any clinically significant active infection in the investigator's opinion. This includes active impetigo at any AD lesion.
5. Subject has known Hepatitis-B, Hepatitis-C, or HIV infection.
6. Subject has excessive body or facial hair that would interfere with the evaluation of safety or with the diagnosis or assessment of AD.
7. 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 AD lesions.
8. Subject has clinically significant or severe allergies that in the investigator's opinion would interfere with participation in the study.
9. Subject has known intolerability to topical treatments e.g., reports excessive burning/stinging or pain with use of topical treatments.
10. Subject has an active or potentially recurring skin conditions(s) other than AD that in the investigator's opinion would interfere with participation in the study.
11. Subject has unstable AD consistent with a requirement for high-potency corticosteroids.
12. Subject has used dupilumab (Dupixent) within 12 weeks prior to the Baseline Visit.
13. Subject has used any biologic therapy, other than dupilumab, within 28 days prior to the Baseline Visit.
14. Subject has used systemic (oral, IV or IM) corticosteroids within 28 days prior to the Baseline Visit. Intra-articular injection for arthroses allowed.
15. Subject has used topical anti-pruritics (e.g., PDE4 inhibitors) within 28 days prior to the Baseline Visit.
16. If subject is taking oral antihistamines, subject has not been on a stable dose of oral antihistamines within 28 days prior to the Baseline visit.
17. Subject has used phototherapy, tanning beds, or any other artificial light device within 28 days prior to the Baseline Visit.
18. Subject has used topical corticosteroids within 14 days prior to the Baseline Visit.
19. Subject has used topical calcineurin inhibitors within 14 days prior to the Baseline Visit.
20. Subjects has used barrier creams (e.g., Mimyx, Atopiclair), within 7 days prior to the Baseline Visit.

21. Subject has an underlying disease that requires the use of interfering topical or systemic therapy.
22. 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, acne or rosacea.

Note: Treatment with any of the medications noted in Exclusion 11 through 22 is prohibited throughout the study. Use of bland emollients once daily to manage dry skin areas around, but not overlapping, the treatable AD involved areas is acceptable.

23. 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 or interfere with the subject's participation in the study. This may include respiratory (including chronic unstable asthma requiring repetitive drug interventions or hospitalization), gastrointestinal, renal, hepatic, haematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, or connective tissue diseases or disorders. Subjects with other dermatologic conditions, including genetic syndromes that have an eczematous dermatitis as a component of the disease (e.g., Netherton's) are excluded.
24. 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.
25. 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.
26. Subject has participated in another investigational drug or device research study within 30 days of the Screening Visit or five half-lives of the drug, whichever is longer.
27. Any other reason that would make the subject, in the opinion of the Investigator or sponsor, unsuitable for the study.

4.3. 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 85 Visit prior to subject withdrawal. Subjects may be replaced after consultation with the sponsor.

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.

- Decision by the investigator or sponsor that termination is in the subject's best medical interest or 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.

4.4. 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 Human Research Ethics Committee (HREC) or Institutional Review Board (IRB) 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 with 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 HREC/IRB.

5. STUDY DRUG

5.1. Study Drug

5.1.1. 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 PCI Pharma Services (PCI) 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.

5.1.2. Formulations, Appearance, Packaging, and Labeling

Botanix Pharmaceuticals' BTX 1204 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. [Olah 2014] CBD is chemically synthesized under Good Manufacturing Practices (GMP) for use in this study.

BTX 1204 4% Liquid Formulation (active) is a clear to slightly yellow liquid solution with a 4% (w/w) concentration of CBD in a formulation of excipients, which have been used extensively in other topical products. These excipients include hexamethyldisiloxane, silicone gum, polypropylene glycol (PPG) 15 stearyl ether, and isopropyl alcohol (IPA). The solution spreads easily and quickly evaporates leaving the CBD on the skin.

Each milliliter of the BTX 1204 4% (w/w) Liquid Formulation contains 30.0 mg of CBD. The Vehicle will be identical to the BTX 1204 4% (w/w), but without the CBD.

Study drug, active and vehicle, will be supplied in 125 mL multi-dose, metered pumps delivering 0.5 mL per actuation. Each pump will contain approximately 100 mL of study drug. Each subject will apply up to 7 mL per dose. This will require 14 actuations of the pump. Each dose will cover all the subject's AD lesions (except scalp and groin).

Pumps for all groups will be labeled identically, except for kit number and bottle number, to maintain the blind.

Study drug will be applied directly to the AD lesion and spread to cover the AD lesion and up to 1 cm of the surrounding non-lesional skin. For lesions that cannot be accessed for direct application, study drug will be pumped into the palm of one hand and applied to the AD lesions.

Adequate study drug will be provided in kits for daily applications (BID) through 4 weeks (Day 28). Prior to distribution, pumps will be weighed by clinical site staff and the weights recorded in the source documents and the eCRF. 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 29 and Day 57 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 29, Day 57, and Day 85 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 1204 or Vehicle
Directions: Use in accordance with study drug application instructions.
FOR TOPICAL APPLICATION ONLY.
Protocol # BTX.2018.003
Flammable. Store between 15-30°C.
Bottle # _____
Kit # _____
Sponsor: Botanix Pharmaceuticals Ltd

5.1.3. 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.

5.1.4. Preparation

No preparation of the study drug is required.

5.1.5. 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 unlock the pump and apply the first dose of the study drug to the subject's AD lesions. Study drug will be applied to the lesions and up to 1 cm of surrounding non-lesional skin. Study drug will not be applied to AD lesions located on the scalp and the groin.

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 approximately 8 to 12 hours later. Subjects will apply study drug at the clinical site during the Day 15, Day 29, and Day 57 Visits. A diary will be maintained documenting compliance with the self-administered applications. All study drug pumps (used and unused) will be returned to the clinical site and weighed on the Day 29, Day 57, and Day 85 Visits.

Study drug should not be applied to the eyes or mouth. If study drug accidentally gets into the eyes, the subject should flush their eyes with clear, running water. 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.

5.1.6. Starting Dose

The dose for all subjects will be up to 7 mL applied BID to cover their AD lesions and surrounding skin, except on the scalp and the groin. No escalation of dose will occur.

5.1.7. Dose Adjustments/Modifications/Delays

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

5.1.8. Duration of Therapy

Subjects will receive BID application of study drug for 84 days with a final application on the evening of Day 84 for a total of 168 doses. If the Day 85 Visit is delayed, the subject should continue dosing through the evening before the scheduled Day 85 Visit.

5.1.9. 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 pumps (used and unused) at visits 29, 57, and 85. The clinical site staff will review the diary and count and weigh used/unused pumps to ensure subject compliance with dosing.

5.2. 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. In case of drug accountabilities discrepancies (missing pump, lost pump or non-compliance cases in which more product was used compared to expected use), investigators should obtain more information and explanation from the subjects.

6. STUDY PROCEDURES AND SCHEDULE

6.1. Study Specific Procedures/Evaluations

At the Screening Visit (Visit 1), all subjects 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 and weight, and a medical history will be obtained by the principal investigator or designee.
- 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 (UDS) will be conducted to ensure that the subject is not taking drugs of abuse.
- The total body surface area (BSA) of atopic dermatitis involvement will be obtained. The BSA can be approximated using the Rule of 9s or the palm (1%) method.
- An IGA will be conducted. The subject must have an IGA score of moderate (3) (see Table 2).
- 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.
- Eligibility criteria will be reviewed to determine if subjects may proceed to study enrollment.
- At selected sites, a target lesion will be identified. Photographs will be obtained of the target lesion and the target lesion will be scored used the Signs of AD scoring.

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
- Signs of AD score will be assessed (See Table 3).
- 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.

Efficacy will be assessed through collection of the IGA, Signs of AD score, BSA of AD, EASI score, and changes in pruritus. An IGA will be conducted at Screening to ensure subject eligibility and again at Baseline (if not same day as Screening Visit) and Days 15, 29, 57 and 85. The IGA assesses the overall status of the AD lesions at the time of the assessment. Every effort should be made to have the IGA conducted by the same investigator/sub-investigator at each visit. No comparisons are made to previous assessments. The IGA is scored from 0 (Clear) to 4 (Severe) based on scoring system provided in Table 2.

Table 2 Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD™)[a]

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting. Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 - Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. *In indeterminate cases, please use extent to differentiation between scores*
   For example:
   - *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*
2. *Excoriations should not be considered when assessing disease severity.*

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The Signs of AD score will be an examination of all lesions on the subject for the presence of erythema, exudation, excoriation, induration/papulation, and lichenification. Each sign will be graded according to the grade and definitions provided in Table 3.

Table 3 Signs of Atopic Dermatitis (Paller)

Score	Grade	Definition
Erythema (redness)		
0	None	No redness
1	Mild	Mildly detectable erythema; pink
2	Moderate	Dull red; clearly distinguishable
3	Severe	Deep, dark red; marked and extensive
Exudation (oozing and crusting)		
0	None	No oozing or crusting
1	Mild	Minor or faint signs of oozing
2	Moderate	Definite oozing or crusting
3	Severe	Marked and extensive oozing or crusting
Excoriation (evidence of scratching)		
0	None	No evidence of excoriation
1	Mild	Mild excoriation
2	Moderate	Definite excoriation
3	Severe	Marked, deep, or extensive excoriation
Induration/papulation		
0	None	None
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Lichenification (epidermal thickening)		
0	None	No epidermal thickening
1	Mild	Minor epidermal thickening
2	Moderate	Moderate epidermal thickening; accentuated skin lines
3	Severe	Severe epidermal thickening; deeply accentuated skin lines

The EASI score will be conducted by the principal investigator or an appropriately trained designee to obtain a score to measure the extent (area) and severity of AD. EASI will be scored using the area score for each of the four regions (head and neck, trunk, upper limbs, and lower limbs) of the body. The area score is the percentage of skin affected by atopic dermatitis (eczema) for each body region:

Area score:	Percentage of skin affected by eczema in each region
0	No active eczema in this region
1	1–9%
2	10–29%
3	30–49%
4	50–69%
5	70–89%
6	90–100%: the entire region is affected by eczema

At each study visit, the subject will complete the Itch Numeric Rating Score (I-NRS).

I-NRS

The subject will be asked, "How would you rate your AVERAGE itch in the past 24 hours, on a scale from 0 to 10, where 0 is No itch and 10 is Worst itch imaginable?"

Prior to morning application of the study drug, the subject will record in their diary the Worst Itch Numeric Rating Score (WI-NRS).

Each day the subject will complete the Worst-Itch Numeric Rating Score (WI-NRS).

WI-NRS

The diary question will read, "How would you rate your WORST itch in the past 24 hours, on a scale from 0 to 10, where 0 is No itch and 10 is Worst itch imaginable?"

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. In addition, subjects will be required to return all used and unused study drug at 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 of study drug used.

6.2. Laboratory Procedures/Evaluations

6.2.1. Clinical Laboratory Evaluations

For all subjects, a CBC, chemistry, and urinalysis will be conducted at the Baseline and Day 85 Visits. If an abnormal laboratory assessment is returned from the Baseline assessments, consideration will be given by the investigator as to the continued participation of the subject in the study. 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 29, 57, and 85 Visits. The assessment will be done using a test kit with a minimum sensitivity of 25 mIU/mL. Details for collecting and testing urine for the UPT are provided in the Laboratory Manual.

6.2.2. Specimen Preparation, Handling, and Storage

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

6.3. Study Schedule

6.3.1. Screening Visit

At the Screening Visit (Day -28 to Day 1), the following will be conducted:

- Obtain written informed consent/assent
- Conduct medical history and review of systems
- Obtain subject's demographics
- Obtain subject's height and weight
- Conduct UPT (WOCBP only)
- Collect urine sample for UDS
- Perform IGA
- Calculate BSA of total AD involvement
- Identify a target lesion (selected photography sites only)
- 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 prior to the Baseline Visit. Subjects found to be ineligible will be screen failed and the reason for screen failure will be recorded. Subjects that do not meet eligibility requirements (e.g. require washout from prohibited medications or have an active infection) may be re-screened once they meet eligibility requirements (e.g. washed out from the prohibited medication(s) or cleared an active infection).

6.3.2. Baseline Visit

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

- Collect blood sample for CBC and chemistry
- Collect urine sample for urinalysis
- Assess Signs of AD prior to application of study drug
- Collect EASI score prior to application of study drug
- Collect I-NRS prior to application of study drug
- Randomize subject to study drug treatment
- Apply study drug on subject's AD lesions (see Section 5.1.5)
- Monitor subject for AEs 15 minutes after application of study drug
- Photographs and Signs of AD scoring of target lesion (selected sites only)
- Train subject in proper application of study drug
- Weigh and dispense study drug
- Dispense study diary (Day 1 through Day 28) and train the subject in entering administration times and daily pruritus score.

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
- Review medical history and review of systems
- Query subject for adverse events since the signing of the informed consent/assent and changes in concomitant medications
- Collect blood sample for CBC and chemistry
- Collect urine sample for urinalysis
- Conduct UPT (WOCBP only)
- Collect urine sample for UDS
- Perform IGA prior to application of study drug
- Calculate BSA of total AD involvement
- Assess Signs of AD score prior to application of study drug
- Collect EASI score prior to application of study drug
- Collect I-NRS prior to application of study drug
- Photographs and Signs of AD scoring of target lesion (selected sites only)
- Randomize subject to study drug treatment
- Apply study drug on subject's AD lesions (see Section 5.1.5)
- Monitor subject for AEs 15 minutes after application of study drug
- Train subject in proper application of study drug
- Weigh and dispense study drug

- Dispense study diary (Day 1 through Day 28) and train the subject in entering administration times and daily pruritus score.

6.3.3. Study Drug Application Period

At the Day 1 Visit, the subject will receive their first study drug application at the clinical site during the Baseline Visit. Subjects will be trained in the correct application of the study drug and provided an ample supply of study drug to complete BID dosing through Day 28. The first application of study drug will occur in the morning and the second application approximately 8 to 12 hours later. A diary will be maintained documenting compliance with application of the self-administered application and daily pruritus score. At the Day 29 Visit, the subject will be provided an ample supply of study drug to complete dosing through Day 56. At the Day 57 Visit, the subject will be provided an ample supply of study drug to complete dosing through Day 84. The final application of study drug will be applied by the subject on the evening of Day 84 or, if the Day 85 Visit is delayed, the evening prior to the Day 85 Visit.

6.3.4. Day 15 Visit

The Day 15 Visit is conducted to ensure the continuing safety of the subject and to monitor compliance with the BID application of study drug. Subjects will be instructed to not apply their morning application of study drug until they are seen in the clinic. If the clinic visit is in the afternoon, the subject should apply their regular morning application and apply the evening application in the clinic, as long as the dose is at least 6 hours after the morning dose. At the Day 15 Visit (Day 15 ± 3 days) the following will be conducted.

- Query subject for any AEs which have occurred since the last visit
- Query subject for changes in concomitant medications
- Perform IGA prior to application of study drug
- Calculate BSA of total AD involvement
- Assess Signs of AD score prior to application of study drug
- Collect EASI score prior to application of study drug
- Collect I-NRS prior to application of study drug
- Photographs and Signs of AD scoring of target lesion (selected sites)
- Have subject apply study drug on their AD lesions (see Section 5.1.5)
- Review study diary and confirm compliance with study drug applications
- Confirm compliance with study drug applications by weighing pumps

6.3.5. Day 29 Visit

Subjects will be instructed to not apply their morning application of study drug until they are seen in the clinic for the Day 29 Visit. If the clinic visit is in the afternoon, the subject should apply their regular morning application and apply the evening application in the clinic, as long as the

dose is at least 6 hours after the morning dose. At the Day 29 Visit (Day 29 ± 3 days) the following will be conducted.

- Query subject for any AEs which have occurred since the last visit
- Query subject for changes in concomitant medications
- Conduct UPT (WOCBP only)
- Perform IGA prior to application of study drug
- Calculate BSA of total AD involvement
- Assess Signs of AD prior to application of study drug
- Collect EASI score prior to application of study drug
- Collect I-NRS prior to application of study drug
- Photographs and Signs of AD scoring of target lesion (selected sites only)
- Have subject apply study drug on their AD lesions (see Section 5.1.5)
- Collect study drug and study diary and confirm compliance with study drug applications by weighing returned pumps
- Dispense study diary (Day 29 through Day 56)
- Weigh and dispense study drug.

6.3.6. Day 57 Visit

Subjects will be instructed to not apply their morning application of study drug until they are seen in the clinic for the Day 57 Visit. If the clinic visit is in the afternoon, the subject should apply their regular morning application and apply the evening application in the clinic, as long as the dose is at least 6 hours after the morning dose. At the Day 57 Visit (Day 57 ± 5 days) the following will be conducted:

- Query subject for any AEs which have occurred since the last visit
- Query subject for changes in concomitant medications
- Conduct UPT (WOCBP only)
- Perform IGA prior to application of study drug
- Calculate BSA of total AD involvement
- Assess Signs of AD score prior to application of study drug
- Collect EASI score
- Collect I-NRS
- Photographs and Signs of AD scoring of target lesion (selected sites only)
- Have subject apply study drug on their AD lesions (see Section 5.1.5)
- Collect study drug and study diary and confirm compliance with study drug applications by weighing returned pumps
- Dispense study diary (Day 57 through Day 84)
- Weigh and dispense study drug.

6.3.7. Day 85 Visit/End of Study Visit

The final application of study drug will occur on the evening prior to the Day 85 Visit. If the Day 85 visit is delayed, the subject should continue BID application until the evening before the Day 85 Visit. At the Day 85 Visit (Day 85 ± 5 days), the following will be conducted:

- Collect and weigh returned study drug pumps
- Collect study diary
- Query subject for adverse events that occurred since the previous visit
- Query subject for changes in concomitant medications
- Collect blood sample for CBC and chemistry
- Collect urine sample for urinalysis
- Conduct UPT (WOCBP only)
- Perform IGA
- Calculate BSA of total AD involvement
- Assess Signs of AD score
- Collect EASI score
- Collect I-NRS
- Photographs and Signs of AD scoring of target lesion (selected sites only)
- Discharge subject from study

6.3.8. 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 85 Visit.

6.3.9. Schedule of Events Table

The Schedule of Events is provided in Table 4.

Table 4 Time and Events Schedule

Parameter	Screening Visit[a] (-28 to Day 1)	Baseline Visit (Day 1)	Day 15 Visit (Day 15 ±3 day)	Day 29 Visit (Day 29 ±3 days)	Day 57 Visit (Day 57 ±5 days)	Day 85 Visit[b] (Day 85 ±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	X[a]				
Demographics	X					
Height and weight measurement	X					
Urine pregnancy test (WOCBP only)	X	X[a]		X	X	X
Urine drug screen	X	X[a]				
Eligibility criteria review	X	X[a]				
IGA	X	X[a]	X	X	X	X
Body Surface Area (BSA) of AD	X	X[a]	X	X	X	X
Signs of AD score		X	X	X	X	X
EASI score		X	X	X	X	X
Pruritus Score (I-NRS)		X	X	X	X	X
Laboratory blood draw (CBC and chemistry)		X				X
Urine collection for urinalysis		X				X
Photographs and Signs of AD scoring of target lesion (selected sites)		X	X	X	X	X
Randomize subject		X				
Study drug administration in clinic		X	X	X	X	
Study drug administration at home		Day 1 pm to Day 84 pm; final application prior to Day 85 Visit				
Concomitant medications query	X	X[a]	X	X	X	X
Adverse experience query		X	X	X	X	X
Weigh and Dispense study drug		X		X	X	
Collect and Weigh study drug			X[c]	X	X	X
Dispense Diary		X		X	X	
Collect Diary and review compliance			X[c]	X	X	X

[a] If subject meets eligibility criteria, Screening and Baseline Visit can occur on the same day. If Screening and Baseline Visit are not concurrent, review of eligibility, Review of Systems, UPT, UDS, BSA of AD, IGA, and concomitant medications query will be repeated at the Baseline Visit.

[b] If subject discontinues treatment early, Day 85 evaluations will be performed when possible.

[c] On Day 15, review compliance only.

6.4. 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 containing products will be reported.

Subjects will use their normal soaps or body washes throughout the study. Changes in soaps and body washes during the study should not occur. Subjects will be instructed to wash their body prior to the Baseline, Day 15, Day 29, and Day 57 Visits. The body should 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 and moisturizers throughout the entire course of the study. Detailed dosing instructions will be provided to the subject.

6.5. Prohibited Medication, Treatment, and Procedures

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

- Treatable AD lesions cannot be washed or shaven 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 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 are permitted)
- Use of any topical agent, other than study drug, to treat AD.
- Use of any oral medication for the treatment of AD.
- Use of any medication that, in the opinion of the investigator, may affect the evaluation of the study product or place the subject at undue risk.
- Use of topical or oral antibiotics. If a subject gets an infection during the study that requires topical or oral antibiotics, the subject can be treated and allowed to remain on the study. The antibiotic use will be noted as a deviation.
- Photodynamic therapy.
- Use of tanning beds.

Subjects may use bland emollients to manage dry skin areas around, but not overlapping, the treatable AD lesions. Sunscreens may be applied to the skin areas around, but not overlapping, the treatable AD lesions.

Subjects should limit exposure of the treatment area to sunlight during the study. Suitable clothing and other protective garments should be worn throughout the study.

Subjects must not shower or wash the study application area for 1 hour after application of study drug. Subjects should avoid swimming and heavy exercise for 1 hour after application of study drug.

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

6.6. Rescue Medication, Treatments and Procedures

Systemic medications for treatment of AD are prohibited (see Section 6.5). If a subject is unable to continue the study without additional treatment for the lesion areas, or if they require systemic treatment, the appropriate treatment should be administered. Exacerbation of AD will be recorded as an AE. The site will notify the study monitor immediately if this occurs. The subject's continuation on the study will be decided on a case-by-case basis.

6.7. 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.

7. ASSESSMENT OF SAFETY

7.1. Specification of Safety Parameters

7.1.1. 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.

7.1.2. 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.

7.2. Classification of Adverse Events

7.2.1. 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 IB). • 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.

7.2.2. 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 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.

7.2.3. Expectedness

For this study, all AEs will be recorded.

The safety and tolerability of BTX 1204 4% (w/w) Solution was evaluated in a Phase 1b study in subjects with mild to moderate atopic dermatitis. This study demonstrated that BTX 1204 4% was safe and well tolerated with up to 3 mL applied BID for up to 28 days. Adverse events reported as related to study drug treatments were administration site conditions including application site erythema, application site pruritus, and application site pain.

Studies of the active ingredient (CBD) administered orally in multiple therapeutic settings has described no consistent findings for systemic AEs. Based on findings in previous studies of CBD, mild skin irritation may occur (see IB for details).

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

All AEs occurring after signing of the consent form through completion of Day 85 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 must 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 not meeting the criteria for SAEs will be recorded. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be recorded in the Medical History eCRF and will be considered as Baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

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.

7.4. Reporting Procedures

7.4.1. 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.

7.4.2. Serious Adverse Event Reporting

Each AE will be independently judged by the investigator in terms of seriousness**.** A SAE is defined in Section 7.1.2.

All SAEs will be reported to the sponsor via e-mail or phone call 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 HREC/IRB 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.

7.4.3. 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. Pregnancy will be followed until the outcome of the pregnancy is known (i.e. miscarriage, abortion or birth), and the newborn condition is reported. No further follow up is required after birth unless specifically requested by the medical monitor. It will be the responsibility of the study's Medical Monitor to follow the subject after the subject's withdrawal from the study.

7.5. Safety Oversight

Oversight of the safety of the study will be the responsibility of the Medical Monitor. No Data Safety Monitoring Board (DSMB) will be convened for this study. Safety data will be regularly reviewed (monthly at a minimum). If unexpected safety signals are observed, the Medical Monitor, the sponsor, and the HREC/IRB, if necessary, will determine if the study requires a pause to further assess the safety signal or termination.

8. 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 Premier Research.

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. Comprehensive source data verification (100%) will be conducted. 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. The sponsor will be provided copies of the draft monitoring reports within 10 days of 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 distribution of monitoring reports.

Independent audits may be conducted by Premier Research auditors, the sponsor, or regulatory agencies to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

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 summarized 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 2a study is to describe the safety and efficacy of treatment with the BTX 1204 4% Liquid Formulation vs Vehicle with BID dosing in subjects with moderate atopic dermatitis. Exploratory analysis of the study drug's effect on AD will be evaluated. None of these assessments will use hypothesis testing to assess their treatment effect.

Should any post-hoc statistical analyses be conducted to present study outcomes, the methods for analysis will be described in the final clinical study report.

9.3. Description of Statistical Methods

9.3.1. General Approach

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 ITT analysis set will consist of all randomized subjects with at least one post-baseline efficacy assessment and will be based on randomized study group, regardless of study drug received. The PP analysis set will be used to support the efficacy findings in the ITT analyses and will include subjects with no major protocol deviations. Safety conclusions will be drawn from the safety analysis set. The safety analysis set will include all subjects that received at least one application of study drug and had at least one post-baseline safety assessment with treatment based on study drug received regardless of randomization group.

Demographics will be summarized using the safety analysis set by baseline age, gender, race, ethnicity, height, and weight. The primary efficacy analysis will be conducted on the ITT population. 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.

9.3.2. Safety Analyses

Safety analyses will include summaries of AEs, TEAEs, serious AEs (SAEs), and changes in laboratory assessments. AEs, TEAEs and SAEs will be coded using the MedDRA dictionary and 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.

Changes in laboratory parameters from Baseline to Day 85 will be summarized using shift tables to evaluate for trends. Abnormal laboratory findings will be summarized and listed by subject.

Concomitant medications 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.

9.3.3. Efficacy Analyses

The efficacy variables include the IGA, BSA of AD, Signs of AD score, EASI score, and pruritus scores (I-NRS) collected at Screening/Baseline and all subsequent study visits and the WI-NRS recorded daily by subjects.

The primary efficacy endpoint for the study is the proportion of subjects with IGA success defined as an IGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline at Day 85. The IGA will be dichotomized into "success" and "failure" at study Day 15, Day 29, Day 57, and Day 85. Success on IGA defined as a score of Clear (0) or Almost Clear (1) and at least a 2-grade improvement from Baseline at Day 15, Day 29, Day 57, and Day 85 will be analyzed using logistic regression, adjusting for Baseline IGA.

Summary statistics will be prepared for the change from Baseline in the percent of BSA affected by AD at Days 15, 29, 57, and 85. The change from Baseline in BSA of AD will be analyzed used ANCOVA with Baseline BSA of AD and treatment as covariates.

Summary statistics will be presented for the change from baseline in each of the Signs of AD scores (erythema, exudation, excoriation, induration/papulation, and lichenification) at each timepoint (Day 15, Day 29, Day 57 and Day 85). A total score will be calculated based on the sum of each of the Signs of AD (0, 1, 2, or 3; max score of 15) and the change from baseline will be summarised for each timepoint. The change from baseline in Signs of AD score at Day 15, Day 29, Day 57, and Day 85 will be analyzed used ANCOVA with Baseline Signs of AD score and treatment as covariates.

The proportion of subjects with an EASI 50 and EASI 75 score will be summarized at Day 15, Day 29, Day 57, and Day 85 and compared using logistic regression, adjusting for Baseline EASI score. Summary statistics will be prepared for the change from Baseline in the EASI score and I-NRS at each timepoint (Day 15, Day 29, Day 57 and Day 85).

Summary statistics will be prepared for the change from Baseline in the Signs of AD score for the target lesion (selected sites) at each timepoint (Day 15, Day 29, Day 57 and Day 85).

Summaries of the pruritus scores (WI-NRS) reported by the subjects in the daily Patient Diary will be presented using daily means by treatment and with graphic presentations.

The percent change from Baseline the EASI will be presented along with the subject's report of pruritus obtained from the Patient Diary. Time to improvement of pruritus and subject's assessment of the change in their AD from Baseline to Day 85 will be presented.

9.3.4. Adherence and Retention Analyses

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

9.3.5. Baseline Descriptive Statistics

Demographics/Baseline characteristics will be summarized by age, gender, race, ethnicity, height, weight, and BSA of AD. The year of AD diagnosis will be captured to calculate and summarize the duration of AD.

9.3.6. Planned Interim Analyses

No formal interim analysis is planned. Blinded subject data will be reviewed as it is generated to monitor for any safety signals and to ensure that the study is being appropriately executed.

9.3.7. Multiple Comparison/Multiplicity

This Phase 2a study is designed to identify the response to BTX 1204 relative to vehicle. Statistical tests applied to the outcomes will be exploratory. No adjustments for Type 1 error will occur.

9.3.8. 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 sensitivity analyses.

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

9.3.9. Tabulation of Individual Response Data

Individual response data will be presented in data listings.

9.4. Sample Size

The sample size for this study is based on clinical considerations only. Subjects will be randomized 1:1 with 100 subjects in each treatment group for a total 200 subjects. This is considered adequate to evaluate the safety and tolerability and preliminary information on efficacy

of twice daily BTX 1204 4% in the treatment of moderate atopic dermatitis in subjects aged 12 to 70 years of age.

9.5. Measures to Minimize Bias

9.5.1. Enrollment/Randomization/Masking Procedures

A randomization code will be prepared by an unblinded statistician. This statistician will be the only person aware of the randomization code. Randomization will be 1:1 (100 active: 100 vehicle) and done by site. Once a subject is deemed eligible to enroll, randomization will occur. The site will contact the IWRS to receive the kit/bottle number(s) to be used for that subject throughout the study.

Study drug, active or vehicle, will be labelled identically except for the kit/bottle numbers. All bottles of study drug will contain 100 mL of either BTX 1204 4% (w/w) Liquid Formulation or Vehicle. The vehicle study drug is indistinguishable from the active study drug.

9.5.2. 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. Sealed, unblinding envelopes will be maintained at the investigators' site only for circumstances where the CRO or sponsor cannot be contacted and the subject is in imminent danger without knowledge of their treatment.

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

10. QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site 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.

11. 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.

11.1. Regulatory, Ethical, and Study Oversight Considerations

11.1.1. 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.

11.1.2. 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.

11.1.3. 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 12.1.1.

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.

11.1.4. 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 a target lesion 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 face will not be included in the photos. 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.

11.1.5. 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.

11.1.6. 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 a target lesion 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 and distributed in Australia by PCI Pharma Services for Australian sites. In the United States, The Coghlan Group (TCG; Bastrop, Texas, USA) is responsible for packaging, labeling, and distribution of the study drug for US sites.

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.

12. DATA HANDLING AND RECORD KEEPING

12.1.1. Data Handling and Record Keeping

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.

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.

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.

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 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.

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.

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.

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.

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.

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.

12.1.2. 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.

12.1.3. 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.

12.2. 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.

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APPENDIX A – CRITERIA OF HANNIFIN AND RAJKA

Hanifin and Rajka Diagnostic Criteria for Atopic Dermatitis (AD)

Major criteria: Must have three or more of:

1. Pruritus
2. Typical morphology and distribution

- Flexural lichenification or linearity in adults
- Facial and extensor involvement in infants and children

3. Chronic or chronically-relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor criteria: Should have three or more of:

1. Xerosis
2. Ichthyosis, palmar hyperlinearity, or keratosis pilaris
3. Immediate (type 1) skin-test reactivity
4. Raised serum IgE
5. Early age of onset
6. Tendency toward cutaneous infections (especially *S aureus* and herpes simplex) or impaired cell-mediated immunity
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor or facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental or emotional factors
23. White dermographism or delayed blanch