CLINICAL STUDY PROTOCOL

Protocol Title: "A Double-Blind, Pilot Study to Evaluate the Efficacy and Safety of Topical AFX 5931 in the Treatment of Mild to Moderate Hand Dermatitis"

Protocol Identifier: CCCR 08-2018

Version Date: 09 May 2018
Version: 1.0

Sponsor:
Afecta Pharmaceuticals

STATEMENT OF CONFIDENTIALITY

CLINICAL STUDY PROTOCOL

Protocol Number:	CCCR 08-2018
Protocol Title:	A Double-Blind, Pilot Study to Evaluate the Efficacy and Safety of Topical AFX 5931 in the Treatment of Mild to Moderate Hand Dermatitis
Phase:	Pilot – Investigator Initiated Trial (IIT)
Investigational Product:	1. Topical AFX 5931
Study Sponsor:	Afecta Pharmaceuticals
Principal Investigator:	Mark Steven Nestor, M.D., Ph.D. Center for Clinical and Cosmetic Research 2925 Aventura Boulevard, Suite 205 Aventura, Florida 33180
Current Version and Date:	Original Protocol – 09 May 2018

The study will be conducted according to the protocol and in compliance with Good Clinical Practice, USFDA ICH E6, ICH Harmonised Tripartite and all other applicable regulatory requirements.

SPONSOR SIGNATURE PAGE

This trial is a double-blind, pilot study to evaluate the efficacy and safety of topical AFX 5931 in the treatment of mild to moderate hand dermatitis.

I agree to conduct this trial in accordance with the requirements of the Clinical Study Protocol and also in accordance with current versions of the following:

- Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000, Note of Clarification on Paragraph 29 added by the World Medical Association General Assembly, Washington 2002)
- The International Conference on Harmonisation (ICH) harmonized tripartite guideline regarding Good Clinical Practice (GCP) (E6 Consolidated Guidance, April 1996)
- Code of Federal Regulation
- Local Laws and Regulations

Sponsor Representative: Bruce W Kovacs, MD
Afecta Pharmaceuticals
2102 Business Center Drive
Irvine, CA
92612

_____ _____
Sponsor Representative Date

INVESTIGATOR ACKNOWLEDGEMENT

INVESTIGATIONAL PRODUCT:

1. Topical AFX 5931

STUDY TITLE: "A Double-Blind, Pilot Study to Evaluate the Efficacy and Safety of Topical AFX 5931 in the Treatment of Mild to Moderate Hand Dermatitis"

PROTOCOL IDENTIFIER: CCCR 08-2018

I have read and understand this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, understand and abide by the requirements for maintenance of source documentation, and provide assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, Code of Federal Regulation, and all applicable regulatory requirements.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this study. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the Sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____ _____

Principal Investigator Date

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PROTOCOL SYNOPSIS

Protocol Title:	A Double-Blind, Pilot Study to Evaluate the Efficacy and Safety of Topical AFX 5931 in the Treatment of Mild to Moderate Hand Dermatitis
Protocol Number:	CCCR 08-2018
Phase/Type:	Pilot - Investigator Initiated Trial (IIT)
Principal Investigator:	Mark Steven Nestor, M.D., Ph.D. Center for Clinical and Cosmetic Research 2925 Aventura Boulevard, Suite 205 Aventura, Florida 33180
Study Center(s):	One (1) study center in the United States: Center for Clinical and Cosmetic Research 2925 Aventura Boulevard, Suite 205 Aventura, Florida 33180
Objectives:	*Primary Objective*: 1. To measure the efficacy of topical AFX 5931 in the treatment of mild to moderate hand dermatitis in subjects 12 years of age and older *Secondary Objective*: 2. To measure the tolerability and safety of topical AFX 5931 in the treatment of mild to moderate hand dermatitis in subjects 12 years of age and older
Study Design:	This is a double-blind, pilot study with 20 subjects to determine the tolerability and efficacy of topical AFX 5931 in the treatment of mild to moderate hand dermatitis. Subjects are screened up to 30 days before the baseline visit. Subjects who meet the eligibility criteria may qualify for the study. Subjects will be randomized in a 3:1 ratio to receive either the active or vehicle medication. 15 subjects will receive the active, therapeutic product and 5 subjects will receive the inactive, vehicle product. Subjects will complete 4 study visits according to the following 4-week timeline: Day [-30] – [-1] (Screening), Day 0 (Baseline), Day 14 (Follow-Up), Day 28 (Follow-up | ET | EOS). At Visit 2, IP will be dispensed and baseline readings of efficacy as well as safety/tolerability assessments will be obtained prior to application of the IP. Subjects will apply IP twice daily and compliance will be monitored by periodically reviewing the subject diary. The evaluations that will be used to measure efficacy of the product will be the Investigator's Global Assessment and Hand Eczema Severity Index. The Subject's Local Dermal Tolerability Assessment and Local Skin Reaction Assessment will be used throughout the course of the study to evaluate tolerability. Additionally, the actions that will be taken to evaluate safety will be the monitoring of adverse events, vital signs, and changes in concomitant medications. Digital photographs will be taken at each visit (excluding Visit 3).

Inclusion Criteria:	1. Subject is a male or non-pregnant female, 12 years of age and older. 2. Subject is willing and able to provide written informed consent for the study. 3. Subject is willing and able to apply the investigational product as directed, comply with study instructions and commit to all follow-up visits for the duration of the study. 4. Subject has clinical diagnosis of mild to moderate hand dermatitis for at least 3 months. 5. Subject has a baseline Investigator's Global Assessment (IGA) score of 2 or 3 (disease severity of mild or moderate). 6. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of hand dermatitis or which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation. 7. Women of childbearing potential (WOCBP) must use an effective method of birth control or must be post-menopausal or surgically sterile. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT) at Baseline.
Exclusion Criteria:	1. Subject is pregnant, lactating, or is planning to become pregnant during the study. 2. Subject is currently enrolled in an investigational drug or device study. 3. Subject has used an investigational drug or investigational device treatment within 30 days prior to Visit 2/Baseline. 4. Subject has active cutaneous bacterial or viral infection in any treatment area (clinically infected hand dermatitis) at Visit 2/Baseline. 5. Subject has used any of the following therapies within 30 days prior to Visit 2/Baseline: • Systemic corticosteroids (oral and injectable [intravenous and intramuscular]) (Intranasal and Inhalational steroids are allowed if use is kept constant during the study) • UVA/UVB therapy • PUVA (psoralen plus ultraviolet A) therapy • Immunomodulators or immunosuppressive therapies • Interferon • Cytotoxic drugs (e.g., methotrexate, cyclophosphamide, azathioprine) • Oral retinoids 6. Subject has used any of the following therapies within 14 days prior to Visit 2/Baseline: • Systemic antibiotics • Topical calcipotriene or other topical vitamin D preparations 7. Subject has used any of the following therapies within 7 days prior to Visit 2/Baseline: • Topical and oral antihistamines • Topical antibiotics • Topical corticosteroids • Topical antifungals 8. Subject has a history of sensitivity to any of the ingredients in the investigational product.

	9. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
Investigational Products:	**Medication Name:** 1. Active Treatment: Topical AFX 5931 - A medication combining a series of small, potent anti-inflammatory molecules that down-regulate the CCL5/CCL2 pro-inflammatory pathway 2. Vehicle
Patient Population:	- 20 healthy, adult male or non-pregnant female subjects - 12 years of age and older
Safety Endpoints:	Safety/tolerability endpoints are monitored by members of the study staff. They include the following: - Changes in local skin reaction - Changes in AEs and serious adverse events (SAEs) - Changes in vital signs and physical examinations - Changes in concomitant procedures/medications - Presence of signs/symptoms of irritation of the skin.
Statistical Methods:	- All analyses of the pooled individual patient data will be performed with the use of SPSS software using a two-way Chi-square test analysis, t-tests, odds ratios, and analysis of variance (ANOVA).
Assessments:	- Hand Eczema Severity Index o Investigator-rated: clinical evaluation of both the extent and intensity of hand dermatitis ▪ Clinical signs: erythema, infiltration/papulation, vesicles, figures, scaling, and edema ▪ Locations: fingertips, fingers (excluding tips), palms of hands, backs of hands, wrists ▪ Extent is graded on a visual 5-point scale ▪ Intensity is graded on a visual 4-point scale - Local Skin Reaction Assessment o Investigator-rated: clinical grading score of erythema, induration/papulation, and lichenification ▪ Each parameter is graded on a visual 4-point scale - Subject's Local Dermal Tolerability Assessment: o Subject-Rated: clinical grading score of pruritus ▪ Each parameter is graded on a visual 4-point scale - See assessments reference at end
Randomization:	- The subjects will be randomized to receive either the active or control medication based on a 3:1 randomization scheme - Out of 20 total subjects, 15 will receive the active treatment while 5 will receive the vehicle
Photography:	- Digital photographs will be taken at proximal and distal views of the dorsal as well as palmar surfaces of the hand

3 OBJECTIVES

3.1 Primary and Secondary Objectives

Primary Objective:

1. To measure the efficacy of topical AFX 5931 in the treatment of mild to moderate hand dermatitis in subjects 12 years of age or older
    a. Assessed via Hand Eczema Severity Index
    b. Assessed via Investigator's Global Assessment

Secondary Objective:

2. To measure the tolerability and safety of topical AFXC 5931 in the treatment of mild to moderate hand dermatitis in subjects 12 years of age or older
    a. Assessed via Subject's Local Dermal Tolerability Assessment
    b. Assessed via Local Skin Reaction Assessment
    c. Assessed via changes in adverse events or concomitant medications

3.2 Overview

This is a double-blind, pilot study with 20 subjects to determine the tolerability and efficacy of topical AFX 5931 in the treatment of mild to moderate hand dermatitis. Subjects are screened up to 30 days before the baseline visit. Subjects who meet the eligibility criteria may qualify for the study. Subjects will be randomized in a 3:1 ratio to receive either the active or control medication, in which 15 subjects will receive the active, therapeutic product and 5 subjects will receive the inactive, vehicle product. Subjects will complete 4 study visits according to the following 4-week timeline: Day [-30] – [-1] (Screening), Day 0 (Baseline), Day 14 (Telephone Call), Day 28 (Follow-up | ET | EOS). At Visit 2, IP will be dispensed and baseline readings of efficacy and safety/tolerability assessments will be obtained prior to application of the IP. Subjects will apply IP twice daily and compliance will be monitored by reviewing the subject diary periodically throughout the study. The assessments that will be used to evaluate efficacy of the product will be the Hand Eczema Severity Index and Investigator's Global Assessment. The Subject's Local Dermal Tolerability Assessment and Local Skin Reaction Assessment will be used throughout the course of the study to evaluate tolerability. Additionally, the actions that will be taken to evaluate safety will be the monitoring of any adverse events or concomitant medications. Digital photographs will be taken at each visit (excluding Visit 3).

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for this study:

1. Subject is a male or non-pregnant female, 12 years of age and older.
2. Subject is willing and able to provide written informed consent for the study.
3. Subject is willing and able to apply the investigational product as directed, comply with study instructions and commit to all follow-up visits for the duration of the study.
4. Subject has clinical diagnosis of mild to moderate hand dermatitis for at least 3 months.
5. Subject has a baseline Investigator's Global Assessment (IGA) score of 2 or 3 (disease severity of mild or moderate).
6. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of hand dermatitis or which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation.
7. Women of childbearing potential (WOCBP) must use an effective method of birth control or must be post-menopausal or surgically sterile. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT) at Baseline.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for this study:

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject is currently enrolled in an investigational drug or device study.
3. Subject has used an investigational drug or investigational device treatment within 30 days prior to Visit 2/Baseline.
4. Subject has active cutaneous bacterial or viral infection in any treatment area (clinically infected hand dermatitis) at Visit 2/Baseline.
5. Subject has used any of the following therapies within 30 days prior to Visit 2/Baseline:
    - Systemic corticosteroids (oral and injectable [intravenous and intramuscular]) (Intranasal and Inhalational steroids are allowed if use is kept constant during the study)
    - Immunomodulators or immunosuppressive therapies
    - Interferon
    - Cytotoxic drugs (e.g., methotrexate, cyclophosphamide, azathioprine)
    - Oral retinoids
6. Subject has used any of the following therapies within 14 days prior to Visit 2/Baseline:
    - Systemic antibiotics
    - Topical calcipotriene or other topical vitamin D preparations
    - Topical retinoids
7. Subject has used any of the following therapies within 7 days prior to Visit 2/Baseline:
    - Topical and oral antihistamines
    - Topical antibiotics
    - Topical corticosteroids
    - Topical antifungals
    - Other topical drug products
8. Subject has a history of sensitivity to any of the ingredients in the investigational product.

9. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.

4.3 Withdrawal and Replacement of Patients

Patients who withdraw consent must be withdrawn from the study. No justification for such a decision is required. Patients must be withdrawn from the study if the investigator considers it in the best interest of the patient that he/she be withdrawn. Patient must notify the principal investigator in writing at the time of their decision. The reasons for withdrawal must be recorded, if available, on the case report form (CRF) and in the patient's medical records. If possible, a complete, final examination should be performed on all patients who withdraw from the study. Patients who are withdrawn will not be replaced.

4.4 Patient Identification

All patients enrolled must be identifiable throughout the study. The investigator will maintain a personal list of patient numbers and patient names to enable records to be found at a later date.

Subjects will receive a patient number as detailed in a separate document located in the investigator's file. Patients who terminate their study participation for any reason after signing the consent form, regardless of whether study medication was taken or not, will retain their patient identification number. In that case, the next patient identification number and bottle in the sequence are to be used. The following patient is given the next patient identification number. Screen failures will not be assigned a patient identification number. Screen failures are not to interrupt the patient identification schema for the enrolled subjects.

5 STUDY MEDICATION

5.1 Identity

Trade Name:	AFX 5931
Manufacturer:	Afecta Pharmaceuticals

5.2 Maintaining the Blind

The subjects will be randomized to receive one of two treatments (active vs. control) in a 3:1 ratio. Thus, out of the total 20 subjects, 15 subjects will receive the active "AFX 5931" medication while 5 subjects will receive the vehicle product. Separate study staff members are assigned to administer the study medication versus conduct study evaluations.

5.3 Administration

The subject will be instructed on how to apply the IP independently for use throughout the rest of the study at the baseline visit (Visit 2).

5.4 Compliance

Subject compliance is based on attending every required study visit and completing applications of the medication twice daily starting from the baseline visit. Subjects will be required to qualify for the study honestly and return for all study visits. Subject will be required to fill out a record of IP applications on a subject diary, which must be filled out throughout the study. Any missing of visits or doses may qualify for withdrawal from the study under the Principal Investigator's discretion.

5.5 Concomitant Medications and Treatments

All medications or treatments ongoing at the screening visit or taken within the previous 30 days must be recorded on the prior and concomitant medications CRF.

Any medication the patient takes during his or her study participation is considered a concomitant medication. This applies to prescription and over-the-counter (OTC) drugs and to herbal supplements, whether taken systemically or applied topically. In addition, any treatment the patient receives other than the study medication is considered a concomitant treatment. All concomitant medications and concomitant treatments must be recorded in the CRFs. Prohibited medication classes and treatments are described in the Exclusion Criteria. In the event that a prohibited treatment is received, it must be documented on the CRFs.

Subjects will not be allowed to use any of the prohibited medications listed in the exclusion criteria during the course of this study and up to 30 days prior to the start of the study. Subjects will be allowed the use of birth control, vitamins, or supplements.

6 VARIABLES AND METHODS

6.1 Safety

6.1.1 Adverse Events

Illnesses present at study entry are considered pre-existing conditions and will be documented as medical history on the CRF provided. All adverse events, including intercurrent illnesses and worsening of pre-existing conditions, must be reported and documented as described below.

6.1.1.1 Definitions

An adverse event is any untoward medical event that occurs in a patient or subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the investigational product, whether or not related to the investigational product.

6.1.1.2 Assessment of Adverse Events

Volunteered, observed, and elicited reports of adverse events will be recorded. This includes adverse events the patient reports spontaneously, those the investigator observes, and those the investigator elicits in response to open-ended questions at the times indicated on the Schedule of Observations. At each visit, the patient should be asked a non-leading question such as: "Do you feel different in any way since your last treatment visit?" Subjects will also be questioned concerning possible skin reactions according to a specific checklist of possible adverse events.

Each adverse event will be assessed by the investigator with regard to the following categories.

Serious/Not Serious

International Conference on Harmonization (ICH) Guidelines and US Federal Regulations define a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. This means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires or prolongs hospitalization (hospitalization defined as ≥24 hours).
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization, but that may jeopardize the patient or require intervention to prevent one of the above outcomes, usually should also be considered serious. Events are considered serious if they result in life threatening events, death, genetic abnormality, persistent disability, or prolonged hospitalization. Examples include pregnancy, allergic bronchospasm requiring treatment at home or in the emergency room, and blood dyscrasias or convulsions not resulting in hospitalization. Medical and scientific judgment should be used to determine whether such events should be considered serious.

- Pregnancy should always be considered as a serious adverse event. As such, pregnancy should be recorded on the adverse event page of the CRF and a serious adverse event form completed and submitted as described.

Serious adverse events will be reported to the IRB/sponsor no more than 7 business days from the beginning of the event.

Severity
The severity of each adverse event must be assessed and recorded on the Adverse Event CRF as mild, moderate, or severe.

Mild:	An adverse event that is usually transient, requires no special treatment, and does not interfere with usual activities.
Moderate:	An adverse event that interferes with usual activities but may be ameliorated by therapeutic measures.
Severe:	An adverse event that is intense or debilitating and that interferes with usual activities. Recovery is usually aided by therapeutic measures and may require the discontinuation of study medication.

Relationship to Study Treatment
The investigator will assess the relationship between the study medication and the adverse event as probable, possible, unlikely, or unrelated as follows.

Probable:	Reports including good reasons and sufficient information to assume a causal relationship in the sense that it is plausible, conceivable, or likely.
Possible:	Reports containing sufficient information to indicate the possibility of a causal relationship in the sense of it not being impossible and not unlikely, although the connection may be uncertain or doubtful (e.g., due to missing data, insufficient evidence, etc.).
Unlikely:	Reports of a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.
Not Related:	Reports excluding the possibility of a relationship between the event and the drug treatment, i.e., no reasonable suspected causal relationship to study medication administration.

6.1.1.3 Recording Adverse Events

All adverse events, regardless of relationship to study treatment, must be recorded on the Adverse Event CRF. All adverse events reports should contain the date the adverse events occurred, a brief description of the event, time of onset, end date or duration of event (if less than 24 hours), intensity, treatment required, relationship to study treatment, action taken, outcome, and whether the event is classified as serious.

6.1.1.4 Follow-Up of Adverse Events

Reporting of adverse events will terminate on the last day of study follow-up. The investigator must follow non-serious events possibly related to the study treatment and all serious adverse events until they resolve or until the investigator assesses them as chronic or stable.

6.1.1.5 Protocol Deviations Due to an Emergency or Adverse Event

Deviations from the protocol will be determined as allowable on a case-by-case basis. All protocol deviations and the reasons for such deviations must be noted on the CRF.

6.1.1.6 Study Medication and Treatment

The medication that a subject will be randomized to apply throughout the study will either be the active investigational product (AFX 5931) or the inactive vehicle product. After applying the IP for the first time at the clinic/study site under supervision of the health staff, subjects will, subsequently, be responsible for applying the treatment independently (twice daily) and recording each application on a subject diary.

6.1.1.7 Photography

Digital photographs will be taken at proximal and distal views of both the dorsal as well as palmar surfaces of the subject's hand (treatment area).

6.2 Laboratory Variables

Laboratory variables are not applicable to this study.

6.3 Schedule of Visits:

CCCR 08-2018	Visit 1	Visit 2	Visit 3	Visit 4
n=20	**Day [-30] – [-1]**	**Day 0**	**Day 14**	**Day 28**
Study Assessments		**±1 Day**	**± 2 Days**	**± 3 Days**
Informed Consent	**X**			
Demographics	**X**			
Inclusion/Exclusion Criteria	**X**			
Medical/Dermatological History	**X**			
Fitzpatrick Skin Phototype	**X**			
Brief Physical Examination	**X**			**X**
Vital Signs	**X**			**X**
UPT for WOCBP		**X**		
Hand Eczema Severity Index	**X**	**X**	**X**	**X**
Investigator's Global Assessment	**X**	**X**	**X**	**X**
Local Skin Reaction Assessment		**X**	**X**	**X**
Subject's Local Dermal Tolerability Assessment		**X**	**X**	**X**
Apply Investigational Product (IP)		**X**	**X**	**X**
IP Accountability (Dispensing/Collecting)		**X**	**X**	**X**
Subject Diary (Dispense/Review/Collect)		**D**	**R**	**R/C**
Digital Photographs	**X**	**X**	**X**	**X**
Concomitant Medications/Therapies	**X**	**X**	**X**	**X**
Adverse Events	**X**	**X**	**X**	**X**
Exit Case Report Form				**X**

6.4 Observations by Visit

6.4.1 Visit 1 (Day -30 to -1): Screening

Subjects can be screened up to 30 days prior to Visit 2/Baseline. If applicable, qualified subjects can washout from prohibited medications and/or therapies prior to Baseline (after obtaining consent). Subjects who require screening period or washout for longer than 30 days will be re-consented but may still be enrolled in the study if they otherwise meet enrollment criteria.

The study requirements and procedures will be reviewed and written informed consent must be obtained prior to the initiation of any study-related procedures. Demographics, inclusion/exclusion criteria, medical/dermatological history, and concomitant medications and therapies will be reviewed to determine eligibility. A brief physical exam will be performed, vital signs will be taken, and Fitzpatrick Skin Phototype will be determined. The Hand Eczema Severity Index and Investigator's Global Assessment will be completed. Digital photographs will be taken at proximal and distal views of both the dorsal as well as palmar surfaces of the subject's hand (treatment area). The subject will be scheduled for Visit 2 (Baseline).

6.4.2 Visit 2 (Day 0): Baseline

The subject will return to the clinic and will be queried for any changes in health status since the previous visit, including concomitant medications and therapies. A urine pregnancy test with negative result confirmed will be performed for all WOCBP. The Hand Eczema Severity Index and Investigator's Global Assessment will be completed. Baseline reading of local skin reactions will be assessed prior to IP application. The Subject's Local Dermal Tolerability Assessment will be performed. IP will be dispensed to the subject. IP will then be dispensed and subject will apply the first dose in clinic. The subject diary will be dispensed. Digital photographs will be taken at proximal and distal views of both the dorsal as well as palmar surfaces of the subject's hand (treatment area). The subject will be scheduled to return to clinic for Visit 3 in accordance with the treatment window.

6.4.3 Visit 3 (Day 14): Follow-Up

The subject will return to the clinic and will be queried for any changes in health status since the previous visit, including concomitant medications and therapies. The Hand Eczema Severity Index and Investigator's Global Assessment will be completed. Local skin reactions will be assessed. The Subject's Local Dermal Tolerability Assessment will be performed. IP will be dispensed at the beginning of the study and collected at the end of the study. IP will be applied by the subject at home in the evening, consistent with their usual twice daily dosing. The subject diary will be reviewed. Digital photographs will be taken at proximal and distal views of both the dorsal as well as palmar surfaces of the subject's hand (treatment area). The subject will be scheduled to return to clinic for Visit 4 in accordance with the treatment window.

6.4.4 Visit 4 (Day 28): Ending Follow-Up | ET | EOS

The subject will return to the clinic and will be queried for any changes in health status since the previous visit, including concomitant medications and therapies. A brief physical exam will be performed and vital signs will be taken. The Hand Eczema Severity Index and Investigator's Global Assessment will be completed. Local skin reactions will be assessed. The Subject's Local Dermal Tolerability Assessment will be performed. IP will be dispensed at the beginning of the study and collected at the end of the study. IP is to be applied at least once before the subject comes in for the scheduled visit. The subject diary will

be reviewed and collected. Digital photographs will be taken at proximal and distal views of both the dorsal as well as palmar surfaces of the subject's hand (treatment area).

6.5 Study Termination

If the study sponsor or investigator discovers conditions arising during the study that indicate the study should be halted, the study must be terminated after appropriate consultation between the study sponsor, project manager, and investigator. Conditions that may warrant termination include, but are not limited to, the following – the discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study, insufficient adherence to protocol requirements.

7 DATA HANDLING AND RECORD KEEPING

7.1 Archiving Study Records

Essential documents should be retained on site for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Once the 2 years have elapsed, essential documents will be transferred off site to a secure location and retained for up to 7 years. The documents will be retained for a longer period if required by the applicable legal and regulatory requirements.

7.2 Statistical Methods
7.2.1 General Statistical Methods

All data collected during the study will be presented in data listings. Summary tables and analyses will be based on the following analysis populations:

Safety population:	All enrolled subjects who received study treatment.
Intention-to-treat (ITT) population:	All enrolled subjects, regardless of whether they received study treatment.
Per protocol (PP) population:	All subjects in the ITT population for whom no major protocol violations occurred.

The primary population for analyses of efficacy data will be ITT population. A supportive analysis will be presented for the PP population if this is significantly different from the ITT population. The assessment of safety will be based on the safety population.

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, median, standard deviation, minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percentages). Ninety-five percent confidence intervals will be constructed for proportions of successes.

Statistical tests will be used for analysis. The analysis will be 2-sided and conducted at the 0.05 significance level. An analysis of means using an independent samples t-test and ANOVA will be used. Primary analysis will be completed with the help of a chi-square analysis and assessment of relative risk and odds ratios.

7.2.2 Sample Size

The total sample size needed is 20 subjects that are 12 years of age and older. Each subject will be randomized in a 3:1 ratio to receive either the active (15 subjects) or vehicle (5 subjects) product throughout the study. Endpoints will be evaluated using a 2-sided Chi-square test and t-test at the 0.05 significance level.

7.2.3 Interim Analyses

An Interim Analyses is not applicable.

7.2.4 Missing Data

Missing data will be left blank.

7.2.5 Patient Disposition

The numbers and percentages of enrolled subjects who completed the study and discontinued from the study will be provided, as well as reasons for earlier discontinuation.

7.2.6 Treatment Compliance

Subjects will complete a subject diary recording daily applications of the medications to the treatment area on the face. Each medication is to be applied twice daily.

7.2.7 Concomitant Medications and Treatments

A log of medications taken and procedures performed during the study will be recorded for each subject.

7.2.8 Efficacy Analyses

Efficacy variables will be analyzed at the time points shown in the visit schedule.

7.2.8.1 Primary Efficacy Analyses

This study is concerned with the efficacy of topical AFX 5931 in the treatment of mild to moderate hand dermatitis. Changes in clinical scores recorded via the Hand Eczema Severity Index and Investigator's Global Assessment will be the primary modes of efficacy evaluation.

7.2.8.2 Safety Analyses

Safety analyses will be performed on the safety population. The Local Skin Reaction Assessment and the Subject's Local Dermal Tolerability Assessment will be the primary modes of tolerability evaluation. Monitoring the record of AEs and changes in concomitant medication throughout the course of the study will be the primary mode of safety evaluation. In addition, the frequency and percentage of subjects with adverse events will be summarized by coded body system and preferred term for each treatment group using the Medical Dictionary for Regulatory Activities (MedDRA). At each level of summarization (global, body system, and preferred term), a patient will be counted once if he/she has reported one or more AEs at that level. Tabular summaries will be presented for all adverse events, by severity, by

relationship to treatment, and for serious adverse events. No statistical testing will be performed. Changes in concomitant medications/procedures will also be monitored.

7.3 Source Documents

The full dataset will be collected for all subjects enrolled. All required data for this study will be collected on paper source document worksheets. The collected data will be entered into a validated database. Database lock will occur once quality assurance procedures have been completed.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of source documents include hospital records, office charts, memoranda, evaluation checklists, photographs, and subject files.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting USFDA guidelines for the handling and analysis of data for clinical trials.

7.4 Data Capture

Data will be captured on CRFs. CRFs are the primary data collection instrument for the study. All data on the CRF will be recorded, and all missing data must be explained. All data collected for the study and entered into the CRF must be traceable to a source document.

The Investigator will review, approve, and sign off on the CRFs. The Investigator's signature will serve as a testament of the Investigator's responsibility for ensuring that all clinical data entered on the CRF are complete, accurate, and authentic. The CRF data is entered into a validated database.

8 ETHICAL, LEGAL AND QUALITY ADMINISTRATIVE ASPECTS

8.1 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the individual treatments as well as the investigator abide by the principles of the Good Clinical Practice (GCP) guidelines of the ICH. The study will be carried out to abide with local legal and regulatory requirements.

Both Sponsor and Principal Investigator confirm this by signing this study protocol (see Page 2-3).

8.2 Changes in Statistical Methods

All changes in statistical methods that are described in the statistical analysis plan (SAP) will be documented in the clinical study report.

8.3 Informed Consent

Before being admitted to the study, informed consent will be obtained from each patient (or his/her legally authorized representative) according to the regulatory and legal requirements of the United States. This consent form must be dated and retained by the investigator as part of the study records.

Should a protocol addendum be made, the patient consent form may be revised to reflect the changes of the protocol.

If the consent form is revised, it is the responsibility of the investigator to ensure that an amended consent is reviewed and approved by the IRB. The approved amended consent form should be signed by all subjects subsequently entered in the study and those currently in the study.

The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the CRF.

8.4 Approval of Study Protocol

Upon finalization of the original study Protocol, the Investigator Signature Page and Sponsor Signature Page are to be executed by each party representative as an acceptance and agreement of the Protocol.

Before the start of the study, the study protocol and/or other appropriate documents will be submitted to the IRB in accordance with local legal requirements.

The sponsor and the investigator must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

8.5 Confidentiality

All study findings and documents will be regarded as confidential.

The anonymity of participating subjects must be maintained. Subjects will be identified on CRFs and other documents by their initials, birth date, and patient number.

8.6 Ethics Committee and Regulatory Authorities

Before enrollment of subjects into this study, the protocol, ICF and any promotional material or advertisements will be reviewed and approved by the appropriate IRB and regulatory authorities, where applicable. The study will commence only when the committee has approved the protocol or a modification thereof and a copy of the approval letter is received.

It is the investigator's responsibility to obtain IRB approval for the protocol and all subsequent major changes, in compliance with local law.

8.7 Monitoring

The study monitor and/or other authorized representatives of the Sponsor is/are responsible for monitoring that each study site conducts the study according to the protocol, SOPs, other written instructions, Code of Federal Regulation (Title 21, CFR Part 812) and applicable regulatory guidelines. The investigator will permit the study monitor or other authorized representatives to visit the study site at appropriate intervals to observe the progress of the study, review study records/documentation, and ensure that informed consent has been obtained for each subject prior to performing any study procedure.

8.8 Auditing

The Sponsor and/or Sponsor's representatives may conduct audits (quality assurance) to evaluate study conduct and compliance with the protocol, SOPs, other written instructions/agreements, Code of Federal Regulation (Title 21, CFR Part 812) and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and information in the informed consent documentation of this clinical trial.

9.0 Research Study Assessments

Primary Endpoint Evaluations

Hand Eczema Severity Index:

Clinical Signs	Fingertips	Fingers (except tips)	Palms of Hands	Backs of Hands	Wrists
Erythema (E)					
Infiltration (I)					
Vesicles (V)					
Fissures (F)					
Scaling (S)					
Oedema (O)					
SUM					
Extent					
Total HECSI Score = _____	**SUM * Extent**	**SUM * Extent**	**SUM * Extent**	**SUM * Extent**	**SUM * Extent**

Reference: Held et al – British Journal of Dermatology – Volume 152 Issue 2 (2005) pages 302-307

Each hand is divided into five areas [fingertips, fingers (except the tips), palms, back of hands and wrists]. The clinical signs of erythema, induration/papulation, vesicles, fissuring, scaling and oedema are graded on the following scale:

0 = no skin changes

1 = mild disease

2 = moderate

3 = severe

Per each location (combining both hands), the affected region was given a score for extent of surface area involvement on the following scale:

0 = 0%;

1 = 1–25%

2 = 26–50%

3 = 51–75%

4 = 76–100%

Finally, the score given for the extent at each location was multiplied by the sum of the intensity of clinical features. The total sum (HECSI score, highlighted above) was calculated, ranging from 0 to a maximum severity score of 360.

Investigator's Global Assessment:

The investigator will rate the subject's hand dermatitis on a visual 5-point scale as follows:

0: Clear:	No signs of HE
1: Almost clear:	Just perceptible scaling and/or erythema;
2: Mild disease:	Mild scaling and/or mild erythema, and/or mild cracking
3: Moderate disease:	Moderate scaling and/or erythema, and/or moderate cracking/fissuring
4: Severe disease:	Severe scaling and/or severe erythema, and/or severe cracking/fissuring

Dorsal and palmar surfaces of the hand are evaluated *together*.
Reference: Diamant et al. - Dermatology Basel - Volume 207, Issue 1 (2003) pages 37-42

Secondary Endpoint Evaluations

Subject's Local Dermal Tolerability Assessment:

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

Pruritus:	Definition: itching
0 = None:	No itching
1 = Mild:	Occasional, slight itching/scratching
2 = Moderate:	Constant or intermittent itching/scratching/discomfort that is not disturbing sleep
3 = Severe:	Bothersome itching/scratching/discomfort that is disturbing sleep

Local Skin Reaction Assessment:

The investigator or designee will describe his/her assessment of the subject's hands at the moment using a 4-point tolerability scale, where 0=None, 1=Mild, 2=Moderate, and 3=Severe.

Erythema:	Definition: abnormal redness of the skin
0 = None:	No erythema
1 = Mild:	Slight pinkness present
2 = Moderate:	Definite, dull redness that is clearly distinguishable
3 = Severe:	Intense, deep redness

Induration/Papulation:	Definition: inflammation, swelling
0 = None:	No elevation
1 = Mild:	Slightly perceptible elevation
2 = Moderate:	Clearly perceptible elevation but not extensive
3 = Severe:	Marked and extensive elevation

Lichenification:	Definition: thickening upper layers of skin
0 = None:	No thickening

1 = Mild:	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2 = Moderate:	Definite thickening of the skin with skin markings exaggerated so that they form a visible crisscross pattern
3 = Severe:	Thickened, indurated skin with skin markings visibly portraying an exaggerated crisscross pattern