DISCLOSURE: REDACTED PROTOCOL

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

Protocol Approval Date: November 24, 2020

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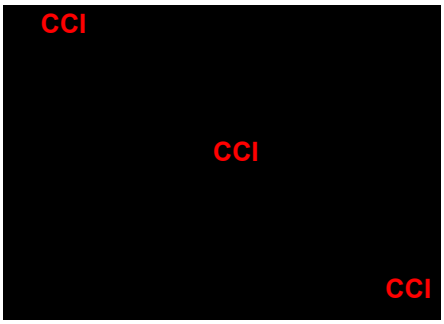
CLINICAL STUDY PROTOCOL

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

STUDY TER-QZTR-001

IND # 107689

Sponsor:	TerSera Therapeutics LLC
Sponsor Contact:	
Version of Protocol:	Version 4.0 Amendment #3
Date of Protocol:	November 24, 2020

CONFIDENTIAL

The study will be conducted according to the International Council on Harmonization harmonized tripartite guideline E6 (R2): Good Clinical Practice, FDA, and EU clinical trial guidelines.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol titled, "A Phase 2 exploratory study of intravenous QUZYTTIR™ (cetirizine hydrochloride injection) versus intravenous diphenhydramine in the prevention of hypersensitivity infusion reactions," including the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

PRINCIPAL INVESTIGATOR:

Signature	Date

Print Name

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AUC∞	Total area under the plasma-concentration-time-curve
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CRO	Contract research organization
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH
eCRF	Electronic case report form
EMR	Electronic Medical Record
ESMO	European Society for Medical Oncology
EDC	Electronic data capture
ETTAU	Efficacy Trial for the Treatment of Acute Urticaria
ED	Emergency department
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
H_1/H_2	Histamine-1/Histamine-2
HCl	Hydrochloride
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IP	Investigational product
ICF	Informed consent form
ICH	International Council on Harmonization
IEC	Independent or Institutional Ethics Committee
IND	Investigational new drug
IRB	Institutional review board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MQA	Medical Quality Assurance

Abbreviation	Definition
NCI	National Cancer Institute, NIH
NCCN	National Comprehensive Cancer Network
NDA	New drug application
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH
PHI	Protected health information
PI	Principal investigator
PK	Pharmacokinetics
PP	Per protocol
QA	Quality assurance
REB	Research ethics board
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
T_{max}	Time to maximum plasma concentration

1. SYNOPSIS

Title of the Study	A Phase 2 exploratory study of intravenous QUZYTTIR™ (cetirizine hydrochloride injection) versus intravenous diphenhydramine in the prevention of hypersensitivity infusion reactions
Objectives	Primary: 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, or syncope) 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). Secondary: • 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). • Document the percentage of patients requiring rescue medication, e.g., epinephrine, bronchodilators, or steroids. • Describe the reasons for the use of rescue drugs. • 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.
Number of Patients	34 patients
Duration of	For each completing patient, approximately 24 hours. The screening period

Study	could be up to 14 days prior to randomization/treatment.
Number of Sites	Approximately up to 10 sites
Enrollment Criteria	**Inclusion Criteria** Patients are eligible to be included in the study only if they meet all the following criteria: • Male or female patients who require treatment premedication with an antihistamine for hypersensitivity infusion reactions associated with an anti-CD20, such as Rituxan® (rituximab) or paclitaxel (first-cycle, retreatment after 6 months or in patients with persistent infusion reactions while on maintenance or retreatment). • 18 years of age or older. • Be willing and able to give informed consent. **Exclusion Criteria** Patients will be excluded from the study if they meet any of the following criteria: • Receipt of an investigational drug or device within the past 30 days. • Patients at high risk of developing tumor lysis syndrome (TLS): patients with auto-lyse, Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL) with bulky disease (single node 7 or more cm or 3 or more nodal sites with size 3 or more cm) • Patients in whom an antihistamine may be contraindicated (e.g., narrow angle glaucoma, symptomatic prostatic hypertrophy). • Patients who, in the opinion of the investigator, may not tolerate an IV injection of diphenhydramine 50 mg or cetirizine HCl 10 mg. • Receipt of any antihistamine (H_1 antagonist) within the past 24 hours prior to the administration of the study drug regardless of the route of administration, e.g., diphenhydramine, cetirizine, loratadine, fexofenadine, levocetirizine, desloratadine. chlorpheniramine, clemastine and doxylamine. • Receipt of an H_2 antagonist within the past 4 hours prior to the administration of the study drug, e.g., ranitidine, cimetidine, famotidine, nizatidine. • Receipt of doxepin within the past 24 hours prior to the administration of the study drug; doxepin is an antidepressant, but it also has

	antihistamine properties. • Receipt of epinephrine (EpiPen® or any other brand) within the past 30 days prior to the administration of the study drug. • Has known allergy to hydroxyzine, cetirizine, or levocetirizine, or diphenhydramine. • Pregnant or breastfeeding. • Any condition that in the view of the investigator makes the patient unsuitable for enrollment in this study. • Major medical or psychiatric illness, other than diagnosed cancer at the time of presentation or in the past that in the investigator's judgement should not be enrolled in this clinical trial. • Inability to provide informed consent. • Patients on concomitant P-glycoprotein inhibitors, including antidepressants, antipsychotics (e.g., olanzapine), and benzodiazepines (e.g., alprazolam), as they may cause an increase in sedation. • Receipt of drugs that cause sedation within the past 24 hours prior to the administration of the study drug.
Test Product	Dose and mode of administration: Cetirizine HCl 10 mg/mL to be administered as a single 1-mL injection via IV push over a period of 1 to 2 minutes.
Reference Therapy	Dose and mode of administration: Diphenhydramine 50 mg/mL to be administered as a single 1-mL injection via IV push over a period of 1 to 2 minutes.
Methodology	This will be a parallel-group, randomized, double-blind pilot study of IV cetirizine HCl 10 mg/mL versus IV diphenhydramine injection 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. After the informed 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, 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 injection of either cetirizine HCl or diphenhydramine (timing based on

site pretreatment protocol).

Prior to the administration of the study medication, the study investigator or designee will record the following baseline data: physical examination, vital signs, and concomitant medication.

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, or syncope. The study investigator will assess if the event is related to the infusion and record the event.

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

Immune System Disorders

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion Reaction	Mild transient reaction: infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences: urgent intervention indicated	Death

Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

CCI [redacted]

	(Accessed October 8, 2019)
	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 (Electronic Medical Record). All rescue medication, e.g., epinephrine, bronchodilators, steroids, will be recorded. In addition, Health Care Provider (HCP)/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 hypersensitivity infusion reaction 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 Before discharge, patients will be instructed on the procedures they should follow when experiencing an adverse event (AE) or serious adverse event (SAE). They will be instructed to expect a follow-up phone call from a member of the site staff at approximately the same time the following day (i.e., 24 hours later) who will ask them a few short questions regarding allergic symptoms. All AEs and SAEs that are reported after the patient signs an informed consent form (ICF) will be recorded in the source documents and captured in the electronic case report form (eCRF). **Up to 28 days post–IV study drug injection, patient self-reported AEs and SAEs will also be included in the eCRF.**

Statistical Methods	A Statistical Analysis Plan (SAP) with analytical details and assumptions will be developed and finalized before database lock and unblinding of the study data. No formal statistical analyses are planned given the exploratory objectives of the study. **Primary Endpoints:** The primary clinical endpoint is 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, or syncope). **Secondary Endpoints** 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). 1. Sedation scores (patient and HCP) at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine HCl or IV diphenhydramine). The patient sedation scores are assessed on a scale of 0-4, with 0=None and 4=Extremely Severe (Asleep, Cannot Self-Rate). The HCP sedation scores are assessed on a scale of 0-4, with 0=None and 4=Extremely severe. 2. Hypersensitivity infusion reactions at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine HCl or IV diphenhydramine). 3. Document the percentage of patients requiring rescue medication, e.g., epinephrine, bronchodilators, or steroids. 4. Describe the reasons for the use of rescue drugs. 5. Document the AEs and SAEs per study group. 6. Describe the distribution of the amount of time spent in the treatment center prior to discharge (time from injection to “Readiness for Discharge”). 7. Document the percentage of patients receiving additional medication, e.g., epinephrine or steroids after discharge.

	8. Effectively treated based on HCP's opinion of CCI 9. Analyze subgroup of patients 65 years of age and older. 10. Analyze subgroup of time from Injection to Readiness for Discharge by chemotherapy received (anti-CD20 or paclitaxel). **Safety:** Safety analyses will be analyzed descriptively by treatment group using the safety analysis set population (SAS). Sedation score will be analyzed descriptively by treatment group using per protocol (PP) analysis set. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary 22.1 and will be summarized by treatment group by severity, seriousness, and relationship. Events occurring more than once in the same patient will be counted only once. Additional safety analyses include summarizing vital signs and physical exam findings descriptively by treatment group. **Sample Size Considerations:** This is an exploratory clinical study to determine process feasibilities and to obtain a baseline clinical response to IV cetirizine HCl and IV diphenhydramine on the primary and secondary clinical outcome measures. As such, no sample size will be calculated for this study. However, the data obtained from this study might be used to calculate the sample size of future studies.

2. BACKGROUND AND RATIONALE

Cetirizine, a human metabolite of hydroxyzine, is an antihistamine. Cetirizine hydrochloride (HCl) is available as an orally administered over-the-counter product indicated for the treatment of acute urticaria in adults and children 6 months of age and older. Cetirizine HCl was originally approved in 1995 as a 10-mg oral-dose prescription drug. Over the past 24 years, the safety profile with cetirizine HCl used chronically has been well established in both children (6 months and older) and adults.

Intravenous cetirizine HCl 10 mg/mL (QUZYTTIR™)[1] was developed to provide a faster or immediate-onset treatment profile over the current 10 mg cetirizine HCl products (Zyrtec®) to alleviate acute symptoms such as urticaria, angioedema, and allergic reactions. Cetirizine HCl is to be injected IV at a dose of 10 mg in adults.

A pilot study (ETTAU-02) was conducted in 33 patients and demonstrated that the investigational drug, IV cetirizine HCl, was not significantly different (and slightly in favor of cetirizine) from the active comparator, diphenhydramine injection, in acute urticaria symptom score reductions (composite score and each individual symptom score, such as: pruritus and extent of urticaria/erythema) at 1 or 2 hours post-injection and at discharge. There were no serious adverse events (SAEs) in either treatment arms. There were no drug-related adverse events (AEs) from the cetirizine HCl arm, but several drug-related AEs were recorded in patients in the diphenhydramine arm.

A pivotal Phase 3 study (ETTAU-03) in 262 patients demonstrated similar results as in the pilot study (ETTAU-02). The pivotal study demonstrated statistically that IV cetirizine HCl is non-inferior to IV diphenhydramine on the primary endpoint (2-hour patient-rated pruritus score change from baseline), and improvement on two key secondary endpoints (time spent in treatment center, and % of patients returned to treatment center). Intravenous cetirizine HCl was also better on several other secondary endpoints such as fewer AEs, less sedation, reduced rescue-drug usage, and higher rate of effective treatment.

Pretreatment with antihistamines for drug-induced hypersensitivity is recommended for biologics, chemotherapy drugs, and other treatments. Hypersensitivity infusion reactions occur in approximately 5% of patients treated with chemotherapy.[2]

Some chemotherapy drugs have a greater potential of causing these reactions. For those with high potential, pretreatment is recommended with an antihistamine and corticosteroids prior to treatment. Severe infusion reactions may require oxygen, epinephrine, and cardiovascular support.[3]

Currently, the only injectable antihistamine is diphenhydramine; however, it is not indicated for pretreatment.[4] Management of hypersensitivity infusion reactions have been provided with guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology.[5,6] Intravenous cetirizine HCl 10 mg/mL has been shown to treat acute urticaria as effectively as diphenhydramine with fewer side effects, and can be used for pretreatment for chemotherapy-induced infusion reactions.

When IV diphenhydramine is unavailable, oral diphenhydramine or other oral antihistamines have been used for pretreatment to prevent hypersensitivity infusion reactions.[2,7] The use of oral antihistamines has limitations; oral cetirizine HCl has a time to maximum concentration (T_{max}) of 1 hour with a delay of T_{max} with food to 1.7 hours (Zyrtec PI[8]).

There is an unmet medical need for injectable pretreatment antihistamines for use with drugs that cause infusion reactions (e.g., biologic chemotherapy). Current literature shows that a second-generation, less-sedating antihistamine such as IV cetirizine HCl could be a viable and clinically meaningful option for patients. Intravenous cetirizine HCl 10 mg/mL has been shown to treat acute urticaria as effectively as diphenhydramine with fewer side effects and could be used for pretreatment for chemotherapy-induced infusion reactions.

3. STUDY OBJECTIVES

3.1. Primary Objectives

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, or syncope) 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).

3.2. Secondary Objectives

- 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).
- Document the percentage of patients requiring rescue medication, e.g., epinephrine, bronchodilators, or steroids.
- Describe the reasons for the use of rescue drugs.
- 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.

4. 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 history, vital signs (including temperature), physical examination, and concomitant medication.

On Antihistamine injection Day (Day 0), before the patient receive randomized antihistamine injection (Study drug), the investigator or designee will record the following information: vital signs (including temperature), Sedation score, Concomitant medication, and Adverse events - Other than infusion reaction.

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.

Table 1. CTCAE Definition of Graded Infusion Reactions

Immune System Disorders					
Adverse Events	**Grade**				
	1	**2**	**3**	**4**	**5**
Infusion Reactions	Mild transient reaction: infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences: urgent intervention indicated	Death

Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.
*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).
CCI (Accessed October 8, 2019)

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 or designee.

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.**

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

5. STUDY POPULATION

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

Inclusion Criteria

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

1. Male or female patients who require treatment premedication with an antihistamine for hypersensitivity infusion reactions associated with an anti-CD20, such as Rituxan® (rituximab) or paclitaxel (first-cycle, retreatment after 6 months or in patients with persistent infusion reactions while on maintenance or retreatment).
2. 18 years of age or older.
3. Be willing and able to give informed consent.

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 at high risk of developing tumor lysis syndrome (TLS): patients with auto-lyse, Burkitt lymphoma and diffuse-large B-cell lymphoma (DLBCL) with bulky disease (single node 7 or more cm or 3 or more nodal sites with size 3 or more cm)
3. Patients in whom an antihistamine may be contraindicated (e.g., narrow angle glaucoma, symptomatic prostatic hypertrophy).
4. Patients who, in the opinion of the investigator, may not tolerate an IV injection of diphenhydramine 50 mg or cetirizine HCl 10 mg.
5. Receipt of any antihistamine (H_1 antagonist) within the past 24 hours prior to the administration of the study drug regardless of the route of administration, e.g., diphenhydramine, cetirizine, loratadine, fexofenadine, levocetirizine, desloratadine. chlorpheniramine, clemastine and doxylamine.
6. Receipt of an H_2 antagonist within the past 4 hours prior to the administration of the study drug, e.g., ranitidine, cimetidine, famotidine, nizatidine.
7. Receipt of doxepin within the past 24 hours prior to the administration of the study drug; doxepin is an antidepressant, but it also has antihistamine properties.
8. Receipt of epinephrine (EpiPen® or any other brand) within the past 30 days prior to the administration of the study drug.
9. Has known allergy to hydroxyzine, cetirizine, or levocetirizine, or diphenhydramine.
10. Pregnant or breastfeeding.
11. Any condition that in the view of the investigator makes the patient unsuitable for enrollment in this study.
12. Major medical or psychiatric illness, other than diagnosed cancer at the time of presentation or in the past that in the investigator's judgement should not be enrolled in this clinical trial.
13. Inability to provide informed consent.
14. Patients on concomitant P-glycoprotein inhibitors, including antidepressants, antipsychotic (e.g., olanzapine) and benzodiazepines (e.g., alprazolam), as they may cause an increase in sedation.[9,10,11] (See Attachment D).
15. Receipt of drugs that cause sedation within the past 24 hours prior to administration of the study drug.

6. DISCONTINUATIONS

Patients 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 patients from the study if he/she feels it is in the best interest of the patient, or if the patient is uncooperative or non-compliant.

Reasons for discontinuation include:

- Violation of inclusion or exclusion criteria found after the study medication has been administered.
- The investigator, patient, or the healthcare professional performing assessments become unblinded to the study medication for whatever reason.
- The investigator decides that the patient should be withdrawn. If this decision is made because of an SAE, the study drug 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 reason for the discontinuation.
- The patient 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.

The reason for any discontinuation will be fully documented on the source document and eCRF.

Should a patient decide to withdraw, every effort will be made to complete and report all study observations, particularly the 24-hour follow-up, as thoroughly as possible (Attachment C). The investigator/designee should contact the patient by telephone to determine as completely as possible the reason for the withdrawal.

7. TREATMENT ADMINISTERED

Patients who fulfill all the inclusion and none of the exclusion criteria will be enrolled into the study. Each patient should read and sign an ICF prior to any study procedures being performed. This study involves a comparison of two injectable products: cetirizine HCl 10 mg/mL and diphenhydramine 50 mg/mL, both administered during a 1- to 2-minute period by IV push using a 1-mL syringe and flush with normal saline as needed. Patients will be randomly assigned to either:

- Cetirizine HCl 10 mg/mL: a single 1-mL injection via IV push over a period of 1 to 2 minutes.
- Diphenhydramine 50 mg/mL: a single 1-mL injection via IV push over a period of 1 to 2 minutes.

Timing to administer the study drug or other pretreatment mediation before starting the chemotherapy will be based on the site's chemotherapy treatment procedure.

7.1. Materials and Supplies

A drug dispensing log will be kept current and will contain the following information:

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

Drug inventory and accountability records (Test Article Accountability Log) will be maintained at the site. A monitor will reconcile drug inventory and review accountability records. Any unused vials of study drug will be collected by the Monitor and returned to the sponsor. Study drugs may be stored at room temperature.

7.2. Method of Assignment to Treatment

Approximately 34 patients will be randomized to 1 of 2 treatment groups in a 1:1 ratio. Specifics for the randomization scheme and blinding plan will be described in the Statistical Analysis Plan (SAP) for the study. Study medication/Investigational Product (IP will be sent to each study site depending on the recruiting capabilities of each site. At the investigational site, each subject will be entered in EDC with a subject ID in the format of ##-###, where the first 2 digits represent site number and the last 3 digits represent a sequential patient number (i.e., 02-009 represents the ninth patient consented at site two).

Upon verification that all eligibility criteria are met the subject can be randomized within EDC. The site will be provided with a blinded treatment code that corresponds to appropriate drug label.

7.3. Rationale for the Control Product and Doses of Study Medication

Investigational Product: IV cetirizine HCl, a single 1-mL injection (10 mg/mL) given by IV push over a period of 1 to 2 minutes.

Control Product: IV diphenhydramine, a single 1-mL injection (50 mg/mL) given by IV push over a period of 1 to 2 minutes.

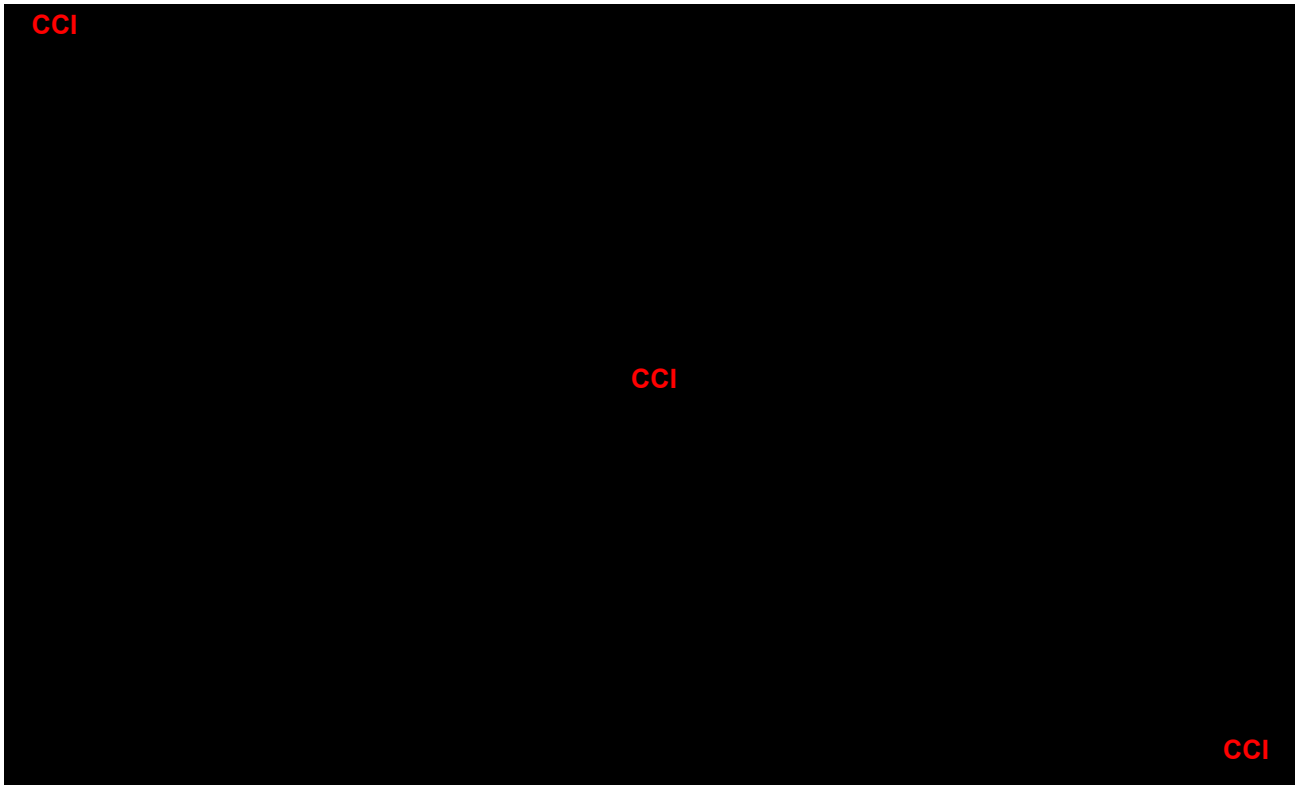
7.3.1. Rationale for Using Diphenhydramine as the Control Product

Intravenous diphenhydramine is the only antihistamine injection available currently for the treatment of reducing the incidence of infusion induced reaction. CCI CCI The approved indication for IV diphenhydramine is as follows:

For amelioration (improvement) 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.[3]

7.3.2. Rationale for Selection of the Dose of IV Cetirizine HCl

The recommended dose of oral cetirizine HCl is 10 mg (Zyrtec). 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 dose occurs within 20 minutes in 50% of patients and within one hour in 95% of patients.



Intravenous cetirizine HCl was demonstrated to be non-inferior to diphenhydramine injection for acute urticaria while in a treatment center, but was demonstrated to be better in the benefits of: less sedation, less rescue-drug usage, shorter time spent in the treatment center, longer duration of action, lower return rate to the treatment centers, less symptom recurrence post-discharge, fewer AEs, lack of anticholinergic effect, and no significant drug-drug interactions.

7.3.3. Study Medication

Intravenous cetirizine HCl 10 mg/mL has been shown to treat acute urticaria as effectively as diphenhydramine with fewer side effects and could be used for pretreatment of chemotherapy-induced infusion reactions. Pretreatment for infusion reactions includes antihistamines where IV diphenhydramine is given as currently the only available injectable antihistamine. IV Cetirizine HCl, a second-generation injectable antihistamine, provides a new option for patients.

7.3.4. Maintenance of Study Blind

This will be a double-blind study; the investigator, the patient, and any healthcare professional involved in patient management or outcome assessment will remain blinded. Both IV cetirizine

HCl and IV diphenhydramine are presented as a clear aqueous solution in 2-mL amber vials containing 1 mL of medication and having the same physical appearance. A blinded and randomized label created for the study conceals the product label of each vial (for both the test drug cetirizine HCl or the comparator diphenhydramine). In the event of an emergency, patient and site may be unblinded.

7.3.5. Breaking the Study Blind

In order to preserve the blinding of the study, site personnel will not have access to the randomization list and treatment assignments before database lock. Study blinding may only be broken if the identity of the study drug is considered vital for the clinical management or to ensure safety of the patients.

7.3.6. Concomitant Medications/Rescue Drugs

To ensure optimal patient management, additional medications, e.g., epinephrine or steroids, may be given at any time during the study if deemed necessary by the investigator. 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.

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 enrollment will be recorded, as well as all concomitant medications administered during the study.

7.4. Clinical and Safety Evaluations

Study procedures and their timing are summarized in the Study Schedule in Attachment A and Symptom Score Assessment in Attachment B.

All patients who received at least 1 dose of study medication will be included in the PP and SAS analyses and safety evaluations.

8. CLINICAL OUTCOME AND PROCESS MEASURE

8.1. Primary Endpoint

The primary clinical endpoint is 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, or syncope).

8.2. Secondary Endpoints

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 analysis set. All other endpoints will be analyzed descriptively by treatment group using the safety analysis set population (SAS).

1. Sedation scores (patient and HCP) at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine HCl or IV diphenhydramine). The patient sedation scores are assessed on a scale of 0-4, with 0=None and 4=Extremely Severe (Asleep, Cannot Self-Rate). The HCP sedation scores are assessed on a scale of 0-4, with 0=None and 4=Extremely severe.

"How drowsy do you feel at the moment?"

- Patient Sedation Score

  0 = None (Not drowsy at all)

  1 = Mild (Slightly drowsy)

  2 = Moderate (Quite drowsy)

  3 = Severe (Extremely drowsy)

  4 = Extremely Severe (Asleep, cannot self-rate)

- HCP Sedation Score

  0 = None (Patient is completely alert. Does not look tired at all.)

  1 = Mild (Patient sitting/lying comfortably, and looks tired)

  2 = Moderate (Drowsy, with occasional eyes closing)

  3 = Severe (Asleep, with eyes closed but responds to minor motor stimulation)

  4 = Extremely Severe (Asleep; does not respond to minor motor stimulation)

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

9. 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.

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.**

The investigator remains responsible for following, through an appropriate healthcare option, AEs or SAEs 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.

9.1. Adverse Events

An 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. Lack of drug effect is not an AE 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 eCRF (Medical History).

If a patient experiences an AE (including a change in documented baseline medical conditions) after the informed consent document is signed, the event will be recorded as an AE in the source document and electronic case report form (eCRF). All AEs will additionally include severity and causality assessments.

The severity of the event will be classified according to CTCAE v 5.0 toxicity grading:

- **Grade 1 Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 Moderate:** minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
- **Grade 3 Severe:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4 Life-Threatening:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 Death:** Death related to AE.

The causality will be classified as:

- **Not related**: Any adverse event that is not related to the product being studied.
- **Possible**: Any adverse event that 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 that can be caused using 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 patient is discontinued as a result of an AE, study site personnel must clearly document the circumstances leading to any such discontinuation of treatment, in the source document and on the eCRF.

Events leading to a study endpoint will be included as part of the safety and efficacy analyses for this study and will not be recorded as AE or SAE unless the investigator believes the event may have been caused by the study drug. The primary endpoint 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, or syncope) and the secondary endpoint is sedation.

9.2. 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 AE from this study that results in one of the following outcomes, or is significant for any other reason:

- Death
- Medically significant
- 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 will be made through the EDC program and sent by email to: CCI [redacted]

The clinical sites need to follow the same processes for SAEs as documented above for AEs in Section 9.1. The Investigator must provide the following information, at a minimum: the patient 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.

9.3. Pregnancy

Should a patient report a pregnancy during the course of the study, it should be recorded in the source documents and electronic case report form (eCRF). The sponsor will follow the pregnancy outcome upon patient consent.

9.4. Safety Monitoring

The Medical Monitor will provide medical expertise in the safety oversight and review of safety information including but not limited to AE, SAE, and other safety listings.

10. DATA QUALITY ASSURANCE

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

- Provide instructional material to the study sites, as appropriate.
- Host a training session to instruct the investigators and study coordinators on the protocol, the completion of the source document, eCRFs, and study procedures.
- Make periodic monitoring 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 eCRF data and use standard computer edit checks 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 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.

10.1. Data Entry and Computerized Systems

Relevant study data will be collected on each subject and entered an Electronic Data Capture (EDC) system. The URL for the EDC system is CCI [redacted] Supported operating systems are Microsoft Windows XP, Microsoft Windows 2000, Microsoft Windows 7 and 8, Microsoft Vista, and Mac OS X. Microsoft Internet Explorer (version 9 and later), Firefox (version 27 and later), Chrome (version 30 and later), and Safari (version 9.0 and later) are acceptable web browsers.

Medrio software supports compliance with regulations such as 21 CFR Part 11, Annex 11, EU Safe Harbor, Good Clinical Practice, and HIPAA. Procedural controls include electronic audit trails of all changes to study data, electronic signatures, data encryption, and access restrictions to Protected Health Information (PHI). Access to the Medrio EDC system will only be granted to study personnel after training is conducted. User accounts are permission based which grants limited access and functionalities dependent upon permissions granted by study administrator.

All data that goes into and out of the server is encrypted using 128-bit Secure Sockets Layer (SSL) and 1024-bit RSA public keys. The servers, hosted by Medrio, are housed in a fully redundant N+1 data center with redundant power, cooling, and network connectivity. All servers reside behind Cisco firewalls and advanced intrusion detection/prevention systems. Medrio performs nightly backups to locations both on-site and off-site and maintains redundant hardware.

Data collection will begin at the signing of informed consent. All data (other than SAEs) should be submitted within 72 working hours of the visit in which data was collected. Edit checks (often called queries) will fire in real time as data is being entered to ensure quality data is provided. In addition to edit checks, manual queries will be generated by Data Managers and Monitors. Sites will have 10 working days to address all edit checks and manually created queries. Source Data Verification (SDV), Data Management Review and electronic signature by site PI will all take place prior to locking data.

10.2. Confidentiality of Trial Documents and Patient Records

The investigator must assure that the patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On the source document, eCRFs, or other documents submitted to the Sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrollment log reconciling patient codes and patient names. The investigator should maintain all patient-related documents in strict confidence. If a patient record such as a discharge report is needed for the study file all names and specific identifiers except for what is used for the study must be redacted.

10.3. 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 at least 2 years after completion or discontinuation of the study. After that period of time, the documents may be destroyed, in accordance with local regulations.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

This is a pilot clinical study to determine process feasibilities and to obtain a baseline clinical response (drug reaction to Rituxan) 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.

11.2. Statistical and Analytical Plans

A Statistical Analysis Plan (SAP) with analytical details and assumptions will be developed and finalized before database lock and unblinding of the study data.

11.2.1. 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 Baseline Sedation score of 0.

The following analysis populations will be identified for this study:

- **Full Analysis Set (FAS)**: The FAS consists of all randomized patients. Patients will be analyzed according to the randomized treatment.
- **Safety Analysis Set (SAS)**: The SAS consists of all patients who received at least 1 dose of study medication. Patients will be analyzed according to the treatment actually received.
- **Per Protocol Analysis Set (PP)**: The PP consists of patients with a 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.

11.2.2. General Considerations

All presentations and analyses will be conducted using SAS version 9.4 or higher, unless otherwise specified. For continuous data, the number of observations (n), mean, median, minimum, and maximum, and standard deviation (SD) values will be presented. For categorical data, the frequency counts and percentages will be presented.

11.2.3. Patient Disposition

Patient disposition (e.g., the number of patients signing the informed consent, randomized, completed, and discontinued) along with the number of patients in each of the analysis populations will be summarized descriptively by treatment group.

11.2.4. Patient Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize patient demographics and baseline characteristics such as medical and surgical history by treatment group. Additionally, demographics will be presented for screen failure subjects.

11.2.5. Concomitant Therapy

The frequency of medications taken prior to study enrollment and while enrolled in the study (concomitant medications) will be summarized using descriptive statistics by treatment group.

11.2.6. Primary Endpoint

The primary endpoint 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, or syncope).

The number and percent of patients experiencing hypersensitivity infusion reactions will be summarized by reaction and treatment group using descriptive statistics. This analysis will be performed using the FAS population.

11.2.7. Secondary Endpoints

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 the per protocol analysis set. All other endpoints will be analyzed descriptively by treatment group using the safety analysis set population (SAS).

1. Sedation scores (patient and HCP) at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine HCl or IV diphenhydramine). The patient sedation scores are assessed on a scale of 0-4, with 0=None and 4=Extremely Severe (Asleep, Cannot Self-Rate). The HCP sedation scores are assessed on a scale of 0-4, with 0=None and 4=Extremely severe.

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

11.2.8. Safety Analyses

Safety analysis will be analyzed descriptively by treatment group using the safety analysis set population (SAS). Sedation score will be analyzed descriptively by treatment group using per protocol analysis set. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary 22.1 and will be summarized by treatment group by severity, seriousness, and relationship. Events occurring more than once in the same patient will be counted only once. Additional safety analyses include summarizing vital signs and physical exam findings descriptively by treatment group.

12. ETHICS

12.1. 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 and that are consistent with "Good Clinical Practice" ICH Tripartite Guideline and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

12.2. 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/institutional review 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 whenever subsequent modifications to the protocol are made.

12.3. 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 patients 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 obtain consent from the patient.

The eCRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (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.

12.4. Protocol Signatures

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to the Sponsor or Sponsor's designee (e.g., CRO).

13. 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.

14. REFERENCES

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Attachment A. Study Schedule

Assessments	Baseline Screening (Day -14 to Day 0)[1]	Antihistamine injection Day (Day 0)	During Infusion	1 hr post-antihistamine injection	2 hr post-antihistamine injection	Discharge	24 hr	Up to 28 days Post-24 hr FU Call
Informed consent	X							
Demographics	X							
Inclusion/exclusion criteria	X							
Medical and surgical history	X							
Vital signs	X	X		X	X	X		
Physical examination	X							
Randomization		X						
Study medication administration		X						
Infusion reaction events			X	X	X	X		
Rescue medication, e.g., epinephrine, bronchodilators, steroids			X	X	X	X	X	
Sedation score		X		X	X	X		
HCP/Staff satisfaction of time spent					X			
HCP/Site staff assessment of ease and readiness for discharge						X		
Time of discharge						X		
Concomitant medication	X	X		X	X	X	X	
Adverse events - Other than infusion reaction [2]	X	X	X	X	X	X	X	
Follow-up Q&A Sheet							X	
Record patient self-reported AEs								X

AE = adverse event; FU = follow-up; Q&A = question and answer

[1] The Screening period is up to 14 days prior to randomization/treatment to allow procedure to be completed. However, screening and randomization/treatment can occur on the same day.

[2] All AEs and SAEs 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.

Attachment B. Symptom Score

A. HCP Assessments

a. Physician/Designee

b. Nurse

c. Other (specify)

1. HCP Sedation Score (baseline, 1 hr post- antihistamine injection, 2 hr post- antihistamine injection and discharge**)**

   0 = None (Patient is completely alert. Does not look tired at all.)

   1 = Mild (Patient sitting/lying comfortably, and look tired)

   2 =Moderate (Drowsy, with occasional eyes closing)

   3 = Severe (Asleep, with eyes closed but responds to minor motor stimulation)

   4 = Extremely Severe (Asleep; does not respond to minor motor stimulation)

2. HCP/Infusion staff overall satisfaction based on antihistamine used for pretreatment

   Amount of time spent during the first 2 hours

   1 = Very satisfied

   2 = Somewhat satisfied

   3 = Somewhat dissatisfied

   4 = not at all satisfied

   How satisfied are you with readiness and ease of discharge?

   1 = Very satisfied

   2 = Somewhat satisfied

   3 = Somewhat dissatisfied

   4 = not at all satisfied

B. Patient Self-Rated Assessments (baseline, 1 hr post- antihistamine injection, 2 hr post-antihistamine injection and discharge)

Patient Sedation Score

Ask the patient "How drowsy do you feel at the moment?"

0 = None (Not drowsy at all)

1 = Mild (Slightly drowsy)

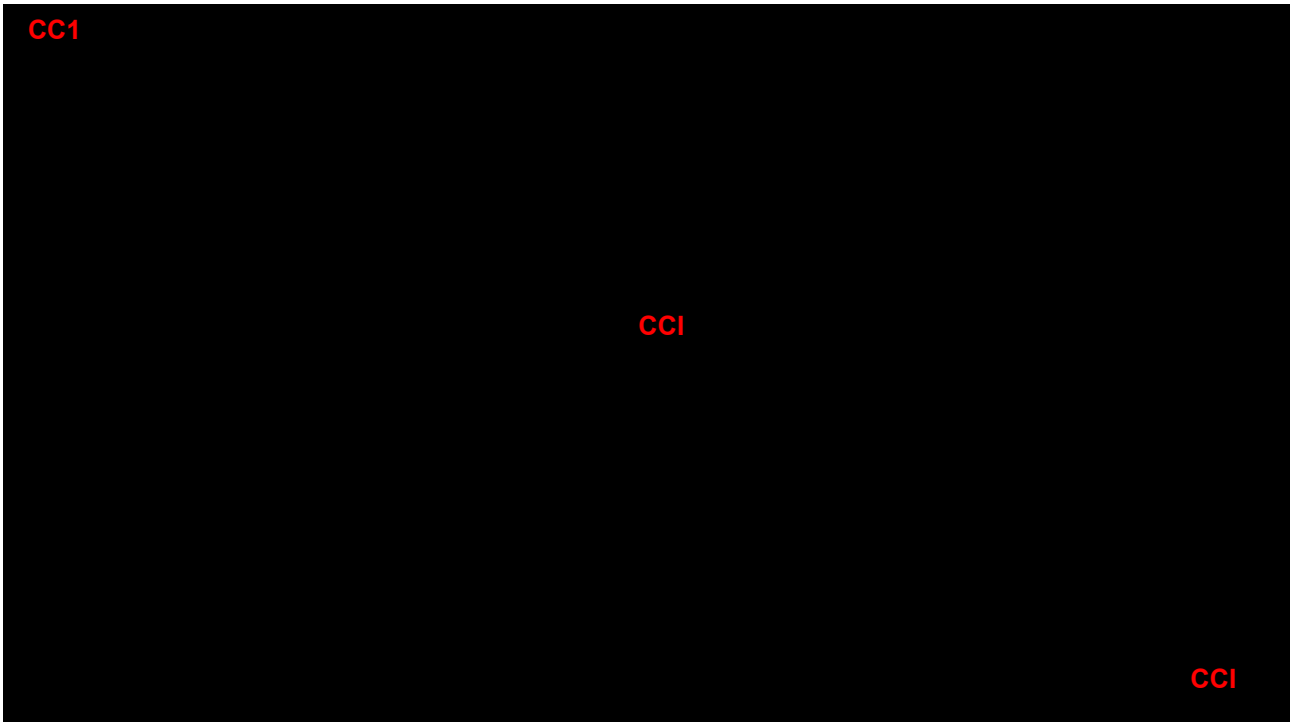
2 = Moderate (Quite drowsy)

3 = Severe (Extremely drowsy)

4 = Extremely Severe (Asleep, cannot self-rate)

C. HCP Readiness for Discharge

Attachment C. 24-Hour Follow-Up Questions



Attachment D. Common P-Glycoprotein Inhibitor (From FDA Drug-Drug Interaction)

1. Examples of in vitro inhibitors for transporters (9/26/2016)

Transporter	Gene	Inhibitor
P-gp	*ABCB1*	Cyclosporine
		Elacridar (GF120918)
		Ketoconazole
		Quinidine
		Reserpine
		Ritonavir
		Tacrolimus
		Valspodar (PSC833)
		Verapamil
		Zosuquidar (LY335979)

2. Examples of clinical inhibitors for transporters (for use in clinical DDI studies and drug labeling) (9/26/2016)

Transporter	Gene	Inhibitor
P-gp[(a)]	*ABCB1*	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil

[a] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A

[redacted]