DISCLOSURE: REDACTED STATISTICAL ANALYSIS PLAN

Title: A Phase 2 exploratory study of intravenous QUZYTTIR™ (cetirizine hydrochloride injection) versus intravenous diphenhydramine in the prevention of hypersensitivity infusion reactions

NCT Number: NCT04189588

Statistical Analysis Approval Date: November 25, 2020

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Statistical Analysis Plan

Protocol No.: TER-QZTR-001

Protocol Title:

A Phase 2 exploratory study of intravenous QUZYTTIRTM (cetirizine hydrochloride injection) versus intravenous diphenhydramine in the prevention of hypersensitivity infusion reactions

Author: CCI [redacted]

Technical Approver:

CCI [redacted]

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Date of Approval

Table of Contents

1. PREFACE

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol TER-QZTR-001, "A Phase 2 exploratory study of intravenous QUZYTTIRTM (cetirizine hydrochloride injection) versus intravenous diphenhydramine in the prevention of hypersensitivity infusion reactions". This SAP was created using Clinical Protocol TER-QZTR-001 Version 4.0 Amendment #3 dated 24NOV2020. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

The table and listing shells will be provided in separate files as attachments to this SAP.

2. STUDY OBJECTIVES AND ENDPOINTS

This is a parallel-group, randomized, double-blind exploratory study of IV cetirizine HCl 10 mg/mL versus IV diphenhydramine 50 mg/mL in approximately 34 patients aged 18 or older, at up to 10 sites. The duration of study is approximately 24 hours for each completing patient.

The objectives of this study are:

The primary objective of this study is to compare the incidence of infusion reactions (flushing, itching, alterations in heart rate and blood pressure, dyspnea, chest discomfort, acute back or abdominal pain, fever, shaking chills, nausea, vomiting, diarrhea, skin rashes, throat tightening, hypoxia, seizures, dizziness, syncope, or other) to treatment with an anti-CD20 such as Rituxan® (rituximab) or paclitaxel, after premedication with intravenous (IV) QUZYTTIR™ cetirizine hydrochloride (HCl) or IV diphenhydramine during the infusion (first-cycle, retreatment after 6 months or in patients with persistent infusion reactions while on maintenance or retreatment).

The secondary objectives are to document the safety of IV cetirizine HCl and to capture additional process-related data, as follows:

- Sedation score (Patient and HCP) at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine HCl or IV diphenhydramine).
- Hypersensitivity infusion reactions at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine HCl or IV diphenhydramine).
- Document the percentage of patients requiring rescue medication, e.g., epinephrine, bronchodilators, or steroids.
- Describe the reasons for the use of rescue drugs.
- Document the AEs and SAEs per study group.
- Statistical calculation to project sample size for future studies.
- Describe the distribution of the amount of time spent in the treating center prior to discharge (time from injection to "Readiness for Discharge").
- Document the percentage of patients receiving additional medication, e.g., epinephrine or steroids after discharge.

- HCP/Staff satisfaction of amount of time spent during the first 2 hours.
- HCP/Staff satisfaction with readiness and ease of discharge.
- HCP/Staff opinion of effectively treated.

The endpoints of this study are:

The primary endpoint of this study is the incidence of hypersensitivity infusion reactions (flushing, itching, alterations in heart rate and blood pressure, dyspnea, chest discomfort, acute back or abdominal pain, fever, shaking chills, nausea, vomiting, diarrhea, skin rashes, throat tightening, hypoxia, seizures, dizziness, syncope, or other).

The secondary endpoints will be to document the safety of IV cetirizine HCl and to capture additional process-related data, as follows. Sedation score and Readiness for Discharge endpoints will be analyzed descriptively by treatment group using per protocol (PP) analysis set. All other endpoints will be analyzed descriptively by treatment group using the safety analysis set population (SAS).

- Sedation score at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine HCl or IV diphenhydramine).
- Hypersensitivity infusion reactions at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine HCl or IV diphenhydramine).
- Percentage of patients requiring rescue medication, e.g., epinephrine, bronchodilators, or steroids.
- Reasons for the use of rescue drugs.
- AEs and SAEs per study group.
- The distribution of the amount of time spent in the treatment center prior to discharge (time from injection to "Readiness for Discharge").
- Percentage of patients receiving additional medication, e.g., epinephrine or steroids after discharge.
- Percentage of effectively treated based on HCP's opinion of CCI
- Analyze subgroup of patients 65 years of age and older.
- Analyze subgroup of Time from Injection to Readiness for Discharge by chemotherapy received (anti-CD20 or paclitaxel.

3. STUDY DESIGN

This will be a parallel-group, randomized, double-blind exploratory study of IV cetirizine HCl 10 mg/mL versus IV diphenhydramine 50 mg/mL in approximately 34 patients who will receive premedication for hypersensitivity infusion reactions associated with an anti-CD20, such as Rituxan® (rituximab) or paclitaxel.

The objectives and purpose of the study will be described to patients presenting at the participating infusion centers. If a patient agrees to participate in the study, an informed consent form (ICF) will be signed by the patient according to the process followed by each center for obtaining informed consent. The screening period could be up to 14 days prior to randomization/treatment. 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 vital signs (including temperature), weight, height, age, previous medical history, 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 IV cetirizine HCl or IV diphenhydramine. The time that the study medication was administered will be recorded in the source documents and in the eCRF.

During the Baseline/Screening period (Day -14 to Day 0), the study investigator or designee will record the following baseline data: medical/surgical history, vital signs (including temperature), physical examination, and concomitant medication.

On Antihistamine injection Day (Day 0), before the patient receives randomized antihistamine injection (Study drug or control), the investigator or designee will record the following information: vital signs (including temperature), Sedation score, Concomitant medication, and Adverse events - Other than infusion reaction. Patients are randomized in a 1:1 ratio to either cetirizine HCl or IV diphenhydramine in a blinded fashion.

During the infusion and afterwards, the study investigator or designee will record each of the events of an infusion reaction: flushing, itching (pruritus), urticaria, alterations in heart rate and blood pressure, dyspnea, chest discomfort, acute back or abdominal pain, fever, shaking chills, nausea, vomiting, diarrhea, skin rashes, throat tightening, hypoxia, seizures, dizziness, syncope, or other. The study investigator will assess if the event is related to the Rituxan (rituximab) or paclitaxel infusion and record the event.

The infusion reactions will be managed following the Common Terminology Criteria for Adverse Events (CTCAE version 5.0) definition of graded infusion reactions or clinical site protocol.

The same measures will be assessed again at 1 hour and 2 hours after the injection of the antihistamine (IV cetirizine HCl or IV diphenhydramine) and at the Time of "Readiness for Discharge." At these same time intervals, participating patients will be asked to self-rate (recorded by study staff) any symptom and their level of sedation. The patient's responses will be recorded by the investigator/designee on the designated outcome measure form (source document). All rescue medication, e.g., epinephrine, bronchodilators, or steroids, will be recorded. In addition, site staff will evaluate overall satisfaction with time spent during treatment at 2 hours and ease of discharge.

The actual time at which the investigator or designee determines the patient is physically and mentally fit to be discharged from the center (Time of "Readiness for Discharge") will be recorded in the source documents. The decision to discharge the patient (Time of "Readiness for Discharge") could be made at any time after the 2-hour assessment of study outcome measures provided the following criteria are met:

1. No symptoms of infusion hypersensitivity reaction
2. Patient is alert enough (sedation score = 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 in the clinic until sedation improves. 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 that the symptoms were not effectively treated, patients will be treated following the standard of care by attending physician.

Before discharge, patients will be instructed on the procedures they have to follow when experiencing an AE or SAE. They will be instructed to expect a follow-up phone call at approximately the same time the following day (i.e., 24 hours later) from a member of the site staff who will ask them a few short questions regarding hypersensitivity infusion reaction symptoms.

All AEs and SAEs that are reported after the patient signs an ICF will be recorded in the source documents and captured in the eCRF. Up to 28 days post–IV study drug injection, patient self-reported AEs and SAEs will also be included in the eCRF.

Please refer to the Protocol, Attachment A, for the schedule of study evaluations.

4. SAMPLE SIZE CONSIDERATIONS

This is a pilot clinical study to determine process feasibilities and to obtain a baseline clinical response (drug reaction to Rituxan or Paclitaxel) with pre-treatment of cetirizine HCl injection and diphenhydramine injection on the primary and secondary clinical outcome measures. As such, no sample size was calculated for this study. However, the data obtained from this study may be used to calculate the sample size of future studies.

5. ANALYSIS POPULATIONS

Patients with baseline Sedation Score greater than 0 may have taken a sedating concomitant or other medication. It may be impossible to confirm that patients did not take a sedating medication prior to receiving treatment. Sedation Score greater than 0 would be a confounding factor and may invalidate the results of endpoints of Sedation score and Readiness for Discharge. Therefore, these two endpoints will only be analyzed by the PP population, defined as patients with both a Patient and Health Care Provider (HCP) assessed Baseline Sedation score of 0.

Patients will be categorized into the following analysis populations:

Full Analysis Set (FAS): The FAS consists of all randomized patients. Analysis will be done according to the treatment patients were randomized to.

Safety Analysis Set (SAS): The SAS consists of all patients who received at least 1 dose of study medication. Analysis will be done according to the actual treatment patients received.

Per Protocol Analysis Set (PP): The PP consists of patients with both a Patient and HCP assessed Baseline Sedation score of 0, and who received at least 1 dose of study medication. Patients will be analyzed according to the treatment actually received.

6. INTERIM ANALYSIS

No interim analyses are planned.

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All statistical analyses will be performed using SAS® Version 9.4, unless otherwise noted. Data will be summarized using descriptive statistics only. Number of patients (n), mean, median, standard deviation, minimum, and maximum will be summarized for continuous variables. Categorical variables will be summarized using frequencies and percentages. The number of patients in the population of interest will be used as the denominator. Percentages will be rounded to one decimal place, and thus may not always add up to exactly 100%. Time to event variables will be summarized using median, Q1 (25^{th} percentile) and Q3 (75^{th} percentile) from the Kaplan-Meier (KM) estimate of survival. Presentations will be by treatment group (IV cetirizine HCl 10 mg/mL, and IV diphenhydramine 50 mg/mL) and overall, unless otherwise noted.

In general, all summary tables will be supported by a relevant patient data listing including all patients who are randomized. The listings will include all data collected, and will be sorted by patient ID, and actual visit date, as applicable, unless otherwise noted.

Concomitant medications will be coded using the WHO Drug Dictionary and adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The dictionary versions will be documented in the Data Management Plan for the study.
Study day 1 is the day of antihistamine injection. Study day is the day relative to the study day 1.

Baseline is the last non-missing valid value prior to antihistamine injection. If a patient is not dosed, baseline will be set to the Screening/Baseline visit value.

7.1 Imputed and Missing Data

No formal imputation of missing data will be performed.

7.2 Hypothesis Testing

This is an exploratory study and no hypothesis testing will be performed.

7.3 Adjustments for Multiplicity

No adjustments for multiplicity will be performed.

7.4 Covariates

No covariates are planned.

7.5 Examination of Subgroups

Subgroup of patients 65 years of age and older will be analyzed.

Time from injection to Readiness for Discharge by chemotherapy received (anti-CD20 or paclitaxel) will be analyzed for this subgroup.

7.6 Premature Discontinuation and Missing Data

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

7.7 Study Centers

Up to 10 study centers will be used in this study.

7.8 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.

7.9 Derived Data

The following data will be derived from collected data:

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[redacted]

7.10 Transformed Data

No data transformations are planned.

7.11 Changes from Protocol Planned Analysis

No changes from protocol planned analysis are planned.

8. STUDY POPULATION

8.1 Patient Accountability

All patients who signed the informed consent will be accounted for in Subject Disposition. The following disposition information will be summarized by the number and percentage of patients, by treatment group and overall:

- Patients who signed the informed consent, and who comprise the FAS, PP and SAS populations
- Patients receiving Rituxan (or anti-CD20 medication) vs Paclitaxel
- Patients who complete the treatment or withdraw prematurely along with the reason for discontinuation

8.2 Demographics

Sex, age (in years), race, and ethnicity will be summarized by treatment group and overall, for all screened patients.

8.3 Medical/Surgical History

The number and percentage of patients in the FAS population with any medical/surgical history will be tabulated by system organ class (SOC) and preferred terms (PT) using the MedDRA dictionary. Medical/surgical history will be counted only once for a patient within each PT and SOC; thus, since a patient may have more than one PT within a SOC, percentages of PT may not sum to the percentages in the SOC.

8.4 Physical Examination

The number and percentage of patients with any clinically significant abnormal findings will be summarized by treatment group and overall, for the FAS population.

8.5 Protocol Deviations

Data on protocol deviations will not be summarized but will be provided as a listing.

9. EFFICACY ANALYSIS

The primary endpoint is the incidence of hypersensitivity infusion reactions. The efficacy analysis will be summarized for the FAS population by treatment group and overall. The number and percentage of patients experiencing any infusion reaction events during the study, and the number and percentage of patients experienced each symptom by CTCAE grade (flushing, itching, alterations in heart rate and blood pressure, dyspnea, chest discomfort, acute back or abdominal pain, fever, shaking chills, nausea, vomiting, diarrhea, skin rashes, throat tightening, hypoxia, seizures, dizziness, syncope, or other) will be summarized.

10. SAFETY ANALYSIS

Safety analysis will be summarized for the SAS population by treatment group and overall. Sedation score endpoint will be summarized for the PP population by treatment group and overall.

10.1 Sedation score at baseline, 1 hour and 2 hours post-injection of antihistamine, and at discharge

The patient sedation score and HCP sedation score will be summarized at baseline, 1 hour and 2 hours post-injection of antihistamine, and at discharge. Change from baseline at each scheduled post-baseline time point will also be summarized. A listing of sedation score, including all time points, will be presented.

10.2 Hypersensitivity infusion reactions at 1 hour and 2 hours post-injection of antihistamine and at discharge (IV cetirizine HCl or IV diphenhydramine)

The number of patients experiencing any infusion reaction events, and the number and percentage of patients experiencing each symptom (flushing, itching, alterations in heart rate and blood pressure, dyspnea, chest discomfort, acute back or abdominal pain, fever, shaking chills, nausea, vomiting, diarrhea, skin rashes, throat tightening, hypoxia, seizures, dizziness, syncope, or other) by CTCAE grade, will be summarized at during infusion, 1 hour and 2 hours post-injection of antihistamine, and at discharge.

10.3 Percentage of patients requiring rescue medication, e.g., epinephrine, bronchodilators, or steroids.

The number and percentage of patients requiring rescue medication CCI will be summarized, and a listing provided.

10.4 Reasons for the use of rescue drugs.

Rescue drugs, if any, will be provided in a listing including the reasons for the use of rescue drugs.

10.5 Adverse Events

All adverse events will be reported and listed, but only treatment emergent adverse events (TEAEs) will be summarized in the tables. A treatment emergent adverse event is defined as an AE that occurs on or after the date of the first study treatment. Safety evaluations will include patient self-reported adverse events and serious adverse events up to 28 days post IV study drug injection.

A summary of all TEAEs by the number and percentages of patients who experienced any of the following will be provided:

- Any TEAE, including CTCAE toxicity grade (Mild, Moderate, Severe, Life-Threatening and Fatal), relationship to study treatment (Not Related, Possible, Probable, Not Assessable), AEs leading to discontinuation of study participation, AEs leading to discontinuation of study treatment.
- Any serious TEAE, including CTCAE toxicity grade (Mild, Moderate, Severe, Life-Threatening and Fatal), relationship to study treatment (Not Related, Possible, Probable, Not Assessable), AEs leading to discontinuation of study participation, AEs leading to discontinuation of study treatment.
- Any fatal TEAEs, including relationship to study treatment (Not Related, Possible, Probable, Not Assessable)

Additionally, the number and percentage of unique patients reporting any TEAE will be summarized by system organ class (SOC) and preferred terms (PT). The number and percent of unique patients reporting any TEAE will also be summarized by SOC, PT, and worst CTCAE

toxicity grade and closest relationship to study treatment. For all AE summaries, patients will be counted once for each SOC or PT, at highest grade of event or closest relationship.

A Listing of all AEs will be provided. This listing will include a flag identifying if an AE is a TEAE and a flag indicating if this AE is patient self-reported.

10.5.1 Summary for Serious TEAEs

For all serious TEAEs the following will be summarized:

- Overall summary of any serious TEAEs by worst CTCAE toxicity presented by SOC/PT
- Overall summary of any serious TEAEs by closest relationship to study treatment presented by SOC/PT

A Listing of all serious AEs will be provided. This listing will include a flag identifying if an AE is a TEAE.

10.5.2 Deaths

Deaths, if any, will be provided in a listing only.

10.6 The distribution of the amount of time spent in the treatment center prior to discharge (time from injection to "Readiness for Discharge")

The KM estimate of survival will be used to summarize the time (in hours) to discharge by treatment group [redacted]

A KM survival curve stratified by treatment group will be provided. A listing of time of discharge will also be provided.

10.7 Percentage of patients receiving additional medication, e.g., epinephrine or steroids after discharge

The number and percentage of patients receiving additional medication [redacted] will be summarized.

10.8 Vital Signs

Vital signs, including blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/min), and body temperature (C), will be summarized. Observed values will be tabulated

at baseline, and at each scheduled post-baseline time point. Change from baseline at each scheduled post-baseline time point will also be summarized. Observed values at the screening visit may be presented if the screening visit is not the baseline.

10.9 Other Analyses

10.9.1 Percentage of effectively treated based on HCP's opinion of CCI

The number and percentage of patients who are effectively treated will be summarized. A listing of the HCP's opinion on effective treatment will also be provided.

10.9.2 Percentage HCP/Staff satisfaction of amount of time spent during the first 2 hours

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10.9.3 HCP/Staff satisfaction with readiness and ease of discharge.

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10.9.4 Prior and Concomitant Medications

Concomitant Medications are defined as medications taken during the trial. The number and percentage of patients taking any prior and concomitant medications will be summarized by WHO classification for therapeutic class (ATC level 3 terms) and preferred medication names. If an ATC level 3 term is not available, the next available level term should be used for the summary. If a patient is taking a medication before the first study treatment and continues during the trial, the medication will be included in both the prior and concomitant medication summary tables.

10.9.5 Concomitant Procedures

A listing of concomitant procedures will be provided.

10.9.6 24 Hr Follow-Up Questionnaire

A listing of 24-hour follow-up questionnaire responses will be provided.

11. REPORTING CONVENTIONS

The following specifications will be used in the production of tables and listings.

1. Page Setup
   Unless otherwise noted, tables and listings will use landscape orientation. Margins will be at least 3/4 of an inch on the left side of page, at least 3/4 of an inch at the top, and 3/8 of an inch on the other sides.
   The following header information should be included:
   - Upper left: Sponsor name and protocol number
   - Center: CONFIDENTIAL; Database Download Date: ddmmmyy
   - Upper right: Page number shown as Page n of N. Page numbers should be sequential within a table or listing.

   The footer should include:
   - Left: the name of the SAS program used to generate the output
   - Center: run date/time and the words "by CTDS".
   - Right: output file name.

2. Footnotes
   Unless otherwise specified, footnotes should appear on all pages within the table.

3. Font
   Font will be 9-point Arial, or smaller if needed for space constraints. If possible, small tables should appear on one page. If tables continue on to multiple pages, there should be a page break after an assessment so that all the statistics for an assessment appear on the same page.

4. Tables
   Table titles should reflect the content of the table. Under the main title, in parentheses, the name of the analysis population being summarized should appear.

   4.1 Summary Statistics - Continuous Data
   Unless otherwise noted, the mean and median and confidence interval (CI) of a set of values should be printed out to one decimal place more than the original value. The standard deviation should be printed out to 2 decimal places more than the original value. The number of patients on whom the parameter is assessed should appear. Minimum and maximum should be consistent with the original value.

   4.2 Summary Statistics - Categorical Data
   Numbers of patients are reported as whole numbers. Null counts are represented as 0. Table percentages should be reported to one decimal unless otherwise noted. Null percentages should be reported as 0.0. For all categories, the total number of patients with data will be presented as N.

5. Patients Included in Listings

In general, patient data listings should include all patients who are randomized. The population flag (FAS/ SAS) should be included in all listings as a column to indicate which population(s) a patient belongs to. If a listing includes a subset of patients who meet a certain condition (eg, patients with SAEs) then this should be clear from the title of the listing. If there is no record for a listing, then a statement, such as There is no serious adverse event in any of the treatment groups, will be presented.