Topical Acetaminophen for Itch Relief: a proof of concept study in healthy subjects

IRB Number: 20190133

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SPONSOR-INVESTIGATOR: Gil Yosipovitch, MD

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Clinical Trial Protocol Statement of Compliance

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 and 45 CFR Part 46, Protection of Human Patients**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of PI responsibilities to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

I understand that my signature constitutes agreement and understanding of acceptance of the defined responsibilities of a Sponsor-Investigator as defined by the protocol, applicable FDA Regulations, and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor-Investigator. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol shall be implemented timely with my review and approval prior to implementation.

INVESTIGATOR'S STATEMENT

I have reviewed the protocol and agree to conduct this study as outlined in the protocol and in compliance with ICH/GCP Guidelines.

I have read and agree to follow the Study procedures as outlined.

_____

Print Name of PI

_____ _____

PI's Signature Date

CLINICAL PROTOCOL SYNOPSIS

Title of Trial:	Topical Acetaminophen for Itch Relief: a proof of concept study in healthy subjects	
UM IRB Number:	20190133	
Sponsor-Investigator:	Gil Yosipovitch, MD	
Trial Duration:	6 months	Phase of Trial: I/IIa
Trial Population:	Healthy volunteers	
Trial Centers:	University of Miami, Department of Dermatology	
Objectives:	Primary: The primary endpoint is to test the antipruritic effect of topical acetaminophen gel formulations using an itch VAS intensity scale as an outcome measure. Secondary: A secondary endpoint is to see if this topical has a relieving effect on heat pain using heat pain thresholds as an outcome measure. Exploratory: An exploratory end point is to see if the topical reduces erythema caused by itch induction using a Likert scale as an outcome measure.	
Trial Design:	double-blinded, vehicle-controlled randomized study	
Number of Patients:	40 healthy subjects, in order for 36 subjects to complete the study.	
Trial Drug(s), Dose, and Mode of Administration:	0.4ml application of each topical gel: 5% APAP, 2.5% APAP, 1% APAP, vehicle	
Trial Drug Supply:	Sponsor-Investigator	
Inclusion Criteria:	1. Healthy subjects must be between 18 and 50 years of age. 2. Must be in general good health with no disease or physical conditions that would impair evaluation of itch and pain perception. 3. No history of chronic itch or pain. 4. Must abstain from the use of any systemic or topical anti-histamine, steroid, or pain relief medications from the week prior to the study till the completion of the study. 5. Must abstain from the use of moisturizers on the arms 24 hours before study visits.	

Exclusion Criteria:	1. Individuals under 18 or over 50 years of age. 2. Inability to complete the required measures. 3. The presence of an itchy skin disease. 4. Diagnosis of diseased that would affect itch or pain perception (e.g. neuropathies). 5. Currently enrolled in any investigational study in which the subject is receiving any type of drug, biological, or non-drug therapy. 6. Use of oral, topical analgesics, or other medications known to interfere with itch or pain perception in the week prior to the study and throughout the study (e.g. antihistamines, anesthetics, opioids, neuroleptics, etc.). 7. Use of emollients on the arms a week prior to the study and throughout the study. 8. Known allergies to acetaminophen and cowhage. 9. Pregnant women. (Women of child bearing potential will undergo an hCG pregnancy test). 10. Currently incarcerated.
Statistical Methodology:	Normality assessment will be tested by visual inspection and Sharpiro-Wilks tests. A repeated measure (between–within) ANOVA will be used for the main analysis and post hoc comparisons will be conducted using the Bonferroni correction in a manner similar to Dunnett's test.

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1 INTRODUCTION

1.1 Background

Currently, topical antihistamines and corticosteroids are mainly used for itching relief. However, the over the counter antihistamines are not effective on all itch conditions. Acetaminophen is a popular and widely used OTC drug for pain relief. Although its mode of action is still unknown, recent studies have shown that acetaminophen indirectly activates cannabinoid CB1 receptors. Recent studies have shown that topical cannabinoid agonists are effective for itch relief, the efficacy of topical acetaminophen will be tested for non-histaminergic itch relief.

1.2 Investigational Product Description

Topical gel formulations of APAP (5%, 2.5%, and 1%) and a vehicle control

1.3 Rationale for the Trial

There is an unmet need to develop effective topical anti-pruritic medications for acute and chronic itch, as currently there are few topical formulations that have a direct effect on itch.

2 TRIAL OBJECTIVES

Primary: The primary endpoint is to test the antipruritic effect of topical acetaminophen gel formulations using an itch VAS intensity scale as an outcome measure.

Secondary: A secondary endpoint is to see if this topical has a relieving effect on heat pain using a heat pain thresholds as an outcome measure.

Exploratory: An exploratory end point is to see if the topical reduces erythema caused by itch induction using a Likert scale as an outcome measure.

3 TRIAL POPULATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the clinical trial:

1. Healthy subjects must be between 18 and 50 years of age.
2. Must be in general good health with no disease or physical conditions that would impair evaluation of itch and pain perception.
3. No history of chronic itch or pain.
4. Must abstain from the use of any systemic or topical anti-histamine, steroid, or pain relief medications from the week prior to the study till the completion of the study.
5. Must abstain from the use of moisturizers on the arms 24 hours before study visits.

3.2 Exclusion Criteria

1. Individuals under 18 or over 50 years of age.

2. Inability to complete the required measures.
3. The presence of an itchy skin disease.
4. Diagnosis of diseased that would affect itch or pain perception (e.g. neuropathies).
5. Currently enrolled in any investigational study in which the subject is receiving any type of drug, biological, or non-drug therapy.
6. Use of oral, topical analgesics, or other medications known to interfere with itch or pain perception in the week prior to the study and throughout the study (e.g. antihistamines, anesthetics, opioids, neuroleptics, etc.).
7. Use of emollients on the arms a week prior to the study and throughout the study.
8. Known allergies to acetaminophen and cowhage.
9. Pregnant women. (Women of child bearing potential will undergo an hCG pregnancy test).
10. Currently incarcerated.

3.3 Discontinuation from Trial Treatment

If a subject experiences an adverse event assessed at ≥ Grade 2 according to CTCAE v4, the subject will not receive additional treatments and will be followed until the adverse event resolves or stabilizes.

3.4 Recruitment Methods

Subjects in this study will be recruited through appropriate IRB-approved flyer advertising around the University of Miami medical campus.

4 TRIAL REGISTRATION

All patients and/or their legal guardians shall receive written and verbal information concerning the clinical trial. This information will emphasize that participation in the clinical trial is voluntary and that the patient may withdraw from the clinical trial at any time and for any reason. All patients will be given opportunity to ask questions and will be given sufficient time to consider before consenting. This trial will be registered on ClinicalTrials.gov.

The signed and dated informed consent to participate in the clinical trial must be obtained prior to any clinical trial related procedure being carried out.

5 TRIAL DESIGN

This will be a double-blinded, vehicle-controlled randomized study in healthy controls to test the efficacy of the topical gel formulation with three differing concentrations of acetaminophen (APAP) for itch relief. To detect medium effects of the treatments with a given α of 0.5 and an error probability of 0.05, with a power of 0.95, the number of participants needed is 36 (10 within post hoc pairwise comparisons).

6 ADMINISTRATION OF TRIAL TREATMENTS

6.1 Trial Treatments

The treatments include topical gel APAP (5%, 2.5%, 1%) and vehicle control gel. Each subject will have all treatments applied to them twice in total, once at each study visit.

Application will be conducted with the investigator wearing nitrile gloves. A 0.4ml volume of the test formulations or the vehicle control will be rubbed gently into the skin.

6.2 Duration of Treatment

Subjects will be in the study for 2 2-hour long visits within 7 days. Each treatment will be applied to the skin once during each study visit. The treatment will be allowed to permeate the skin for 30 minutes prior to any other study procedure commencing at the test site.

6.3 End of Trial

Study stoppage will occur if 36 subjects complete the study or if a severe adverse event occurs. Interim analysis will be used to analyze data for statistical significance and power. If study reaching significance with adequate power, the study may be concluded before 36 subjects complete the study.

6.4 Prior and Concomitant Medications

Select prior and concomitant medications will be collected at each study visit. A history of prior medications in the past week will be collected for any systemic or topical anti-histamine, steroid, or pain relief therapies (i.e. any medications known to interfere with itch or pain perception). These will also be collected as concomitant medications until the last study visit.

7 DOSE MODIFICATIONS

Does modification will not occur.

8 TRIAL ASSESSMENTS AND TREATMENT

Procedure	Visit 1	Visit 2 (± 6 days)
Informed consent	X	
Inclusion/exclusion	X	
Medical history/demographics	X	
Pregnancy test	X	
Prior/Con meds	X	X
Vitals	X	X
Selection of test sites	X	X

Treatment with IP	X	X
Itch induction	X	X
Itch Intensity VAS	X	X
Erythema grading	X	X
QST (HPT)	X	X
AE/SAE collection	X	X

8.1 Screening

Subjects will be asked to participate in two 2-hour study visits within a one week time period. Following signed informed consent, obtained in the presence of the investigator or designee, the inclusion and exclusion criteria will be confirmed and vitals will be taken. The screening can be performed the same day or within 24 hours as treatment visit 1.

8.2 Trial Treatment Period

For each visit, four 4 cm x 4 cm square test areas will be used on the subject's volar forearms (two squares on the left arm and two squares on the right arm). These squares will be separated by another 4 cm. Only one area will be tested at a time, and there will be a 5-minute wait period before the next area will be tested. The placement of the treatments in these test areas will be randomized.

The itch induction method, cowhage or histamine, for visit 1 and visit 2 will be randomized.

For the cowhage induction study visit, each test area will be pretreated by gently rubbing in a 0.4ml volume of either one of the test formulations (5% APAP; 2.5% APAP or; 1% APAP) or the vehicle control to the skin area based on a randomization scheme. Thirty minutes after pretreatment, the area will be wiped clean with a dry lab wipe and itch will be evoked by the application of 40-45 cowhage spicules (Papoiu, Tey, Coghil 2011). The spicules will be rubbed gently within the test area for 45 seconds. Subjects will rate their itch intensity every 30 seconds until the itch sensation has completely subsided using a numerical 10 cm visual analog scale (VAS), from 0 (no itch) to 10 (most unbearable itch). After the itch has subsided, the cowhage spicules will be removed using adhesive tape.

For the histamine induction study visit, each test area will be pretreated by gently rubbing in a 0.4ml volume of either one of the test formulations (5% APAP; 2.5% APAP or; 1% APAP) or the vehicle control to the skin area based on a randomization scheme. Thirty minutes after pretreatment, the area will be wiped clean with a dry lab wipe and itch will be evoked by iontophoresis of a 1% histamine solution. 0.2ml of the 1% histamine

solution will be placed in an anode delivery electrode placed on the test area, while a cathode grounding electrode is placed on the subject's arm at a certain distance (< 10 cm away) from the test area (but not in the test area). The iontophoresis device, a battery-powered stimulus isolation unit (Perimed PF 3826, Perilont Power device, Sweden) generates a current of no more than 500 μA for 60 sec. Subjects will rate their itch intensity every 30 seconds until the itch sensation has completely subsided using a numerical 10 cm visual analog scale (VAS), from 0 (no itch) to 10 (most unbearable itch).

Reduction of erythema will also be measured by using a Likert scale before itch is induced, 90 seconds after itch is induced, and once the itch subsides at all test sites.

Heat pain thresholds will be assessed using the TSA-II neurosensory analyzer at all test sites once itch as subsided for at least 5 minutes (Angst, Tingle, Phillips 2009). A thermode probe will warm the skin surface from a baseline of 32 °C to a maximum of 50°C at 0.4°C increments. The threshold will be determined 3 times by the ascending method of limits, where the subject will be instructed to press a response button upon detection of a painful stimulus.

8.3 Post-Treatment Follow-up Visit

Study subjects will be instructed to report any adverse events up to one week after the study is completed.

8.4 Patient Withdrawal

The following medical and other reasons justify a premature termination (by patient or investigator) of the investigational treatments:

- Withdrawal of informed consent,
- SAEs,
- Patient's request,
- Patient is lost to follow-up, and/or
- Investigator's judgment.

If a patient withdraws from the study, all efforts will be made to complete a final evaluation, if possible, including the reason for withdrawal.

Withdrawals due to non-attendance or non-compliance must be followed up to obtain the reason for non-attendance or non-compliance. Withdrawals due to intercurrent illness or adverse events (AEs) are to be fully documented with supplementary information where available and appropriate. Patients discontinued due to an AE will be followed until the AE is resolved, a reasonable explanation is provided for the event, or the patient is referred to his/her own primary medical doctor. The specific AE in question will be recorded on the appropriate source document.

9 INVESTIGATIONAL PRODUCT

9.1 Cowhage

Cowhage (Mucuna pruriens) is a tropical legume also known as Velvet bean or cowitch and it is found in Latin America, the Caribbean, India, Africa and Florida. M. pruriens is a climbing vine and considered variously as an annual or perennial. The plant consists of a vine with slender stems that bear numerous alternate, trifoliolate leaves approximately 10cm long. The flowers are typically purple, red or green-yellow. The fruit pods range from 3-10 cm in length, are curved and, when mature, are covered with dark hairs/spicules that provide a velvety appearance. The pods contain 4-6 seeds that are approximately 1 x 1 cm.

The dry pods are collected by cutting the stems from the plant and letting them fall directly into a clean, dry polythene bag. The spicules are separated from the pods by shaking the bag. Forceps are used to remove the pods and retain the spicules. The cowhage spicules are shipped at room temperature since they are stable unless exposed to extreme heat and pressure via autoclaving (>100°C), which renders them chemically inert.

Once it reaches the lab, Dr. Yosipovitch's staff documents on the tube the date of arrival. This batch is labeled the "master batch". The tube of cowhage is then stored under dry conditions in a 4°C refrigerator. Also upon arrival, the spicules are examined under a microscope to confirm the material is cowhage. The dimensions of the spicules (2-4 mm length, 1-3 µm tip diameter) are measured [40].

The investigator then tests the spicules for the itch induction ability with the same application method used in studies [57]. Forty to forty-five spicules (a dose found to induce a consistent and reproducible itch sensation) are counted under the microscope and then rubbed in to a 4x4 cm area on the volar forearm for 45 seconds in a circular motion. Approximately 0.2 mm of the spicule tip enters the skin. Forty-five spicules of cowhage are equivalent to 45 µg of material, containing about 90-140 ng of mucunain [45]. The spicules usually induce itch after ~30-90 seconds of the application. If 2 minutes pass without itch being induced, the spicules are deemed inactive and the batch will not be used for itch induction in studies. If itch is induced, the itch sensation will last ~7 minutes and itch intensity is rated using a 0-10 numerical rating scale (NRS) every 30 seconds until the itching subsides. Cowhage spicules are removed from the skin using tape, which is disposed of in a biohazard trash bin. The itch subsides quickly once the spicules have been removed. Itch is only felt at the site of induction and mild temporary erythema at the induction site is common.

For studies using cowhage to induce itch, a small portion of the master batch of cowhage is aliquoted into smaller 5 ml tubes as a "working batch". The date of separation from the main batch is marked on the smaller tube. This tube then remains at room temperature for the duration of the study. The potency of the cowhage is preserved for many years when stored in a dehumidified area at room temperature or at 4°C, but the potency is checked every 3 months and before the start of any study.

9.2 1% Histamine Iontophoresis Solution (200ml)

Methylcellulose (USP Hypromellose HY124; Spectrum Chemicals, New Brunswick, NJ) and histamine (>99% histamine dihydrochloride; Sigma-Aldrich, St. Louis, MO) is dissolved in 0.9% sodium chloride (USP Diluent; Hospira, Lake Forest, IL) until the solution thickens into a gel. The gel solution is kept in a tight, light resistant container at 4°C. The container is labeled: "1% Histamine Solution. For Investigational Use Only.

9.3 Topical Acetaminophen

Gel Formulations

For each 100 ml:	
Acetaminophen (APAP)	5g, 2.5 g, or 1g
Stearic Acid	2.0 g
Carbomer 980	0.5 g
Triethanolamine	2.0 g
Denatured Alcohol	35 ml
Purified Water	to 100 ml

Preparation

50 ml of water is heated to 75 C. Carbomer is added to the water with vigorous mixing. The APAP and Stearic Acid are added to the alcohol. The mixture is heated to 75 C and mixed. The water and alcohol mixtures are combined and triethanolamine is added during mixing. The liquid gel is place in a sonic bath for 15 minutes. The gel will form during cooling. A vehicle control will be prepared using the same materials and methods without the active ingredient.

Labeling:

Acetaminophen or Placebo Gel
External Use Only!
"Caution: New Drug- Limited by Federal (or United States) law to investigational use"
Store at Room Temperature
Lot Number: xxxxxxx
Expiration: xx/xx/xxxx.

Formation expirations:

As per USP 795 standards on compounding with a water-containing base, these formulations have an expiration of 30 days. The expiration date will be on the label.

Storage:

The formulations will be stored at room temperature in a locked cabinet in the Dermatology research clinic that only study personnel will have access with a key. Ambient temperature and min/max of the storage cabinet will be recorded once a day

(except on weekends). Logs of formulation delivery and use per subject will be kept.

Application:

Application will be conducted with the investigator wearing nitrile gloves. A 0.4ml volume of the test formulations or the vehicle control will be rubbed gently into the skin.

9.4 Risks Associated with the Study

Topical APAP application: Liver damage is the most serious side effect of APAP overdose. The recommended daily dose of APAP is no more than 4,000mg to prevent overdose. Rarely serious skin reactions can occur. Participants will be will be instructed to contact the study team at any time after application of topical APAP if they have any problems.

Cowhage Application: No specific serious risks or adverse effects are associated with the application of cowhage spicules on the skin. At the site of application, subjects may experience a mild to moderate burning/stinging sensation apart from the itch sensation itself, which may last up to 5-7 minutes. Cowhage is not an allergen and does not cause contact dermatitis or chemical irritation. We do not expect a tachyphylactic reaction or an additive affect from multiple cowhage applications because we will apply only once in the same site. In the event of an allergic reaction, the study will be stopped and appropriate treatment administered (use of EpiPen).

Following use of EpiPen, the patient will be referred to the emergency room, where basic vitals including heart rate, blood pressure, and oxygen saturation in the blood will be monitored. A respiratory exam will also be given to assess the quality of breathing. Steroids to prevent additional airway closure and fluids to maintain blood pressure will be given as necessary. The patient will be monitored in the emergency room for 6 hours, and then sent home with an additional EpiPen to guarantee immediate access to self-injectable epinephrine. The patient will be instructed on EpiPen usage. The patient will also be educated to watch for symptoms of biphasic anaphylaxis, which may occur up to 72 hours after initial symptoms of anaphylaxis.

Histamine Application: No specific serious risks or adverse effects are associated with the application of histamine to the skin. The histamine application will cause brief itching and tingling, with a standard wheel and flare response. The wheel and flare response should disappear about one hour after the histamine is applied to the skin. We do not expect a tachyphylactic reaction or an additive affect from multiple histamine applications because we will apply only once in the same site. In the event of an allergic reaction, the study will be stopped and appropriate treatment administered (use of EpiPen).

Following use of EpiPen, the patient will be referred to the emergency room, where basic vitals including heart rate, blood pressure, and oxygen saturation in the blood will be monitored. A respiratory exam will also be given to assess the quality of breathing. Steroids to prevent additional airway closure and fluids to maintain blood pressure will be given as necessary. The patient will be monitored in the emergency room for 6 hours, and then sent home with an additional EpiPen to guarantee immediate access to self-injectable epinephrine. The patient will be instructed on EpiPen usage. The patient will also be educated to watch for symptoms of biphasic anaphylaxis, which may occur up to 72 hours after initial symptoms of anaphylaxis.

Heat Pain Sensory Testing: Heat pain will be assessed using a thermode probe raising the temperature of circulating water from 32ºC to 50ºC. This heat pain is marginally unpleasant and a bit bothersome, but relatively easily tolerated. If the pain is unbearable, the thermode can be immediately removed to alleviate the painful sensation.

10 RESPONSE EVALUATIONS AND MEASUREMENTS

The investigator(s) will make the following assessments on each patient during the study:

1. Itch intensity after cowhage and histamine itch induction
2. Erythema grading
3. Heat pain threshold

10.1 Safety Evaluation

Local and systemic adverse events will be monitored during the study. Dermatologic evaluations for rash, erythema (outside of administration area), urticaria, eruptions, and epidermal necrolysis will be performed throughout the study visit. Anaphylaxis and hypersensitivity (erythema multiforme) will also be monitored for.

10.2 Statistical Considerations

To detect medium effects of the treatments with a given α of 0.5 and an error probability of 0.05, with a power of 0.95, the number of participants needed is 36 (10 within post hoc pairwise comparisons).

Normality assessment will be tested by visual inspection and Sharpiro-Wilks tests. A repeated measure (between–within) ANOVA will be used for the main analysis and post hoc comparisons will be conducted using the Bonferroni correction in a manner similar to Dunnett's test.

11 SAFETY REPORTING AND ANALYSIS

Safety and tolerability assessments will consist of ongoing monitoring and recording of all adverse (AE) and serious adverse event (SAE) reports, the regular monitoring of signs and symptoms of cutaneous irritation, and regular measurements of vital signs.

11.1 Safety Analyses

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs) and other protocol-specified tests that are deemed critical to the safety evaluation of the trial drug.

11.2 Adverse Events

The PI is responsible for identifying, documenting and reporting adverse events to the IRB and FDA as applicable.

11.2.1 Definitions of Adverse Events

An adverse event is the development of an undesirable medical condition, or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., chest pain), signs (e.g., tachycardia), or the abnormal results of an investigation (e.g., laboratory findings).

11.2.2 Recording of Adverse Events

All adverse events of any patient during the course of the trial will be reported in the source document, and the investigator will give his opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). If the adverse event is serious and related to the IP, it will be reported within 24 hours to the IRB as per UM policy. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs (i.e., AEs that occur prior to assignment of trial treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs, regardless of seriousness or relationship to trial treatment, spanning from the start of trial treatment until 7 days after study completion are to be recorded in the source document.

11.2.3 Abnormal and Vital Signs

If an abnormal vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated vital sign should be considered additional information that must be collected on the relevant source document.

11.2.4 Handling of Adverse Events

All adverse events resulting in discontinuation from the trial should be followed until resolution or stabilization. Patients must be followed for AEs for 7 calendar days after discontinuation or completion of protocol-specific treatment (e.g., chemotherapy, radiation, oral medications, targeted therapy, and surgery). All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the source document.

11.3 Serious Adverse Events

11.3.1 Definitions of Serious Adverse Events

The definitions of serious adverse events (SAEs) are given below. The principal investigator is responsible for ensuring that all staff involved in the trial are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that: results in death, is immediately life-threatening, requires at least a 24-hour inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial), does not require reporting as a serious adverse event.

11.3.2 Serious Adverse Event Reporting

It is important to distinguish between "serious" and "severe" adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the CRF and SAEs on the SAE Report Form.

Adverse events classified by the treating investigator as serious require documentation and reporting to the IRB according to UM policies and procedures in order to comply with regulatory requirements. Serious adverse events may occur at any time from the signing of the informed consent form start of trial treatment through the 7-day follow-up period after the last trial treatment. To report a SAE, the SAE log should be completed with the necessary information.

All SAEs and medically confirmed deaths (regardless of causality assessment) occurring on trial treatment or within 7 days of last trial treatment must be reported on the SAE log and followed until resolution (with autopsy report if applicable).

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3.3 SAE Reporting Requirements

UM is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

UM is responsible for reporting unexpected fatal or life-threatening events associated with the use of the trial drugs to the regulatory agencies and competent authorities via telephone or fax within 7 calendar days after being notified of the event. UM will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs associated with the use of the trial medication to the appropriate competent authorities

(according to local guidelines), investigators, and IRBs by a written safety report within 15 calendar days of notification.

11.4 Recording of Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE and AE logs. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE/SAE logs and be reported accordingly.

11.4.1 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the AE log. If a persistent AE becomes more severe or lessens in severity, it should be recorded separately on the AE log.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an AE log.

11.4.2 Deaths

All on-trial deaths, regardless of attribution, will be recorded on an SAE log.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE log. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Death NOS”.

11.4.3 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolonged hospitalization should be documented and reported as an SAE. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE.

11.4.4 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the Medical History source document. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an AE/log, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

12 CLINICAL MONITORING

12.1 Site Monitoring Plan

Site monitoring shall be conducted to ensure the human patient protection, trial procedures, laboratory, trial intervention administration, and data collection processes are of high quality and meet Sponsor, GCP/ICH and, when appropriate, regulatory guidelines. The Site Monitoring Plan shall define aspects of the monitoring process.

The Sponsor-Investigator is responsible to the regulatory authorities for assuring the proper

conduct of the clinical trial with regard to protocol adherence and validity of the data recorded in the source documents. The Sponsor-Investigator is responsible for advising the investigator on the collection and maintenance of accurate, complete, legible, well organized, and easily retrievable data for the clinical trial. In addition, he/she will explain to the investigator the procedures for implementing the protocol, including a review of the protocol objectives, assessments and timelines, and source documentation requirements. The obligations of the investigator in conducting investigational product studies will also be reviewed.

In order to perform their role effectively, the monitors and persons involved in quality assurance and inspections (see above) will need direct access to primary patient data, e.g., medical records, laboratory reports, appointment books, etc. Because this affects the patient's confidentiality, this fact is included on the Informed Consent Form.

13 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

13.1 IRB Approval

The trial protocol, ICF, IB, available safety information, patient documents, patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the trial start.

The PI will follow all necessary regulations to ensure appropriate, initial, and ongoing, IRB trial review. The PI must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document.

13.2 Regulatory Approval

As required by local regulations, the PI will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, the PI will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

The informed consent form will be submitted for approval to the IRB that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been

obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the trial design or the potential risks to the patients, the patient's consent to continue participation in the trial should be obtained.

13.4 Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPPA). HIPPA regulations require that, in order to participate in the trial, a patient must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR, it is a requirement that the investigator and institution permit authorised representatives, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and initials will identify patients on the CRF or other documents. Patients will be informed of their rights within the ICF.

13.5 Financial Information

University of Miami will provide funding for the study. The trial drug for all trial participants will be provided free of charge by the sponsor-investigator for the duration of the trial.

13.6 Record Retention and Documentation of the Trial

13.6.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

All amendments require review and approval of the Principal Investigator supporting the trial.

Amendments specifically involving change to trial design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities as applicable, after IRB approval and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

13.6.2 Data Collection

All study data will be collected on study source documents and logs. All of the data, including records of subjects, source documents, and inform consent will be kept in the study center under lock for 6 years after the study finished.

13.7 Trial Monitoring, Auditing, and Inspecting

The investigator will permit trial-related monitoring, quality audits, and inspections by, government regulatory authorities, of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities.

13.8 Quality Assurance and Quality Control

In addition to the Clinical Monitoring component of this protocol, Quality Assurance (QA) to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

13.9 Disclosure and Publication Policy

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential.

The financial disclosure information will be completed prior to trial participation from all PIs and Sub-Investigators who are involved in the trial and named on the FDA 1572 form.

The Sponsor-Investigator will register the trial on www.clinicaltrials.gov. In addition, Sponsor-Investigator will publish the results of the trial.

14 REFERECES

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