DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

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# Statistical Analysis Plan

**Protocol No.: ETTAU-03**

**Protocol 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.

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**Abbreviations and Definitions:**

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| CI | Confidence Interval (confidence limits) |
| ETTAU | Efficacy Trial for the Treatment of Acute Urticaria |
| ED | Emergency Department |
| MedDRA © | Medical Dictionary for Regulatory Activities |
| N | Number (typically refers to subjects) |
| NI | Non-inferiority |
| SAP | Statistical Analysis Plan |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| WHO | World Health Organization |

## 1. PREFACE

This document describes in detail the statistical methods that will be used to summarize and analyze the background, safety, and efficacy data from protocol ETTAU-03 entitled "*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."* (dated April 10, 2017).

## 2. STUDY OBJECTIVES AND ENDPOINTS

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 254 subjects with acute urticaria requiring treatment in Emergency Departments (ED), hospitals, Urgent Care Centers, or Allergy Clinics.

The objectives of this study are:

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. The secondary objectives are as follows:

1. Record the percentage of subjects who return to treatment center after discharge (i.e. 2$^{nd}$ 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 subjects experiencing adverse events (AEs) or serious adverse events (SAEs) from the both study drugs.
7. Document the percentage of subjects requiring rescue medication prior to discharge, e.g. epinephrine, bronchodilators, steroids, etc.,
8. Record symptom recurrence rate and additional symptoms occurrence within 24-48 hours after subject discharge from treatment centers.
9. Record the need for medication after discharge.

The primary demonstration of efficacy will be non-inferiority of cetirizine to diphenhydramine with regards to the change from baseline in patient rated pruritus severity at 2 hours post-treatment.

The following outcomes that will provide key support to the primary efficacy claim:

- *Return to Treatment Center*: During the 24 and 48 hr follow up questions, subjects will be asked if they had to return to a treatment facility for their urticaria. Subjects will be flagged as either YES or NO.

- *Time Spent at Treatment Center*: This will be defined as the difference between the time of treatment administration and of Readiness for Discharge. If a patient is admitted to hospital (not to go home), or stayed in ED observation overnight, the time to "Readiness for Discharge" is not recorded. These subjects will not be included in the summary analyses.

In addition, the following outcomes will be assessed by treatment as supportive information for the application:

1) *Pruritus Treatment Success*: A subject will be defined as having treatment success if the patient rated pruritus severity score at 2 hrs is at least 1 unit less than at baseline.

2) *Patient Rated Pruritus Severity Scores change at other time points*: The scores change/reduction from baseline at other assessment times (i.e.: 1 hr and at discharge)

3) *Sedation Score*: Subjects will be asked to rate their sedation at baseline, 1 hr, 2 hr and discharge.

4) *Physician Rated Extent of Urticaria/Erythema Scores:* Physicians will rate the percentage of body area affected and the intensity of redness on scales from 0 (none) to 3(severe) at baseline, 1 hr, 2 hr and discharge. The average of body area and intensity scores at each assessment time will be the Extent of Urticaria/Erythema score for that assessment time. This outcome will have the range from 0 to 3 with increments of 0.5 units.

5) *Proportion of Subjects Needing Rescue Medication:* A subject will be defined as needing rescue, if at any time after study drug and prior to readiness for discharge, the subject requires other medications for the symptoms of urticaria.

6) *Effectively Treated:* The investigator's judgment of a subject's effective treatment of symptoms (Yes/No).

7) *Symptom Recurrence:* Subjects will be followed up after 24 and 48 hours after discharge and asked if they have had any recurrence of symptoms since discharge.

8) *Need for Prescription Medications:* During the 24 and 48 hr follow up questions, subjects will be asked if they took any medications prescribed at discharge since discharge.

9) *Need for Additional Medications*: During the 24 and 48 hr follow up questions, subjects will be asked if they took any additional medications since discharge.

10) *Return to Normal Activity*: During the 24 and 48 hr follow up questions, subjects will be asked if they had returned to their normal activities.

See Section 10.4 for detail on the specific analyses to be performed for each outcome.

## 3. 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 254 subjects 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.

Subjects, or their guardians, will sign an informed consent and will be evaluated for eligibility for inclusion to treat. Eligible subjects will be assessed for baseline characteristics, medical and surgical histories, concomitant medications and given a brief physical exam. Then subjects will be randomized, in a 1:1 ratio, to blindly receive either cetirizine 10 mg/mL injection or diphenhydramine 50 mg/mL injection. At randomization, the subjects will be given a Subject ID Number that corresponds to the randomization schedule and administered study medication based on the kit contents. Neither the subjects, nor study personnel will know which study drug is given.

Efficacy assessments will include patient rated severity of pruritus, and physician assessments of Extent Urticaria/Erythema, etc. Subjects will remain in the treatment center for at least after the 1 hr assessment, after which they may be discharged at the physician's discretion.

Safety will be monitored through the reporting of 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. After 24 and 48 hours after discharge, subjects will be contacted by phone for follow up questions regarding recurrence of symptoms, new symptoms, additional medication taken, side effects from medication taken after discharge, relapse requiring a return to treatment center and return to normal activities. The schedule of assessments is outlined in Table 1.

**Table 1 Schedule of Assessments**

| Assessments | Arrival at the site | Baseline | 0 Hr | 1 Hr | 2 Hrs | Time of Discharge | 24 Hr Follow Up | Up To 28 days post 24 Hr FU |
|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | |
| Demographics | X | | | | | | | |
| Medical and Surgical History | X | | | | | | | |
| Vital signs | X | X | | X | X | X | | |
| Physical examination | 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 subject self-reported AEs | | | | | | | | X |

## 4. SEQUENCE OF PLANNED ANALYSES

All analyses outlined in this document will be carried out after:

- The study database has been authorized by the Sponsor Clinical team as complete and final.
- Protocol deviations have been identified.
- The study is officially unblinded to treatment assignments

## 5. DEFINING NON-INFERIORITY MARGIN

The effect of diphenhydramine injection based on patient recorded pruritus scores in comparison to placebo is unknown. Given the length of time (usually several hours) subjects indicated that urticaria started prior to ED/clinic admission or started while in ED for other diseases, it is reasonable to assume that if left untreated, there would be no spontaneous resolution within 2 hours of ED/clinic admission.

CCI

CCI

CCI

## 6. SAMPLE SIZE CONSIDERATIONS

Assuming the diphenhydramine treated group respond similar to ETTAU-02 results, the common standard deviation is expected to be around CCI . A sample size of CCI subjects per arm (total CCI is needed to provide 90% statistical power to determine that Cetirizine will be non-inferior to diphenhydramine. The sample size was calculated based on the CCI as the non-inferiority limit of the difference, using 1-sided test at alpha CCI CCI . Sample size estimation was performed using CCI two-group t-test of equivalence in means (MTE0-1).

## 7. 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 to receive.

**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.).

## 8. INTERIM ANALYSES

No interim analyses are planned for this study.

## 9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All statistical analyses and summaries will be performed using SAS for PC, version 9.4 (SAS Institute, Cary, NC). Continuous and quantitative, variable summaries will include the number of patients (N) assessed (with non-missing values/valid cases), mean, standard deviation, minimum.

Categorical and qualitative variable summaries will include the frequency and percentage of subjects who are in the particular category. The denominator for each percentage will be the number of subjects within the population of the treatment arm (unless otherwise specified).

The assumed overall type I error rate/significance level for the primary efficacy outcome is 5%, two-sided, unless otherwise specified. Two-sided confidence limits will be evaluated at 95%, p-values from inferential tests comparing specific cohorts or subgroups will be compared to 5%.

### 9.1. Imputed and Missing Data

The primary efficacy analysis will be performed on the ITT population. Subjects may be discharged at any time after 1 hr post-treatment assessment, which would result in missing data at the 2 hr post-treatment assessment time. Therefore, assessments of pruritus, extent of urticaria, and sedation for subjects discharged prior to the 2 hr assessment will be carried forward from the last recorded score to 2 hrs and beyond.

In addition, subjects may receive rescue medication at any time post-study drug and prior to Readiness for Discharge if the attending physician deems it necessary. Any assessment of pruritus, extent of urticaria and sedation after administering rescue medication will be confounded with the response to rescue medication. If a subject is given one or more rescue medications prior to the 2 hr assessment, the last pre-rescue assessments will be carried forward to the 2 hr assessment and to any post-rescue assessments.

Since the use of rescue would always occur prior to readiness for discharge, the use of rescue will always supersede early discharge with regards to carrying the last observation forward. As long as rescue drug

is used, the pre-rescue score will be carried forward to all subsequent assessment including the 1hr, 2hr, and readiness-for-discharge-assessment.

Examples:

i) If the earliest rescue is used at 30 minutes after study drug, and the patient's readiness-for-discharge is at 1.5hr, the baseline scores (the last pre-rescue score) will be carried forward to the 1hr, 2hr and discharge assessments, regardless of the existing assessments at 1hr and 1.5hr (the discharge assessment).

ii) If the earliest rescue is used at 30 minutes after study drug, and the patient is ready for discharge at 2.5hr post study drug, the baseline scores (the last pre-rescue-score) will be carried forward to the 1hr, 2hr and discharge assessments, regardless of the existing assessments at 1hr, 2hr and 2.5hr (the discharge assessment).

iii) If the earliest rescue is used at 3hrs after study drug, and the patient's readiness-for-discharge is at 4hrs, the 2hr scores (the last pre-rescue-scores) will be carried forward to the discharge assessment regardless the existing 4hr assessment (the discharge assessment).

iv) For a patient without rescue drug, if readiness-for-discharge occurs at 1.5hr, the discharge assessment (1.5hr, the last obtained score) will be carried forward to 2hr.

v) For a patient without rescue drug, if readiness-for-discharge occurs at the same time as the 1hr assessment, the 1hr assessment (the last obtained score) will be carried forward to 2hr and to the discharge assessment.

vi) For a patient without rescue drug, if readiness-for-discharge occurs at the same time as the 2hr assessment, the 2hr assessment will be carried forward to the readiness-for-discharge assessment.

### 9.2. Hypothesis Testing

The purpose of this study is to determine if the effectiveness of cetirizine 10 mg/mL injection is non-inferior to the effectiveness of diphenhydramine 50 mg/mL. The non-inferiority margin will be set at CCI See Section 5 for the rationale.

The null hypothesis is that cetirizine is inferior to diphenhydramine if the difference is CCI with 95% confidence. The null hypothesis is stated as:

H0: CCI CCI

where D2 is the change from baseline of the 2 hr patient rated severity of pruritus for each treatment. The alternative hypothesis to be tested is:

H1: CCI CCI

If the null hypothesis is rejected in favor of the alternative (e.g., cetirizine is not inferior to diphenhydramine) and if the treatment difference CCI then the alternative

hypothesis will be further refined in a stepwise manner to test for superiority of cetirizine over diphenhydramine:

H2: CCI CCI

This stepwise process of testing for superiority only after rejecting the null for non-inferiority will spare type I error. Details of the methods to be used are provided in Section 10.1,

### 9.3. Adjustments for Multiplicity

There is only one primary endpoint being tested to determine efficacy of cetirizine 10 mg/mL injection on 2hr patient rated pruritus severity. Key secondary endpoints will be used to support the claims of the primary efficacy outcome. There are 2 outcome measures that are key in supporting the efficacy claim: the need to return to treatment center after study discharge and time spent at the treatment center (time from treatment administration to readiness for discharge). Family-wise error rate will be controlled using Holm-Bonferroni method of rejecting individual hypotheses (Holm, 1979).

Although nominal p-values will be reported for treatment differences, none of the other secondary endpoints will be used to evaluate for superiority or non-inferiority of cetirizine compared to diphenhydramine, therefore no adjustments for multiplicity are planned.

### 9.4. Covariates

No covariates are planned. However, in the event there are some treatment disparities in baseline characteristics (e.g., age or weight), covariates may be added to the analysis of the primary endpoint as part of the per protocol analysis.

### 9.5. Examination of Subgroups

No subgroup analyses are planned.

### 9.6. Premature Discontinuation and Missing Data

For any subject who withdraws prematurely from the study, all available data up to the time of discontinuation will be included in analyses.

### 9.7. Study Centers

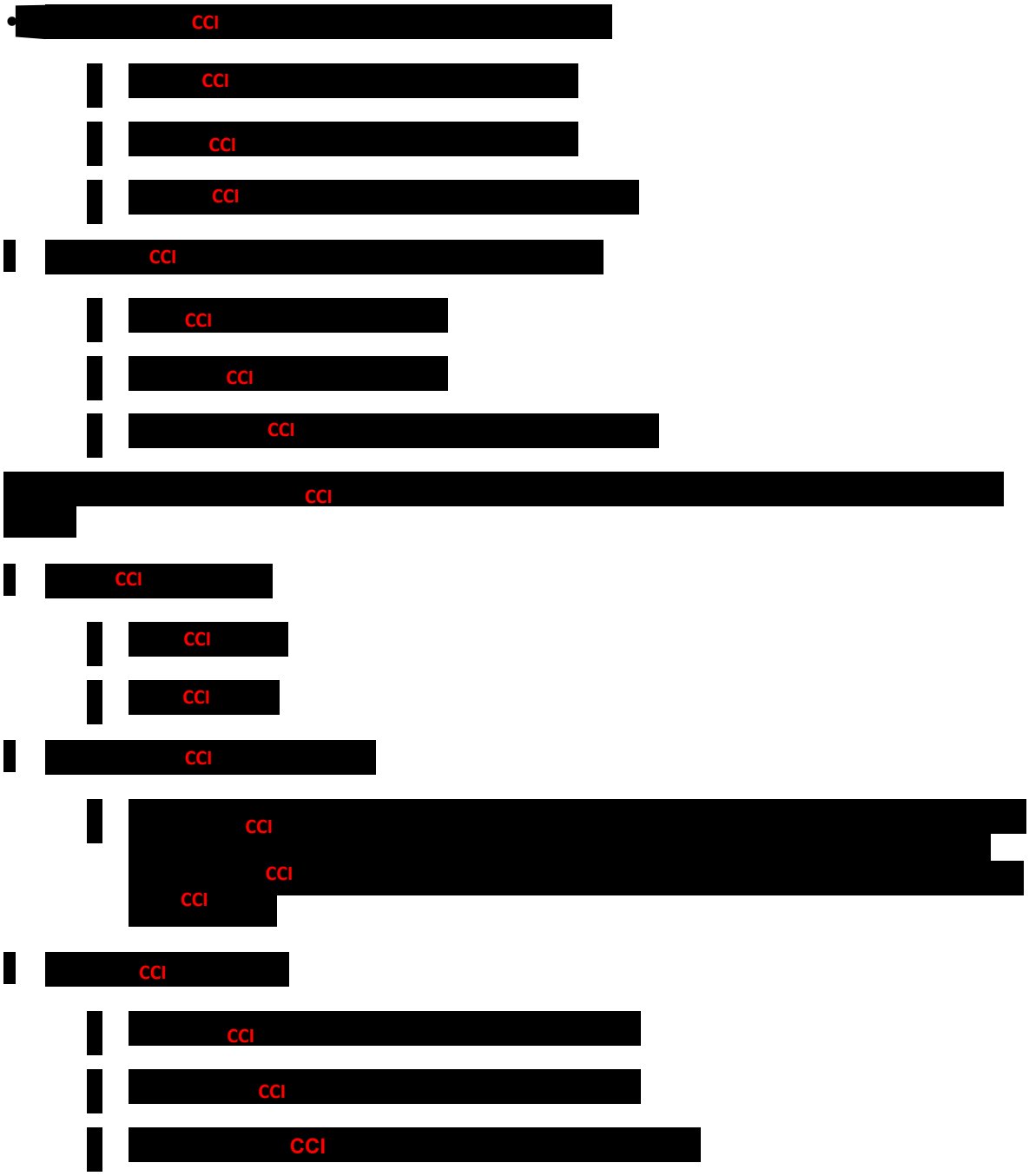
A total of 22 study centers will be used in this protocol. The likelihood that all centers enroll an equal number of subjects is small. No center will be allowed to enroll more than 20% of the entire study population (N=87). In the event there is a discrepancy of more than 10% between the largest enrolling center and smallest, centers will be pooled from the ranked extremes until the pooled centers are within of each other (e.g. the smallest center will be pooled with the largest, and so forth). Study centers will be added to the analysis of variance model for the primary endpoint. See Section 10.1 for details of methods.

### 9.8. Data Review

Prior to unblinding of the study database, the data will be reviewed by the Clinical Project Manager. The investigational centers will be queried about any discrepancies or unclear data and, if necessary, these will be corrected in the database.

### 9.9. Derived Data

The following data will be derived from collected data:



### 9.10. Transformed Data

No data transformations are planned.

### 9.11. Changes from Protocol Planned Analysis

The protocol included collecting information on the reason for use of rescue drugs (secondary objective #7), however, it was determined at the time of CRF development that capturing such data would not add to the determination that a rescue medication was given. Therefore, this was not captured.

The sample size justification in the protocol was not updated to match the final methodology used. While both the protocol and the SAP sample size justifications results in the need for 127 subjects per treatment arm, the assumptions in this SAP are more indicative of the actual assumptions and methodology used to arrive at this sample size.

The protocol did not make provisions for subjects who needed to be hospitalized or kept in the ED overnight for observations. The SAP covers the needs to treat the time spent at the treatment center to "missing" for these subjects.

## 10. STUDY POPULATION

### 10.1. Subject Accountability

The disposition of all subjects, including those who discontinued, will be summarized by treatment group, using frequencies and percentages in each population. Subjects will be categorized into ITT, SAF, and PP populations. Screen failures and excluded-prior-to-enrollment will not be summarized.

### 10.2. Protocol Deviations

All randomized subjects will be included in the ITT and SAF populations. If a violation hinders the ability to assess an efficacy outcome, the following approaches can be taken:

Examples:

i) If patient does not have the disease intended to treat, the outcome for the 2 hr assessment will be set to the baseline values and the subjects will be considered a treatment failure. In this example, the "readiness for discharge" time will be missing, since the discharge time is confounded by the wrong disease.

ii) if a subject receives an antihistamine within 2 hrs prior to baseline (not meeting exclusion #4), that subject will be considered a failure with change from baseline to 2 hr pruritus score and with change from baseline to 2 hr extent of urticaria score set to zero (0). In this example, sedation score will be missing since sedation is confounded by the antihistamine prior to baseline.

Inclusion of subjects in other efficacy endpoints will be dependent on availability of data for each assessment times point. Subject data will be reviewed for major protocol violations by a qualified clinical reviewer prior to database lock and unblinding. Subjects with any major protocol violations will be identified and excluded from the Per Protocol Population. A summary list of the individual subjects excluded, will be provided, sorted by treatment group with description of their protocol violation/deviation.

### 10.3. Treatment Compliance

All subjects will receive their treatment in the treatment center; therefore, there will be no need to confirm treatment compliance.

### 10.4. Other Descriptions of Study Population

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

#### 10.4.1. Medical/Surgical History and Physical Exam Findings

Medical and surgical history and physical examination findings 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 for the ITT population, but will not be tabulated and summarized by treatment group.

#### 10.4.2. Prior and 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. Concomitant medications will be summarized by incidence as counts and percentages within ATC and preferred names for each treatment group. The SAF population will be used to summarize all concomitant therapies by treatment group.

## 11. EFFICACY ANALYSES

### 11.1. Primary Endpoint

The primary clinical outcome measure is patient rated severity of pruritus at 2 hr post-treatment. The primary analysis will test for the non-inferiority of cetirizine to the active comparator, diphenhydramine, for the mean change from baseline in patient rated pruritus at 2 hours. See Section 9.9 for derivation of this endpoint. Using the notation of Gupta, 2011, the NI margin of -0.50 will be used to test the hypothesis:

$H_0$: CCI CCI

Computationally, if the lower bound of the 95% CI of [redacted] then cetirizine is non-inferior to diphenhydramine and if lower bound of the 95% CI > 0 and the p-value ≤ 0.05 for treatment difference, then cetirizine will be determined to be superior to diphenhydramine.

The point estimate of the treatment differences of D2 and the 95% CI will be calculated using 2-side t-test from a generalized linear mixed-effects model [redacted] adjust for site and site by treatment interactions. If there are treatment disparities in baseline characteristics, such as age or gender, these may be added as covariates (See Section 9.4). An example of [redacted] code that may be used to perform this analysis follows:

The primary analysis will be performed on the ITT population with LOCF used to impute 2 hr scores if subjects are discharged prior. If different from ITT, the primary analysis will also be performed on the PP population as a test of sensitivity to protocol deviations and discontinuations.

In the event that a rescue medication is used prior to the 1 hr assessment, D1 will be set to zero (0) for that subject. Otherwise, if rescue drug is given, then the last observation prior to rescue will be carried forward (LOCF) for subsequent calculations of change.

### 11.2. Key Secondary Efficacy Analyses

The following key secondary efficacy analyses are intended to support the primary analysis findings.

1. *Return to Treatment Center*: The number and proportion of subjects who returned to a treatment center for additional treatment of their urticaria will be summarized by response (YES, NO, UNK) for each follow up time and by treatment group. The difference in treatments will be tested using Fisher's 2-sided Exact test of frequencies of returns.

2. *Time Spent at Treatment Center*: The time spent in a treatment center (for the initial treatment) will be summarized by treatment group for the number of subjects in each group, the mean, SD, median, minimum and maximum. The average time in treatment center will be tested for treatment differences using the same model as proposed for the primary endpoint.

Rejection of the null-hypothesis that $P_{cet} = P_{diph}$ will be adjusted based on the order of p-values from all key secondary tests, using the Holm-Bonferroni method (Holm, 1979).

### 11.3. Other Efficacy Analyses

1. *Pruritus Treatment Success*: The number and proportion of success in each treatment group will be summarized.

2. *Patient Rated Pruritus Severity Scores Change (D1, D3)*: The scores and change from baseline at each assessment time (baseline, 1 hr and discharge) will be summarized by treatment group for the number of subjects in each group, the mean, SD, median, minimum and maximum.

3. *Sedation Score Change (E1, E2, E3)*: The patient reported Sedation Scores Change at each assessment time will be summarized by treatment group for the number of subjects in each group, the mean, SD, median, minimum and maximum.

4. *Physician Rated Extent of Urticaria/Erythema Scores Change (C1, C2, C3):* See Section 9.9 for details of how this endpoint is derived. Physician scores will be summarized by treatment group and assessment time for the number of subjects in each group, the mean, SD, median, minimum and maximum.

5. *Proportion of Subjects Needing Rescue Medication:* The number and proportion of subjects who needed rescue while in the treatment center will be summarized by treatment group.

6. *Effectively Treated:* The number and proportion of effectively treated subjects in each treatment group will be summarized.

7. *Symptom Recurrence:* The number and proportion of subjects with symptom recurrence or a new symptom will be summarized by response (YES, NO, UNK) for each follow up times and by treatment group.

8. *Need for Prescription Medications:* The number and proportion of subjects who needed to take a prescription medication after discharge will be summarized by response (YES, NO, N/A, UNK) for each follow up time and by treatment group.

9. *Need for Additional Medications*: The number and proportion of subjects who needed additional medications (not prescription) will be summarized by response (YES, NO, UNK) for each follow up time and by treatment group.

10. *Return to Normal Activity*: The number and proportion of subjects who returned to their normal activity will be summarized by response (YES, NO, UNK) for each follow up time and by treatment group.

## 12. SAFETY ANALYSES

Safety assessments include reporting of adverse events (AEs) throughout the study as well as monitoring of vital signed at specified intervals within the treatment period. Safety assessments will be summarized by treatment group, but no inferential analyses of treatment differences will be performed. In the event that inferences are needed, ANOVA will be used on continuous variables, and Fisher's Exact Test will be

used on categorical variables. All tests will be two-sided at $\alpha$= 0.05. All safety summaries will be performed on the SAF population.

### 12.1. Vital Signs

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. The vital signs to be summarized include systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiration rate (bpm), and body temperature (C).

### 12.2. Adverse Events

Adverse events with onset after the start of study drug will be summarized and grouped by MedDRA System Organ Class (SOC) and specific adverse event. Results will be displayed in order of decreasing frequency, both across SOC and within each SOC term.

For presentation, adverse event verbatim text will be coded into a MedDRA term, and classified by SOC and preferred term. A cross reference listing, which will relate SOC, preferred term, and verbatim text will be provided.

In addition, summaries may be provided by gender, severity (mild, moderate, severe), and by relationship to study drug (Related, Unrelated). "Possibly Related", "Probably Related" and "Almost Certain" will be grouped as 'Related'. "Not Likely to be Related" will be grouped with "Unrelated".

Serious adverse events and adverse events leading to discontinuation will be summarized by treatment group and listed.

## 13. REPORTING CONVENTIONS

Reporting conventions will adhere when possible to the International Conference on Harmonization (ICH) Guidance document E3, “Structure and Content of Clinical Study Reports”. Some specific conventions are outlined below:

1. All tables and listings will be in landscape format.
2. All SAS output for tables and listings will be distributed in PDF files.

## 14. REFERENCES

International Conference on Harmonization, Guidance E3. (www.ich.org)

NQuery Advisor. Statistical Solutions, Ltd (www.statsol.com)

SAS Institute, Inc. (www.SAS.com)

Gupta, Sandeep (2011) “Non-inferiority clinical trials: Practical issues and current regulatory perspective” Indian J Pharmacol. 2011 Jul-Aug; 43(4): 371–374. doi:10.4103/0253-7613.83103

Holm, S. (1979). “A simple sequentially rejective multiple test procedure”. Scandinavian Journal of Statistics 6 (2): 65-70.