DISCLOSURE

REDACTED PROTOCOL

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Clinical Protocol # : ETTAU-03

IND# : 107689

A Phase III, multi-center, double blind, randomized, active controlled clinical trial to evaluate the Non-Inferiority comparing Cetirizine Injection 10 mg to Diphenhydramine Injection, 50 mg, for the treatment of acute urticaria.

SPONSOR:

JDP Therapeutics Inc.

Jie Du, Ph.D.
President and Chief Scientific Officer

Signature _____

Date April 10, 2017

Version: 4/10/2017
(Note: the terms "patient" and "subject" are interchangeable in this protocol.)

List of Abbreviations

AE	Adverse Event/Adverse Experience
AUC_{inf}	Extrapolated Area Under the Plasma Concentration Time Curve to infinity
CFR	Code of Federal Regulations
CI	Confidence Interval (confidence limits)
CIOMS	Council for International Organizations of Medical Sciences
CIU	Chronic Idiopathic Urticaria
C_{max}	Maximum Observed Plasma Concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH
DSMB	Data Safety and Monitoring Board
DSMC	Data Safety and Monitoring Committee
ETTAU	Efficacy Trial for the Treatment of Acute Urticaria
ED	Emergency Department
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MedDRA ©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NCI	National Cancer Institute, NIH
NDA	New Drug Application
NEJM	New England Journal of Medicine
NI	Non-inferiority
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event/Serious Adverse Experience
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
Tmax	Time of maximum measured plasma concentration; if it occurs at more than one time point, Tmax is defined as the first time point with this value
WHO	World Health Organization

PRINCIPAL INVESTIGATOR'S ACKNOWLEDGEMENT

I have read and understand this protocol, agree to conduct the study as outlined herein, and provide the necessary assurances that this study will be conducted according to all stipulations of the protocol, complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 312 and all applicable local, state, and federal regulations and ICH guidelines.

Principal Investigator Signature _____

Principal Investigator Name (print) _____

Date _____

Name of Investigational Site _____

1. Protocol Summary

Title:
A Phase III, multi-center, double blind, randomized, active controlled clinical trial to evaluate the Non-Inferiority comparing Cetirizine Injection 10 mg to Diphenhydramine Injection, 50 mg, for the treatment of acute urticaria.

Phase:
Phase III

Population:
Males or females aged 18 years and older, with acute urticaria requiring treatment in Emergency Departments, hospitals, Urgent Care Centers and Allergy Clinics will be included in this study.

Number of Patients and Number of Sites:
Approximately 256 patients, and approximately 20 sites

Study Duration:
Approximately 48 hours.

Study Medications:

Investigational Product:
Cetirizine injection, 10 mg/mL – a single 1 mL injection via intravenous slow push (~2 minutes)

Comparator:
Diphenhydramine injection, 50mg/mL – a single 1 mL injection via intravenous slow push (~2 minutes)

Objectives:

Primary Objectives:

1. The primary objective of this study is to establish the non-inferiority of Cetirizine injection with respect to Diphenhydramine injection in reducing patient reported pruritus severity score at 2 hours after treatment of acute urticaria.

Secondary Objectives:

The secondary objectives will assess, for each treatment group, the following parameters:

1. Record the frequency of patient's return to treatment center after discharge (i.e. 2nd visit within ~24 hours after discharge)
2. Record and compare sedation scores between treatments
3. Record and compare time-to-discharge between treatments.
4. Record and compare changes in patient reported pruritus severity score at 1 hr post treatment and at time of discharge.
5. Record and compare Extent of Urticaria/Erythema scores, and their changes from baseline at various time points after treatment.

6. Document the percentage of patients experiencing adverse events (AEs) or serious adverse events (SAEs) from the study drugs.
7. Document the percentage of patients requiring rescue medication, e.g. epinephrine, bronchodilators, steroids, etc., and the reasons for the use of rescue drugs.
8. Record symptom recurrence rate and additional symptoms occurrence within ~24 hours and/or ~48 hours after patient discharge from treatment centers.
9. Record the need for medication after discharge.

Description of Study Design:

This will be a multicenter, parallel group, randomized, double-blind, active controlled, Phase III clinical study of cetirizine injection, 10 mg/mL, compared to diphenhydramine injection, 50 mg/mL (Benadryl or generic equivalent), in approximately 256 patients (1:1 ratio) with acute urticaria requiring treatment in Emergency Departments, hospitals, Urgent Care Centers, Allergy Clinics, and etc.

2. Background and Rationale

Urticaria (hives) is a vascular reaction of the skin marked by the transient appearance of smooth, slightly elevated patches (wheals) that are erythematous and almost always associated with severe pruritus. Acute urticaria is often part of the acute allergic reactions, for examples: about 90% of anaphylaxis patients and most angioedema patients have urticaria symptoms at the same time; acute urticaria can also be the only symptom in an acute allergic reaction. Individual lesions usually resolve without scarring in less than 24 hours. Acute urticaria eruption rarely lasts more than several days, but sometimes it may recur over the course of several weeks, but less than 6 weeks. [Note: Chronic urticaria is defined as urticaria with recurrent episodes lasting longer than 6 weeks [1, 2], which is not the patient population of this protocol.]

The development of urticaria is often an isolated event without systemic manifestations. Sometimes, it may be a prelude to the development of an anaphylactic reaction. If any features of anaphylaxis (e.g. hypotension, respiratory distress, stridor, gastrointestinal distress, swallowing problems, joint swelling, joint pain) develop, immediate medical intervention is required.

Acute urticaria, frequently a symptom of acute allergic reactions, is common in hospitals because many medications could induce allergic reactions, such as antibiotics, intravenous (i.v.) contrast media, aspirin/NSAIDS, anesthetics, blood material, opioids, muscle relaxants, chemotherapy agents, *etc*. Acute urticaria, frequently a symptom of acute allergic reactions, is also common in emergency rooms and allergy clinics, mostly food allergies (seafood, nuts, etc.), exercise induced allergy, latex allergy, bee stings, *etc*. In these conditions, antihistamines injections (such as diphenhydramine injection) are usually used together with epinephrine, steroids, or other medications for severe cases, or used alone for less severe cases.

In the 2009 US National Hospital Ambulatory Medical Care Survey [3], it was noted that almost 5 million visits were made to hospital emergency departments for acute allergic reactions. Acute urticaria is reported to be the most common symptom associated with acute allergic reactions treated in the emergency department (ED) [4, 5, 6].

The management of acute urticaria in the ED is usually not dependent on the underlying etiology. Most cases of acute urticaria respond to pharmacotherapy, with antihistamines being first-line treatment[7]. To provide rapid relief of the symptoms and associated pruritus, the parenteral route is preferred, but the only antihistamine available for intravenous administration is diphenhydramine injection. Consequently, during the US National Hospital Ambulatory Medical Care Survey period between December 2008 and December 2009, diphenhydramine was used over 4 million times during patient visits to the ED [3]. Unfortunately, diphenhydramine (a short acting antihistamine) causes sedation, impairs mental performance, and results in unwanted anticholinergic effects (e.g.: urinary retention, dry mouth/eyes, etc.) in a large percentage of patients [8, 9, 10, 11] all of which complicate patient management and ED discharge. In contrast, cetirizine, a second generation antihistamine, is associated with a lower rate of sedation, a 24-hour duration of action, and is devoid of anticholinergic effects [10, 11, 12, 13] and other sides effects associated with diphenhydramine.

Development work for cetirizine injection 10 mg/mL was initiated by JDP in 2009. Several clinical trials have been conducted to date:

- Relative bioavailability of cetirizine injection has been investigated in the pharmacokinetics & tolerability study (study # CTN-P0-741) via IV and IM, against the oral tablet of cetirizine. This study was greatly successful. It demonstrated that the AUCs between cetirizine tablet (Zyrtec) and the injection are equivalent, and C_{max} of the cetirizine injection is about 3.5 times of that of the tablet. In addition, JDP's Cetirizine injection did not cause significant adverse events.

- A 2nd relative bioavailability study (Study # CTN-P1-571) on cetirizine injection 10 mg, via IM injection, was also successful without any significant adverse events.

- A pilot phase III clinical study (ETTUAU-02) with a similar study design as the current study ETTAU-03 was conducted as a preparation for the current study to streamline recruiting, IRB process, and IND, etc. ETTAU-02 demonstrated a similar efficacy in acute urticaria symptom score reductions while in treatment centers between the two treatment groups (Cetirizine injection and diphenhydramine injections), demonstrated an earlier patient discharge from treatment centers with the cetirizine group, and also demonstrated a lower sedation levels and symptom recurrence rate with the cetirizine group, etc.

Since acute urticaria, frequently a symptom of an acute allergic reaction, is an acute condition and typically seen in emergency departments (ED) and urgent care centers, it is not feasible to conduct a placebo controlled clinical trial on actual patients. Therefore, non-inferiority clinical trials have been suggested by IRB and regulatory agencies. Currently, Diphenhydramine injection is the standard of care for this condition (although not specifically indicated for the condition), and is the most commonly used antihistamine injection for acute urticaria. It is either used alone for moderate or mild cases, or as an adjunct therapy with other medications for severe cases. Therefore, diphenhydramine injection is proposed as an "active comparator" for a phase III clinical trial.

The present study will confirm the primary endpoint and secondary endpoints via the multi-center, double blind, randomized, active controlled study design to evaluate the efficacy Non-Inferiority comparing Cetirizine Injection 10 mg to Diphenhydramine Injection, 50 mg, for the treatment of acute urticaria in various clinical settings.

3. Study Objectives

3.1 Primary Objectives

The primary objective of this study is to establish the non-inferiority of Cetirizine injection with respect to Diphenhydramine injection in reducing patient reported pruritus severity score at 2 hours after treatment of acute urticaria.

3.2 Secondary Objectives

The secondary objectives will assess, for each treatment group, the following parameters:

1. Record the percent of patients who return to treatment center after discharge (i.e. 2nd visit within ~24 hours after discharge)
2. Record and compare sedation scores between treatments
3. Record and compare time-to-discharge between treatments.
4. Record and compare changes in patient reported pruritus severity score at 1 hr post treatment and at time of discharge.
5. Record and compare Extent of Urticaria/Erythema scores, and their changes from baseline at various time points after treatment.
6. Document the percentage of patients experiencing adverse events (AEs) or serious adverse events (SAEs) from the study drugs.
7. Document the percentage of patients requiring rescue medication prior to discharge, e.g. epinephrine, bronchodilators, steroids, etc., and the reasons for the use of rescue drugs
8. Record symptom recurrence rate and additional symptoms occurrence within ~24-48 hours after patient discharge from treatment centers.
9. Record the need for medication after discharge.

4. Study Design

This is a multi-center, parallel group, randomized, double-blind, active controlled, phase III clinical trial of

cetirizine injection 10 mg/mL versus diphenhydramine injection 50 mg/mL (Benadryl or generic equivalent) in approximately 256 patients (1:1 ratio) who either present to Emergency Departments, Hospitals, allergy clinics or Urgent Care Centers with acute urticaria, or developed acute urticaria following allergen challenge at an Allergy Clinic.

The objectives and purpose of the study will be described to subjects presenting at the participating clinical centers. If a subject agrees to participate in the study, an informed consent form (ICF) will be signed by the subject according to the process followed by each center for obtaining informed consent. After consent is received, the study investigator or designee will verify all inclusion and exclusion criteria to ensure patient eligibility and capture all baseline data such as baseline urticarial symptom scores, vital signs, age, previous medical history, cause of the symptoms (if known), and prior medication use, including all medication taken prior to coming to the facility. Once these data have been collected, the patient will be randomized to receive either cetirizine injection or diphenhydramine injection. The time that the study medication is administered will be recorded in the source documents and/or in the eCRF.

Just before the study medication is administered, the study investigator or designee will record the following baseline data: vital signs, the extent of urticaria and erythema, the severity of pruritus by patient, and the level of sedation by patient. See Attachment B for detailed description of symptom assessment. The same measures will be assessed again at 1 hour and/or 2 hours after the injection, and/or at the Time of "Readiness for Discharge" which can happen at any time after the 1-hour assessment if the symptom score has reached zero at 1hr. If symptom score is not zero prior to 2 hr, patient must be kept at the treatment center for at least 2 hours. At these same time intervals, participating patients will be asked to self-rate (recorded by study staff) the severity of their pruritus and their level of sedation. The patient's responses will be recorded by the investigator/designee on the designated Source Document or eCRF) as "patient assessment scores". The time that the investigator/designee determines that patient is physically and mentally fit to be discharged from the center (Time of "Readiness for Discharge"), , will be recorded in the source documents. If the Time of "readiness for discharge" happens longer than 20 minutes from the previous assessment, then the "readiness for discharge assessment" should be done. If the Time of "readiness for discharge" happens within 20 minutes of the previous assessment and the symptom score does not change from the previous assessment, then the "readiness for discharge" assessment is not needed, because the previous assessment can be treated as the "readiness for discharge assessment".

Site staff should ensure that the patient has appropriate transportation to their destination; under no circumstances should a study participant be permitted to drive themselves if the sedation score is at "1" or higher. The time that the patient actually leaves the treatment center is also recorded.

Before discharge, patients will be instructed that a member of the site staff will telephone them at approximately the same time or the next convenient time (e.g.: if patient is discharged at 3 am, the site staff will telephone the patient at ~8 am) the following day, and the day after (i.e. ~24 hours, and ~48 hours later) to ask them a few short questions to follow up on the treatment of their acute urticaria (See attachment C). Patients will be asked to provide contact telephone number where they can be reached and also given a telephone number for them to call in the event that they are not contacted. Patients will also be instructed to call this number to report any AEs or SAEs they may have experienced.

The decision to discharge the patient (Time of "Readiness for Discharge") can be taken by the Investigator/designee provided the following criteria are met:

1) Symptoms of the acute allergic reaction have been effectively treated based on investigator/designee's opinion (*Note: if rescue drugs are used, patients are deemed not effectively treated by the study drug, but effectively treated by rescue drugs.*)
2) Patient is alert enough (sedation scores = 0) to understand Discharge Instructions
3) Based on the investigator's judgment, the patient is fit to be discharged

Note:

i) *If patient is fit to be discharged, but not alert enough to drive home when the sedation score is at "1" or higher, he/she may be kept for a maximum of 5 hours (to make it practical for research personnel). But appropriate arrangement must be done, such as: call for a taxi, arrange a friend or relative to help drive, or ask patient to stay in the waiting room until sedation goes away, etc.*

ii) *Standard discharge instruction should be given. If medications are prescribed at discharge, instruct patients take them "as needed"*

iii) *In the event if the symptoms were not effectively treated, patients will be treated following the standard of care by attending physician.*

iv) *If "Time of Readiness for Discharge" happens prior to the 2 hour assessment, the "patient Pruritus Score" must be Zero, otherwise the patient has to be kept in the treatment center for at least 2 hours.*

All AEs and SAEs that are reported after the patient signs an ICF will be recorded in the source documents and/or captured in the CRF.

Study procedures and their timing are summarized in the Study Schedule, Protocol Attachment A.

5. Study Population

Subjects who meet all of the inclusion criteria and none of the exclusion criteria and have signed an ICF will be eligible for study participation.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

1) Male or female patients with a diagnosis of acute urticaria who need treatment with antihistamine to alleviate their symptoms;
2) 18 years of age or older;
3) Be willing and able to give informed consent;
4) Patients with a Patient rated Pruritus Severity Score ≥ 1

Note:

- *Patients who, in the opinion of the investigator, have acute urticaria caused by a reaction to a medication (e.g. antibiotics, NSAIDs, etc.) that they are currently taking, but who can stop the medication after presenting to the site may be included in the study.*
- *Patients on regular medications for chronic conditions may be included in the study.*
- *Patients presenting with angioedema in addition to acute urticaria are also eligible to participate.*
- *If patients present acute urticaria together with anaphylaxis, after anaphylaxis symptoms have been alleviated, these patient can also be included in the study as long as urticaria still presents.*
- *Any patients who meet the inclusion/exclusion criteria may be considered for participating in the study, including homeless (if can be reached for follow up by phone), handicapped, etc.*

5.2 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

1) Receipt of an investigational drug or device, within the past 30 days;

2) Patients in whom an antihistamine may be contraindicated (e.g. narrow angle glaucoma, symptomatic prostatic hypertrophy);
3) Patients who, in the opinion of the investigator, may not tolerate an IV injection of diphenhydramine 50 mg, or cetirizine 10 mg;
4) Receipt of any antihistamine (H1 antagonist) within the past 2 hours regardless of the route of administration, e.g. diphenhydramine, cetirizine, loratadine, fexofenadine, levocetirizine, desloratadine;
5) Receipt of an H2 antagonist within the past 2 hours;
6) Receipt of doxepin within the past 2 hours; doxepin is an antidepressant, but it also has antihistamine properties;
7) Receipt of steroids by the oral, IV, IM, or inhalational routes route within the past 4 hours to manage an acute allergic reaction;
8) Receipt of epinephrine (EpiPen or any other brand) within the past 20 minutes;
9) Anaphylaxis prior to the acute anaphylactic symptoms having been treated.
10) Has known allergy to hydroxyzine, cetirizine or levocetirizine, or diphenhydramine;
11) Pregnancy or breastfeeding;
12) Patients who have an acute allergic reaction to medication they are taking (e.g. antibiotics, NSAIDs, etc.) and who cannot stop the medication;
13) Patients who, based on their medical history or in the opinion of the investigator, have chronic urticaria, hereditary angioedema, urticaria refractory to antihistamines, or dermatological disease that interferes with evaluation of a therapeutic response;
14) Any condition that in the view of the investigator makes the subject unsuitable for enrollment in this study;
15) Major medical or psychiatric illness, other than acute urticaria, at the time of presentation;
16) Inability to provide informed consent.
17) Patients on concomitant p-glycoprotein inhibitors

5.3 Discontinuations

Subjects have the right to withdraw from the study at any time for any reason without compromising their clinical management. The investigator also has the right to withdraw subjects from the study if he/she feels it is the best interest of the subject, or if the subject is uncooperative or non-compliant. The discontinued patients will be followed to resolution of any ongoing AEs.

Reasons for discontinuation include:

- Violation of Inclusion or Exclusion criteria found after the study medication has been administered
- The investigator, patient, or the health care professional performing assessments, become un-blinded to the study medication for whatever reason;
- The investigator decides that the patient should be withdrawn. If this decision is made because of a serious adverse event, the study drug, if any, is to be discontinued and appropriate measures are to be taken. The investigator will notify the Sponsor immediately;
- Administrative decision by the Sponsor or Regulatory Authorities. All patients will be discontinued from the protocol and notified of the reasons for the discontinuation;
- The subject may withdraw from the study for any other reason, including withdrawal of consent.

An excessive rate of withdrawal can make the study results difficult to interpret. Any patient who discontinues for a reason other than the occurrence of an adverse event will be replaced by enrolling an additional patient.

The reason for any discontinuation will be fully documented on the Source Document and/or CRF.

Should a patient decide to withdraw, every effort will be made to complete and report all study observations, particularly the 24 hour and/or 48-hour follow-up, as thoroughly as possible. The investigator/designee should contact the subject either by telephone, or through a personal visit if necessary, to determine as completely as possible the reason for the withdrawal.

Note:

- *After discharge, two follow-up phone calls are planned at ~24 hours and ~48 hours. However, sometimes patients do not like to answer phone calls. It is possible only one follow-up can be obtained. In this case, this patient is not considered as discontinued or as protocol deviation.*

- *If rescue medication is needed very shortly after study drug administration (e.g. within ~10 -15min), this indicates that the patient might have or develop into anaphylaxis. This patient should be withdrawn from the study, because he/she should have been excluded during screening.*

6. Treatment

6.1 Treatments Administered

Subjects who fulfill all the inclusion and none of the exclusion criteria will be enrolled into the study. Each subject should read and sign an ICF prior to any study procedures being performed. This study involves a comparison of two injectable products: cetirizine injection, 10 mg/mL, and diphenhydramine injection, 50 mg/mL, both administered during a ~2-minute period by intravenous slow push. The injections can be injected directly or after dilution with saline depending on the internal standard procedure at each treatment center related to i.v. diphenhydramine. Subjects will receive pre-randomized treatment drugs of one of the following:

- Cetirizine, 10mg/mL; a single 1 mL injection via intravenous slow push over a period of ~2 minutes
- Diphenhydramine, 50mg/mL; a single 1 mL injection via intravenous slow push over a period of ~2 minutes.

6.2 Materials andSupplies

Treatment drugs (Investigational drug and Control) will be pre-randomized and blinded before arriving at each investigational site. A drug dispensing log will be kept current and will contain the following information:

- The identification of the subject to whom the drug was dispensed
- The date, quantity, and lot number of the drug dispensed to the subject

Drug inventory and accountability records (Test Article Accountability Log) will be maintained at each site. A monitor or designated site staff will reconcile drug inventory and review accountability records. Any unused vials of cetirizine will be returned to the sponsor or destructed on site per sponsor request. Study drugs are to be stored at room temperature.

6.3 Method of Assignment to Treatment

Approximately 256 patients will be randomized to either one of two treatment groups in a 1:1 ratio. A randomization list in blocks of four will be generated centrally by the sponsor/or CRO for each site.

Approximately 13 blocks, i.e. enough study medication for a maximum of 52 patients will be sent to each study site prior to patient enrollment. A treatment vial, consisting of one vial of either cetirizine or diphenhydramine, based on the treatment assignment of the centralized randomization schedule, will be packaged for each randomization number and labeled by the randomization number, using a blinded label to cover the product name. A list will contain assignment of sequential numbers to one of the two treatment groups. The original randomization list will be kept secured until the study blind is broken. At the investigational site, each randomized subject will be assigned a subject identifier number. This identifier number ("Subject Number" or "Subject Identification Number") will be used on all subject documentation. Subject Numbers will be assigned in ascending sequential order. The Subject Number will consist of two digits (site number) followed by three digits (subject number), e.g. 02-009 (the 9th patient enrolled at site #2).

The randomization number (Treatment Number) for each subject with its Subject Number will be allocated at baseline and entered in the source document or eCRF, after verifying the inclusion and exclusion criteria.

6.4 Control Product and Study Medication

- *Investigational Product:* cetirizine injection, a single 1.0 mL injection (10 mg/mL) given by slow intravenous push (~2 minutes).
- *Control Product:* IV diphenhydramine, a single 1.0 mL injection (50 mg/mL) given by slow intravenous push (~2 minutes).

6.4.1 Rationale for Using Diphenhydramine as the Control Product

IV diphenhydramine is the only antihistamine injection available for the treatment of acute urticaria. [redacted] CCI The approved indication for IV diphenhydramine is as follows:

> *For amelioration of allergic reactions to blood or plasma, in anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled, and for other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated*[14].

6.4.2 Rationale for Selection of the Dose of cetirizine injection

The recommended dose of oral cetirizine is 10 mg (Zyrtec®/Reactine® Prescribing Information). This dose has been shown to strongly inhibit the wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10 mg oral dose occurs within one hour in 95% of subjects.

[redacted] CCI

Although direct comparisons between IV diphenhydramine and IV cetirizine in the medical literature are lacking, the generally recommended doses to manage acute allergic reactions are 50 mg and 10 mg, respectively [11]. Furthermore, cetirizine, 10 mg oral tablet is commonly used to treat acute urticaria by allergists[11,12]. Cetirizine 10 mg is also the Reference Listed Drug (RLD) dose specified by the FDA.

JDP conducted its direct comparison study between IV cetirizine 10 mg and IV diphenhydramine 50 mg in a pilot phase III clinical trial (ETTUAU-02) with a similar study design as the current study (ETTAU-03) as a preparation for the current study to streamline recruiting, IRB process, and IND, etc. ETTAU-02 demonstrated a similar efficacy in acute urticaria symptom score reductions while in the treatment centers between the two treatment groups (Cetirizine injection 10 mg and diphenhydramine injection), demonstrated an earlier patient discharge time from treatment centers with the cetirizine group than the diphenhydramine group, and also demonstrated a lower symptom recurrence rate with the cetirizine group within ~24 hours after discharge than with the diphenhydramine group, etc. The 10 mg Cetirizine dosage in an injection form was shown to be similarly effective as diphenhydramine injection in the pilot phase III study, and thus was selected for the current study.

6.4.3 Randomization and Maintenance of Study Blind

This will be a double-blind study; the investigator, the patient, and any health care professional involved in patient management or outcome assessment will remain blinded. Both cetirizine injection and IV diphenhydramine are presented as a clear aqueous solution in 2 mL amber vials containing 1.0 mL of medication, and having similar physical appearance. A blinded and randomized label created for the study conceals the product label of each vial for both the Investigational drug cetirizine and the comparator diphenhydramine. To further maintain blinding, the randomized medication can be drawn up into a syringe for administration by a staff member who is not involved in patient management or outcome assessment. The healthcare professional involved in patient management and outcome assessment is completely blinded.

Treatment drugs (Investigational drug and Control) will be pre-randomized and blinded at 1:1 ratio by the Sponsor or CRO, according to the randomization schedule (see Section 6.3), prior to being delivered to each investigational site. At the investigational site, the trial randomization code will remain secure at all times, but may be accessed in the event of an emergency.

6.4.4 Breaking the Study Blind

In order to preserve the blinding of the study, site personnel will not have access to the randomization code and treatment assignments before data base lock. Study blinding may only be broken if the identity of the study drug is considered vital for the clinical management of the subject.

Since this is an acute care study it is impractical to notify the Sponsor and Medical Monitor prior to breaking the blind for a patient should it be necessary. However, all emergency code breaks must be reported to the Sponsor, CRO, the Medical Monitor and/or the Project Manager in a timely fashion. The time, date, the reason and who broke the blind, must be documented in the source documents and/or will be captured in the eCRF.

If the investigator, patient, or health care professional performing the assessments, is unblinded for whatever reason, the patient will be included in all analyses of the study results, but a replacement patient will be recruited by the center. No assigned Subject ID Numbers will be reused for any subjects.

6.4.5 Concomitant Medications/Rescue Drugs

To ensure optimal patient management, additional medications, e.g. epinephrine, steroids, or etc., may be given during the study if deemed necessary by the investigator/designee. However, if without medical complication, all effort should be made to have the patient complete at least the 1 hour assessments prior to administration of the rescue medication. If rescue medication is needed very shortly after study drug administration (e.g. within ~10 -15min), this indicates that the patient might have anaphylaxis. This patient should be withdrawn from the study, because he/she should have been excluded during screening.

The product label of the rescue drugs should be followed to determine the appropriate dose.

The identity, dose, frequency and route of administration of all medications being taken prior to study enrolment will be recorded, as well as all concomitant medications administered during the study (rescue drug).

6.5 *Clinical and Safety Evaluations*

Study procedures and their timing are summarized in the Study Schedule, Protocol Attachment A. All subjects who received at least one dose of study medication will be included in all analyses and safety analyses.

7. Clinical/Efficacy Outcome and Measures

7.1 Primary Clinical Efficacy Measure

The primary clinical efficacy outcome measure is the 2-hour patient rated Pruritus Severity Score Reduction/Change from Baseline (**D2**) as defined under Attachment B**,** comparing between the two treatment groups.

7.2 Key Secondary Clinical/Efficacy Measures

The following key secondary clinical or efficacy measures will be assessed for each patient:

1) The need to return to treatment center after study discharge (i.e. 2nd visit within approximately ~24 hours after discharge)

2) Time spent at the treating center (time from treatment administration to Readiness for discharge)

7.3 Other Clinical/Efficacy Measures

The following other clinical or efficacy measures will be assessed for each patient:

1) Pruritus treatment success (% of patients), defined as a patient who had the Pruritus Severity Score Reduction of at least 1 unit for the 2-hour patient rated Pruritus Severity score from Baseline (**D2**) as defined under Attachment B**,** comparing between the two treatment groups.
2) Patient rated pruritus severity scores reduction/change from baseline (D1 & D3) at 1 hour and at "time of discharge"
3) Sedation Scores, at baseline, 1hr, and/or 2hr, and/or Readiness for Discharge (B2)
4) Physician rated Extent of Urticaria/Erythema Scores and their reduction/change from baseline at 1 hour, 2 hours and "time of discharge" (C1, C2, C3).
5) Use of rescue medication, e.g. epinephrine, bronchodilators, steroids, etc., and the reasons for the use of rescue drugs
6) "Effectively treated" based on investigator's opinion of Yes or No.
7) Symptom recurrence and additional symptom occurrence within ~24 - 48 hours after patient discharge from treatment centers.
8) The need for prescribed medication within ~24-48 hours after discharge.
9) The need for additional medication, including any over-the-counter medications, within ~24 -48 hours after discharge.

10) Ability of returning to normal activity after discharge

8. Safety Evaluations

The safety population is defined as all patients who received study medication. Investigators are responsible for monitoring the safety of patients who are participating in this study and for alerting the Sponsor of any event that seems unusual, even if this event may be considered as an unanticipated benefit to the patient. The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following through an appropriate health care option for adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up is left to the discretion of the investigator.

In this study, safety will be evaluated by recording any adverse events for up to 28 days following treatments and by monitoring vital signs at planned intervals from admission into the treating facility until readiness for discharge.

8.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship to the treatment. Cases of pregnancy should be reported for tracking purposes. Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish a drug effect.

Prior to enrollment, study site personnel will note the occurrence and nature of each patient's medical condition(s) in the appropriate section of the source document or CRF (Medical History).

If a patient experiences an adverse event after the informed consent document is signed, the event will be recorded as an adverse event in the Source Document and/or CRF. All AEs encountered will be described in the source documents and/or in the CRF.

The severity of the event will be classified according to the following terms:

- **Mild:** symptom is manifest but is tolerated.
- **Moderate:** normal activity affected.
- **Severe:** severe effect or inability to work or necessary to discontinue the study medication

The causality will be classified as:

- **Not related**: Any adverse event which is not related to the product being studied.
- **Possible**: Any adverse event which can be caused by the use of the product being studied, but for which another explanation can be found – for example, the existence of a concomitant treatment or concurrent disease(s) – or for which the relation in time is not obvious.
- **Probable**: Any adverse event which can be caused by the use of the product being studied. The relationship in time is suggestive (for example, if the event disappears when the treatment is interrupted). Another explanation is less probable – for example, the existence of a concomitant treatment or concurrent disease(s).
- **Not-assessable**: It is impossible to attribute the event to any of the categories above, because the information obtained is insufficient, incomplete or contradictory. Additional information is necessary to determine the causal relationship with the product being studied.

If a subject is discontinued as a result of an adverse event, study site personnel must clearly document the circumstances leading to any such discontinuation of treatment, in the source document and/or on the CRF.

Events leading to a clinical outcome will be included as part of the safety and efficacy analyses for this study, and will not be recorded as AE unless the investigator believes the event may have been caused by the study drug.

8.2 Serious Adverse Events

A serious adverse event (SAE) is any experience that suggests a significant hazard, contradiction, side effect or precaution. Study site personnel must report immediately to the Sponsor by the designated transmission method any adverse event from this study that results in one of the following outcomes, or is significant for any other reason:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

All SAEs must be reported to the Sponsor (or to the Sponsor's designated person) **within 24 hours** of the Investigator's knowledge of the event. Notification can be made by fax or email to:

The Investigator/designee must provide the following information, as a minimum: the subject number in the study, the nature of the event, the date of onset of the event and the relationship with the study treatment according to the information available at the time of reporting.

An SAE occurring after a subject is discontinued from the study will be reported regardless of causality to the study medication or a protocol procedure. Should an investigator be made aware of any SAE occurring any time after the active reporting period, it must be promptly reported to the Sponsor or designate.

8.3 Safety Monitoring

The Medical Monitor will review safety data, including vital signs, adverse events, and serious adverse events on an ongoing basis.

Vital signs, which include sitting systolic and diastolic blood pressures, heart rate, temperature and respiration rate, will be collected on each subject at arrival at the treatment center, at baseline (just prior to treatment administration) at 1 hr and/or 2 hrs post treatment and at the time of discharge.

9. Data Quality Assurance

To ensure accurate, complete, and reliable data, the Sponsor or CRO will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor an Investigator/coordinator training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the source document, CRFs, and study procedures.
    - Make periodic visits to the study site.
    - Be available for consultation and stay in contact with the study site personnel by mail,

email, telephone, and/or fax.
- Review and evaluate the source document and/or CRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

- Verify the quality of the data.

In addition, the Sponsor representative will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Medical Quality Assurance (MQA) and/or regulatory agencies at any time. Investigators will be given notice before an MQA audit occurs.

9.1 Direct Data Entry and Computerized Systems

An electronic data capture system may be used in this trial. Some or all of a patient's data may be directly entered into the system on an eCRF at the time that the information is obtained. In instances where eCRF is not feasible, data may be recorded manually directly to the Source Document first; then later transferred to the eCRF. Monitored and verified data will subsequently be transferred to the sponsor.

9.2 Confidentiality of Trial Documents and Subject Records

The investigator must assure that the subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On the source document, CRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by an identification code. The Investigator should keep a subject enrolment log reconciling subject codes and subject names. The Investigator should maintain all subject related documents in strict confidence.

9.3 Investigator's Files/Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories, namely Investigator Study File and Patient Clinical Source Documents.

The Investigator must keep these two categories of documents on file for the duration required by local regulation, after completion or discontinuation of the study. After that period of time the documents may be destroyed, in accordance with local regulations.

10. Sample Size and Statistical Methods

10.1 Determination of Sample Size

Assuming the diphenhydramine treated group responds similar to ETTAU-02 results, the common standard deviation is expected to be around [redacted]CCI A minimum sample size of [redacted]CCI subjects per arm is needed to provide 90% coverage probability (90% power) that the width of the 95% confidence interval of the treatment differences will remain within [redacted] if cetirizine is to be non-inferior to diphenhydramine. [redacted]CCI [redacted]CCI [redacted] the sample size of [redacted]CCI per treatment arm is recommended for a total enrollment of [redacted] subjects to ensure sufficient numbers of completers at 2 hrs. The sample size estimation was performed using [redacted]CCI

10.2 Statistical and Analytical Plans

10.2.1 *Patient/Subject Disposition and Analysis Populations*

The disposition of all subjects, including those who discontinued, will be summarized by group, using counts and frequencies in each population. Subjects will be categorized into the following analysis populations:

- **Intent-To-Treat (ITT) Population**: Includes any subject who was randomized and given a Subject ID Number with intent to treat with one of the blinded study drugs. All efficacy and non-inferiority analyses will be performed on the ITT population with subjects grouped by the treatment they were randomized toreceive.

- **Safety Population (SAF)**: Includes any subjects in the ITT population who actually receives a blinded study drug, regardless whether or not they complete all assessments, withdraw or are discontinued by the investigator. All safety summaries will be performed on the SAF population with subjects grouped by the treatment they actually received.

- **Per Protocol Population (PP)**: Includes subjects in the SAF population who complete all necessary assessments without any incidence that would potentially affect the ability to objectively assess treatment response (e.g. discontinuation, protocol deviation, use of rescue medication, etc.).

10.2.2 Patient/Subject Characteristics

Descriptive statistics will be used to summarize participant demographics and baseline characteristics by treatment group. Characteristics such as weight, height and/or age will be summarized as continuous variables with means, SD, medians, minimums and maximums. Demographics, such as ethnicity and/or race will be summarized as counts and frequencies. The ITT population will be used to summarize baseline characteristics and demographics by treatment group.

10.2.3 Medical/Surgical History and Physical Exam Findings

Upon arrival subjects will be asked about their medical/medication and surgical histories, and allergy history. This information will be used in the event that it may help to explain any adverse reactions or other unexpected outcomes. The findings will be provided in data listings, but will not be tabulated and summarized by treatment group.

10.2.4 Concomitant Therapy

The medications taken by each group, prior to study enrollment and during the treatment period, will be coded using the latest WHO-Drug Coding Dictionary for anatomical therapeutic class (ATC) and preferred medication names and summarized by incidence as counts and frequencies within ATC and preferred names for each treatment group. The SAF population (safety population) will be used to summarize all concomitant therapies by treatment group.

10.2.5 Safety Assessment

Safety parameters include assessment of adverse events (AEs) throughout the study. The safety analysis set will include all patients who received the study medication. All safety data will be displayed and analyzed 'as randomized' using descriptive statistical methods such as incidence rates. Events occurring more than once in the same patient will be counted only once. No formal inferential analysis is planned for safety comparisons.

AEs will be coded for system organ class (SOC) and preferred terminology using the latest MedDRA coding dictionary. Incidences of AEs will be summarized as counts and frequencies within the SOC and preferred terms for each treatment group. The SAF population will be used to summarize all AEs by treatment group.

Vital signs will be summarized as continuous data with means, SD, medians, minimums and maximums for each vital sign for each assessment time, by treatment group.

10.2.6 Primary Efficacy Assessment

All patients who received the study medication will be included in the full set analyses (FAS) the analyses.

The primary clinical outcome measures of **D2** as defined under Attachment B, will be summarized for each study group in cross classified tables for the 2-hour assessment.

The hypothesis is defined as: the **D2** score for the investigational drug is not worse than the comparator at the 2-hour time point, based on 95% confidence interval [redacted]. See the statistical analysis plan for details.

10.2.7 Key Secondary Efficacy Analyses

Key secondary clinical outcomes as detailed under Section 7.2 will be summarized using descriptive statistics (frequencies, proportions, means, standard deviation, median and/or range, etc.). Inferential treatment comparisons will be performed for each outcome with adjustments made for multiplicity as described in the statistical analysis plan.

10.2.8 Other Efficacy Analyses

Other clinical outcomes as detailed under Section 7.3 will be summarized using descriptive statistics (frequencies, proportions, means, standard deviation, median and/or range, etc.). No inferential treatment comparisons will be made on these outcomes.

11. Ethics

11.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1996) and that are consistent with "Good Clinical Practice" ICH Tripartite Guideline (January 1997) and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

11.2 Ethical Review

It is the understanding of the Sponsor that this protocol (and any amendment) as well as appropriate consent procedures, will be reviewed and approved by a Research Ethics Board (REB/IRB). This Board must operate in accordance with the current Federal regulations. A letter or certification of approval will be sent by the Investigator to the Sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

11.3 Informed Consent

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

The CRFs for this study contain a section for documenting informed subject consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefice assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and asked to give their consent to continue in the study.

11.3.1 Protocol Signatures

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to the Sponsor (Page 5 of the Protocol).

11.3.2 Publication Policy

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

12. References

1. Kaplan AP, Greaves, M. Pathogenesis of chronic urticaria. Clin Exp Allergy; 2009 ;39: 777-787
2. Frigas E, Park M.A. Acute urticaria and angioedema: diagnostic and treatment considerations. Am J Clin Dermatology; 2009; 10: 239-250
3. National Hospital Ambulatory Medical Care Survey: 2009 Emergency Department Summary Tablesa=v&q=cache:gvyu34jAfOIJ:www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2009_ed_web_tables.pdf+national+hospital+ambulatory+medical+care+survey+2009+emergency+department+summary&hl=en&gl=ca&pid=bl&srcid=ADGEESgDP5OTVY6CDN_XqvW3m32WMkQhnPbh5dJh8u0quP3uRI05tZHuQrPlgsrqidvBH_jNLUclR_7WuBAIIBJy4yY33xcg3NchuXWUOnKcgkEDGQds8-She91S59w0j-DL-NzStOGq&sig=AHIEtbQW7x57INfnud0QvmmimCyBJTSguQ Accessed October 28th 2012
4. Simonart,T et al. Particularities of urticaria seen in the emergency department. Eur J Emerg Med 1994; 1; 80-82
5. Gupta R, et al. Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. BMJ: 2003; 327, 1142-1143
6. Champion, R.H et al. Urticaria and Angio-Edema a Review of 554 patients. Br. J. Derm: 1969, 81, 588-597
7. Zuberbier,T et al. EAACI/GALEN/EDF/WAO Guideline: definition, classification and diagnosis of urticaria. Allergy 2009; 64: 1417–1426
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9. Kay, G et al. Initial and Steady-State Effects of Diphenhydramine and Loratadine on edation, Cognition, Mood, and Psychomotor Performance. Arch Intern Med. 1997;157:2350-2356
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12. Park, J. et al. Comparison of cetirizine and diphenhydramine in the treatment of acute food-induced allergic reactions. J Allergy Clin Immunol: 128; 1127-1128
13. JDP Therapeutics Inc., Clinical Study Report No CTN-P0-741. Date of Report: 2011/09/11. Protocol Title: Single Dose Crossover Pharmacokinetics Study of Cetrizine Injection at 5 mg and 10 mg Intravenous doses and 10 mg Intramuscular dose compared to oral Cetrizine 10 mg tablets in healthy male and female volunteers. Fastingstate
14. JDP Therapeutics Inc., Clinical Study Report No CTN-P4-427 (ETTAU-02). Date of Report: 2015/02/06. Protocol Title: Multicenter pilot study to assess the feasibility of conduction phase III trial comparing i.v. administration of cetirizine injection 10 mg, to i.v. injection of diphenhydramine injection 50 mg, for the treatment of acute urticaria associated with an acute allergic reaction.
15. Benadryl® (Diphenhydramine Hydrochloride Injection, USP) 2006 Product Information Sheet.

Protocol Attachment A
Study Schedule

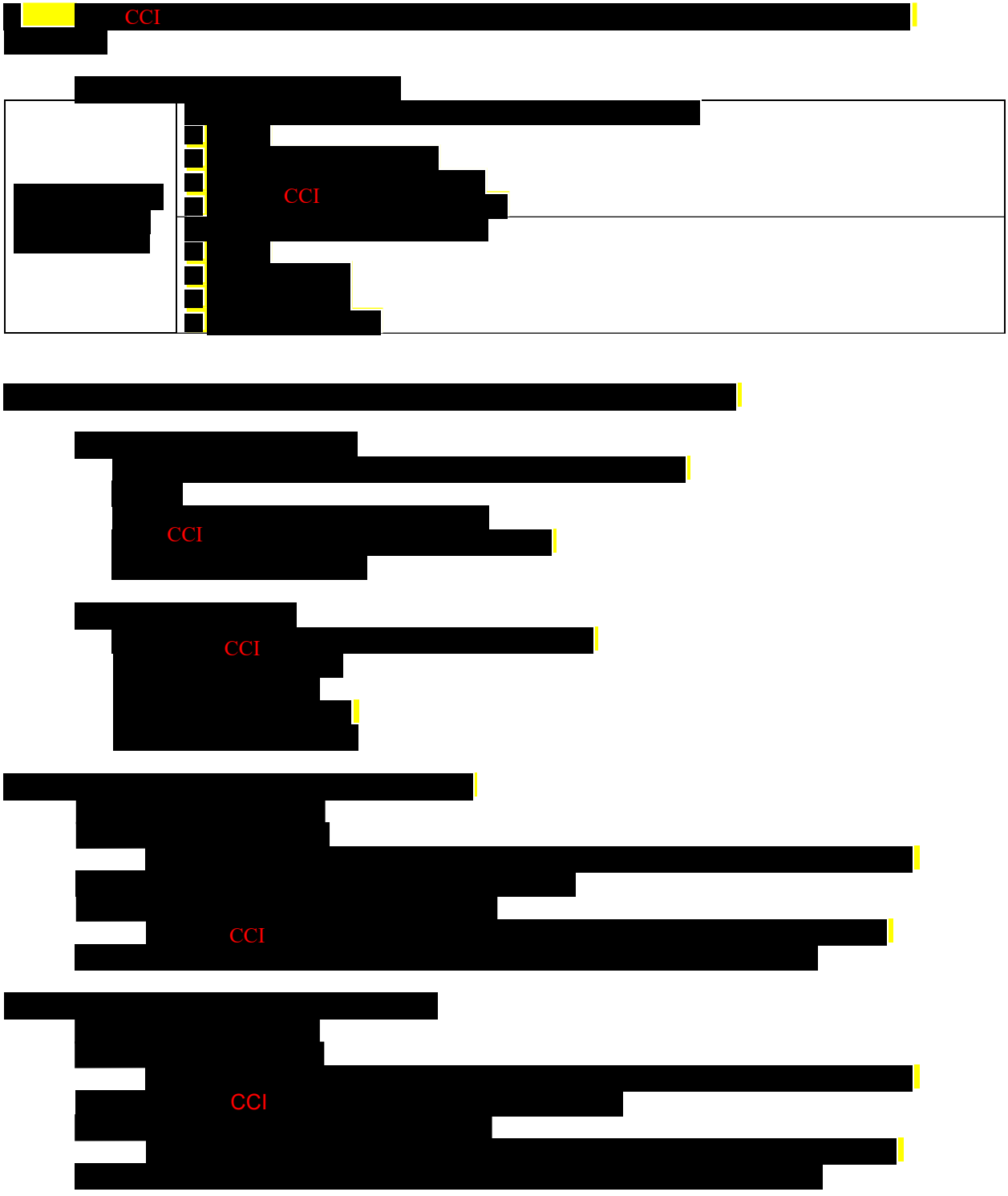
Assessments	Arrival at the site	Baseline	0 Hr	1 Hr	2 Hrs	Time of Discharge	24 Hr Follow Up	p To 28 days post 4 Hr FU
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical and Surgical History	X							
Vital signs	X	X		X	X	X		
Study Medication Administration			X					
Extent of urticaria/erythema)[1]		X		X	X	X		
Pruritus Severity Score[2]		X		X	X	X		
Sedation Score[2]		X		X	X	X		
Time of Discharge						X		
Concomitant medication	X	X		X	X	X	X	
Adverse events	X	X		X	X	X	X	
Follow-up Q&A Sheet							X	
Record patient self-reported AEs								X

1 Assessed only by the doctor

2 Assessed by the doctor and the patient

Protocol Attachment B

Symptom Scores



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Protocol Attachment D
Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, and other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the

publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.