NDA/BLA Multidisciplinary Review and Evaluation

Application type	NDA
Application number(s)	211415
Priority or standard	Standard
Submit date(s)	December 7, 2018
Received date(s)	December 7, 2018
PDUFA goal date	October 7, 2019
Division/office	Division of Pulmonary, Allergy, and Rheumatology Products
Review completion date	October 3, 2019
Established/proper name	Cetirizine
(Proposed) Trade name	Quzyttir
Pharmacologic class	Histamine-1 (H_1) receptor antagonist
Applicant	JDP Therapeutics
Dosage form	Intravenous solution: 10 mg/mL
Applicant-proposed dosing regimen	Adults and adolescents ≥12 years: 10 mg Children 6 to 11 years: 5 or 10 mg Children 6 months to 5 years: 2.5 mg Recommended dosage regimen is once every 24 hours as needed.
Applicant proposed indication(s)/population(s)	Treatment of acute urticaria in adults and children 6 months of age and older
Recommendation on regulatory action	Approval
Recommended indication(s)/population(s) (if applicable)	Same as proposed
Recommended dosing regimen	Same as proposed and clarified as needed for acute urticaria.

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BA	bioavailability
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CIU	chronic idiopathic urticaria
DPARP	Division of Pulmonary, Allergy & Rheumatology Products
DPV-I	Division of Pharmacovigilance I
EOP2	end-of-phase 2
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GLP	good laboratory practice
GMR	geometric mean ratio
ICH	International Conference on Harmonisation
IM	intramuscular
IND	investigational new drug
iPSP	initial pediatric study plan
ITT	intent-to-treat
IV	intravenous
LOCF	last observation carried forward
NDA	new drug application
NI	noninferiority
NOAEL	no observed adverse effect level
OSE	Office of Surveillance and Epidemiology
OSIS	Office of Study Integrity and Surveillance
OTC	over-the-counter
PAR	perennial allergic rhinitis
PeRC	Pediatric Review Committee
PK	pharmacokinetics
PO	oral
PP	per protocol
PRO	patient-reported outcome
SAE	serious adverse event
SAR	seasonal allergic rhinitis
T/R	test/reference
TQT	thorough QT

1. Executive Summary

1.1. Product Introduction

JDP Therapeutics submitted a 505(b)(2) new drug application (NDA) for cetirizine hydrochloride (HCl) 10 mg/mL solution for intravenous (IV) injection for the treatment of acute urticaria in adults and children 6 months of age and older. This NDA presents a new dosage form, route of administration and indication for cetirizine, a second-generation histamine-1 (H1) receptor antagonist. The proposed dosing is: 2.5 mg (6 months to 5 years of age), 5 mg or 10 mg (6 to 11 years of age), and 10 mg (12 years of age and older). The proposed dosing regimen is once every 24 hours as needed for acute urticaria. The Applicant has referenced both oral cetirizine (Zyrtec®) and oral levocetirizine (Xyzal).

Oral cetirizine in the tablet form was first approved in 1995 for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) and the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria (CIU; NDA 19835). Oral cetirizine in the syrup formulation was later approved in 1996 (NDA 20346). Oral cetirizine is approved for adults and children 6 months of age and older for PAR and CIU and for 2 years and older for SAR, dosed 2.5 to 10 mg daily. In November 2007, oral cetirizine was approved for over-the-counter (OTC) use in adults and children 2 years of age and older for the treatment of upper respiratory allergy symptoms and itching due to hives.

Levocetirizine is the R-enantiomer of cetirizine and was approved in tablet form (NDA 22064) in May 2007 and as an oral solution (NDA 22157) in January 2008. Levocetirizine is approved for the indications of PAR and the treatment of uncomplicated skin manifestations of CIU in adults and children 6 months of age and older, dosed 1.25 mg to 5 mg once daily. Levocetirizine is also approved OTC for patients 2 years of age and older.

For the remainder of the review, cetirizine HCl solution for IV injection will be referred to as IV cetirizine.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action from a clinical and statistical perspective is approval of IV cetirizine for the treatment of acute urticaria in patients 6 months of age and older. To support the indication of cetirizine in a new dosage form and route of administration (IV) for the new indication of acute urticaria, the Applicant submitted efficacy data from three trials (ETTAU-01, ETTAU-02, and ETTAU-03). ETTAU-01 is a single center, randomized, crossover trial to assess safety, tolerability, and pharmacokinetics (PK) in 24 healthy adult volunteers. ETTAU-02 is a double-blind, randomized, active-controlled pilot trial in 33 adults with acute urticaria comparing IV cetirizine to IV diphenhydramine to inform the noninferiority margin that was subsequently to be used in ETTAU-03. ETTAU-03 is a double-blind, randomized, active-controlled, noninferiority efficacy trial comparing IV cetirizine to IV diphenhydramine in 262 adults with acute urticaria. Trial ETTAU-03 provided the pivotal efficacy data as it was powered

to assess the non-inferiority of IV cetirizine compared to IV diphenhydramine. The primary clinical efficacy outcome was the change from baseline in the 2-hour patient-rated pruritus severity score. Based on a pre-specified agreed upon non-inferiority margin, IV cetirizine was found to be noninferior to IV diphenhydramine. The key secondary endpoints of the number of patients returning to any emergency department or clinical and time spent in the treatment center also favored treatment with cetirizine.

No pediatric clinical studies were conducted. Efficacy in children < 18 years of age is extrapolated from an adequate and well-controlled adult trial of IV cetirizine given the similar clinical presentation of both adult and pediatric acute urticaria, consistency in therapeutic approach and mechanism of action, and relevance of the clinical endpoints for both efficacy and safety. The extrapolation was supported by PK analyses showing similar cetirizine exposure at the recommended doses for patients 6 months to 17 years of age with oral cetirizine.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This 505(b)(2) NDA is for cetirizine hydrochloride (HCl) 10 mg/mL solution for intravenous (IV) injection for the treatment of acute urticaria in adults and children 6 months of age and older. Cetirizine is a second-generation histamine-1 (H1) receptor antagonist. The oral formulation was initially approved in 1995 for the indications of seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria and is approved down to 6 months of age and available over-the-counter down to 2 years of age. This application is for the support of a new dosage form (solution), route of administration (IV) and indication (acute urticaria).

The Applicant provides data from three clinical trials (ETTAU-01, ETTAU-02, and ETTAU-03) to support this new dosage form, route of administration and indication. ETTAU-01 is a safety, tolerability, and PK trial in 24 healthy adult volunteers. ETTAU-02 and ETTAU-03 are double-blind, randomized, active-controlled trials in adults with acute urticaria comparing IV cetirizine to IV diphenhydramine. Trial ETTAU-02 enrolled 33 adults and informed the noninferiority margin. Trial ETTAU-03 enrolled 262 adults and provided the pivotal efficacy data as it was powered to assess the non-inferiority of IV cetirizine compared to IV diphenhydramine. Based on a pre-specified agreed upon non-inferiority margin, IV cetirizine was found to be noninferior to IV diphenhydramine for the primary endpoint of change from baseline in the 2-hour patient-rated pruritus severity score. The key secondary endpoints also favored treatment with cetirizine.

No new safety concerns were identified compared to the well-known safety profile of oral cetirizine. PK in adults demonstrate an increased peak concentration (Cmax) for IV cetirizine compared to oral cetirizine. Safety for the increased Cmax is supported by an oral cetirizine thorough QT (TQT) study with 60 mg of oral cetirizine which resulted in higher Cmax than would be expected with 10 mg IV cetirizine. Common AEs for IV cetirizine occurring with an incidence of less than 1% included dyspepsia, feeling hot, dysgeusia, headache, paresthesia, presyncope, and hyperhidrosis. Sedation was also lower for IV cetirizine compared to IV diphenhydramine.

No pediatric clinical studies were conducted. Efficacy in children < 18 years of age is extrapolated from adequate, well-controlled adult studies of IV cetirizine data based on the similar clinical presentation of both adult and pediatric acute urticaria, consistency in therapeutic approach, mechanism of action, relevance of the clinical endpoints for both efficacy and safety, and PK showing similar oral cetirizine exposure for the recommended doses across different age groups. Pediatric safety is supported by the oral cetirizine pediatric studies down to 6 months of age. Cmax is expected to be higher than oral cetirizine in pediatric subjects based on the adult PK data with IV cetirizine and PK data with oral cetirizine in children down to 6 months of age demonstrating a linear

PK. As IV cetirizine is indicated for an acute condition administered in a medically supervised setting, the safety data for the higher Cmax in pediatric patients is supported by overdose cases identified in the FDA Adverse Event Reporting System (FAERS) which include sufficient exposures.

Overall, the data submitted by the Applicant supports a favorable benefit-risk assessment for the use of IV cetirizine for the treatment of acute urticaria in patients aged 6 months or older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Acute urticaria is characterized by the development of hives, which may or may not be accompanied by swelling. Acute urticaria contributes to decreased quality of life, and is responsible for urgent care/emergency department visits. Acute urticaria may also be a part of anaphylaxis, however, this application does not support the treatment of anaphylaxis.	Acute urticaria is reported to be the most common symptom associated with acute allergic reactions treated in the emergency department. IV cetirizine would be the first approved treatment for acute urticaria.
Current Treatment Options	There are currently no approved therapies for the indication of acute urticaria. At this time, standard of care for the treatment of acute urticaria consists of diphenhydramine, and other antihistamines, with or without steroids.	There are currently no approved therapies targeted to treat acute urticaria. While antihistamines and steroids are considered standard of care for the treatment of urticaria, it would be beneficial to have an approved treatment option.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	An adequate, well-controlled pivotal trial in adults with acute urticaria demonstrated that IV cetirizine is noninferior to IV diphenhydramine. Sedation scores were lower at all timepoints for IV cetirizine compared to IV diphenhydramine. No pediatric clinical studies were conducted. Efficacy in children < 18 years of age is extrapolated from adult studies of IV cetirizine data based on the similar clinical presentation of both adult and pediatric acute urticaria, consistency in therapeutic approach, mechanism of action, relevance of the clinical endpoints for both efficacy and safety, and PK showing similar oral cetirizine exposure for the recommended doses across different age groups.	IV cetirizine is a clinically relevant, beneficial treatment for acute urticaria in patients 6 months of age and older.
Risk and Risk Management	No new safety concerns were identified compared to the well-known safety profile of oral cetirizine which include somnolence, fatigue, dry mouth, pharyngitis, and dizziness. The risk analysis differs for IV cetirizine compared to oral cetirizine. Unlike oral cetirizine which is approved for chronic conditions, such as perennial allergic rhinitis and chronic idiopathic urticaria, IV cetirizine is proposed for treatment of an acute condition and will be administered under medical supervision. No risk evaluation and mitigation strategies are proposed.	The side effect profile for IV cetirizine is similar to that for oral cetirizine, with the most prominent side effect being sedation. In the prescribing information, prescribers are encouraged to counsel patients to be cautious with regards to somnolence and sedation and to exercise caution when driving a car or operating potentially dangerous machinery. IV cetirizine is given as a single dose in 24 hours under medical supervision, which should mitigate the risk profile.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		X	Patient-reported outcome (PRO)	8.1.7
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data were not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Urticaria is marked by the transient appearance of elevated patches (wheals) that are erythematous and typically associated with pruritus. Each individual lesion lasts about 30 min to 24 hours with the skin returning to normal. When urticaria lasts for less than 6 weeks duration, the condition is termed acute urticaria. When urticaria lasts for more than 6 weeks duration, the condition is termed chronic urticaria. Acute urticaria is typically an isolated event, however, at times it may precede and be a feature of anaphylaxis. Angioedema can also accompany urticaria.

There were nearly 5 million visits to hospital emergency departments for acute allergic reactions according to the 2009 U.S. National Hospital Ambulatory Medical Care Survey (Centers for Disease Control and Prevention 2009). Acute urticaria is reported to be the most common symptom associated with acute allergic reactions treated in the emergency department (Simonart et al. 1994).

Acute urticaria is more frequently associated with identifiable conditions (i.e., viral infection, food/drug allergy, or adverse drug reactions etc.) while chronic spontaneous or inducible urticaria, previously referred to as chronic idiopathic urticaria (lasting greater than 6 weeks duration), is less likely to be associated with an identifiable cause.

Since acute urticaria typically resolves spontaneously, laboratory evaluation for chronic illness is not required unless supported by clinical history or physical examination. Empiric elimination diets are also not recommended. Although many cases of acute urticaria are caused by viral or other infectious illnesses, extensive evaluation for specific viral pathogens or antiviral therapy is not indicated unless suggested by the clinical history. For acute urticaria, skin testing or immunoassays to identify specific triggers for acute urticaria can be helpful if an allergic cause is suggested by the history. Skin testing in this scenario would usually be done after the resolution of acute urticaria. Common causes of acute urticaria and angioedema, including medications and foods, should be identified by history and eliminated if possible (Bernstein et al. 2014).

2.2. Analysis of Current Treatment Options

At the present time, there are no approved therapies for the treatment of acute urticaria. Acute urticaria is typically treated with antihistamines and corticosteroids. Current guidelines support the use of first- and second-generation antihistamines (hydroxyzine (Atarax), diphenhydramine hydrochloride (oral (PO) Benadryl), oral cetirizine (Zyrtec®), levocetirizine (Xyzal), fexofenadine (Allegra), loratadine (Claritin), and desloratadine (Clarinex)) for the treatment of acute urticaria (American Academy of Allergy Asthma & Immunology 2019). All antihistamines can cause sedation. First-generation antihistamines, such as hydroxyzine and diphenhydramine are considered to be more sedating as they cross the blood-brain barrier whereas newer (second-generation) antihistamines such as cetirizine, levocetirizine, fexofenadine, loratadine, and

desloratadine are less likely to be sedating (American Academy of Allergy Asthma & Immunology 2019). In patients who have a poor response to antihistamines, a brief course of oral corticosteroids might also be required while attempting to eliminate suspected triggers and develop an effective treatment plan. See Table 1 for a complete list of currently approved and available antihistamines.

Table 1. Currently Available Antihistamines

Product(s) Name	Formulation	Rx, OTC, Both	Indication	Age Range
Semprex- D (Acrivastine)	Capsule	Rx	Allergic rhinitis	12 y and older
Brompheniramine	Syrup, Tablet	Rx (Syrup) OTC (Tablet)	Cough, Nasal congestion associated with allergic rhinitis or common cold	Syrup: 2 y and older Tablet: 6 y and older
Carbinoxamine Maleate	Tablets, Liquid	Rx	SAR, PAR, Allergic conjunctivitis, Allergic skin manifestations (urticaria and angioedema), dermatographism, therapy for anaphylactic reactions adjunctive to epinephrine	2 y and older
Zyrtec (Cetirizine)	Capsule, Chewable Tablet, Tablet, Syrup	Both	SAR, PAR, CU	6 mo and older
Chlorpheniramine	Tablet	OTC	AR	6 y and older
Clemastine	Tablet, Syrup	Both (Tablet – OTC and Rx, Syrup – Rx)	AR, Urticaria	Syrup 6 y and older Tablet 12 y and older

Cyproheptadine	Syrup, Tablet	Rx	AR, Urticaria	2 y and older
Desloratadine	Tablet, Syrup	Rx	SAR, PAR, CU	6 mo and older
Benadryl (Diphenhydramine)	Capsule, Chewable Tablet, Tablet, Syrup, IV	Both	SAR, Urticaria, Motion sickness, insomnia	Syrup 2 y and older Tablet 6 y and older
Allegra (Fexofenadine)	Tablet, ODT, Syrup	Both	SAR, CU	6 mo and older
Hydroxyzine	Capsules, Tablets, Syrup	Rx	Itching associated with skin allergies	6 y and older
Xyzal (Levocetirizine)	Tablets, Oral solution	Both	SAR, PAR, CU	6 y and older
Claritin (Loratadine)	Tablets, RediTabs, Syrup	OTC	AR, CU	2 y and older
Claritin-D (Loratadine)	Tablets	OTC	AR	12 y and older

Source: Adapted from American Academy of Allergy Asthma & Immunology (2018)
AR - allergic rhinitis, CU – chronic urticaria, ODT – orally dissolving tablet, OTC – over the counter, PAR – perennial allergic rhinitis, Rx – prescription, SAR – seasonal allergic rhinitis, y – years, mo – months

When patients present to an acute care setting with acute urticaria, the mainstay of therapy is IV diphenhydramine as it is the only antihistamine that is currently available IV. IV diphenhydramine often causes sedation and results in unwanted anticholinergic effects (i.e., urinary retention, dry mouth/eyes, etc.) and therefore often extends time to discharge from the emergency department (Gengo et al. 1989; Banerji et al. 2007). IV diphenhydramine prescribing information contains warnings for subjects with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction and precautions for subjects with bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension. The prescribing information also notes adverse reactions of sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, and thickening of bronchial secretions.

Cetirizine is available as tablets, chewable tablets, and syrup. Table 2 details cetirizine approvals, formulations, indications, and populations treated.

Table 2: Cetirizine Approvals, Formulations, Indications, and Populations Treated

Approval	NDA#	Formulation	Indications	Population
12/8/1995	19835	5, 10 mg tablet	SAR, PAR, CIU	Adults Children ≥ 12 y
9/27/1996	20346	1 mg/mL syrup	SAR, PAR, CIU	Adults Children ≥ 6 y
5/15/1998	sNDA 19835/S-005 sNDA 20346/S-002	Tablets Syrup	SAR, PAR, CIU	Adults Children 2-6 y
8/10/2001	21150	With pseudoephedrine 120 mg (Zyrtec®-D)	Relief of nasal & non-nasal symptoms with SAR & PAR	Adults Children ≥ 12 y
10/21/2002	sNDA 19835/S-015 sNDA 20346/S-008	Tablets Syrup	SAR, PAR, CIU	Adults Children ≥ 6 mo
3/16/2004	21621	Chewable Tablets	SAR, PAR, CIU	SAR: Adults & Children ≥ 2 y PAR/CIU: Adults & Children ≥ 6 mo
11/16/2007	sNDA 19835/S-022 sNDA 21621/S-005 22155	Tablets Chewable Tablets Syrup	AR, itching with hives Tab/chewable: Full OTC switch Syrup: partial OTC switch	AR/hives: Adults & Children ≥ 6 y AR: Children 2-5 y

Source: Adapted from Lopez (2007), Table 1, page 9
AR – Allergic rhinitis, CIU – Chronic idiopathic urticaria, OTC – Over the counter, PAR – Perennial allergic rhinitis, SAR – Seasonal allergic rhinitis, y - years, mo - months

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

IV cetirizine is not currently marketed outside the United States. A summary of the regulatory history of oral cetirizine and IV cetirizine are provided in Table 3 and Table 4, respectively.

Table 3. Summary of U.S. Regulatory Actions and Marketing History for Oral Cetirizine (Zyrtec®)

Date	Remarks
Dec 8, 1995	Cetirizine tablets approved (NDA 019835) for adults and children 12 years of age and older for seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU).
Sept 27, 1996	Cetirizine syrup (1 mg/mL) approved (NDA 020346) for adults and children 6-11 years of age for SAR, PAR, and CIU.
May 15, 1998	Cetirizine tablets and syrup approved for adults and children 2-5 years of age for SAR, PAR, and CIU.
Aug 10, 2001	Cetirizine 5 mg combination product with pseudoephedrine 120 mg approved for adults and children 12 years of age and older for the relief of nasal and non-nasal symptoms associated with SAR and PAR.
Oct 21, 2002	Cetirizine tablets and syrup approved for the relief of symptoms associated with SAR, PAR, or CIU in adults and children 6 months of age and older.
Nov 16, 2007	Cetirizine approved for nonprescription use in adults and children 2 years of age and older for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 4. Summary of Presubmission/Submission Regulatory Activity for IV Cetirizine

Interaction	Date	Remarks
PIND	Mar 19, 2010	Applicant proposed drug development for treatment of (b) (4) [redacted] FDA noted that the proposed indication was too broad and should be based on a specific disease.
IND opened	Feb 5, 2014	IND 107689

Interaction	Date	Remarks
EOP2 – Type B	Mar 18, 2015	Advised that participants be enrolled for treatment of acute urticaria and exclude patients with anaphylaxis. Primary endpoint will be patient rated pruritis score change at 2 hrs and physician score will be a secondary endpoint. Follow-up 48 hrs post discharge. Thorough QT study not needed. A single pivotal phase 3 may be sufficient. Need to re-adjust noninferiority (NI) margin.
Agreed iPSP	Nov 18, 2015	For the proposed cetirizine injection, the NDA's safety profile of the adult population will be based on the pivotal study, the previous pilot study, the injection PK studies, and the large amount of safety data from oral cetirizine. Agency agreed to the iPSP/pediatric assessment plan including: The pediatric safety is supported by safety data from the IV cetirizine adult data and from oral cetirizine's pediatric data. The Agency agreed to the plan to request a waiver for less than 6 months as there are few patients and difficult to diagnose this age group.
Noninferiority margin (NI)	Oct 2016	JDP initially proposed NI margin of (b) (4)% but agreed to the Agency's proposal of a NI margin of 0.5.
Proprietary name requests	Jan 9, 2018 & Aug 17, 2018	Tradename (b) (4) rejected (1/2018) and Tradename (b) (4) rejected (8/2018)
NDA submitted	Dec 7, 2018	An NDA was received for IV cetirizine.
Accepted name	Jan 2019	Tradename QUZYTTIR accepted

Abbreviations: C_{max} = maximum concentration; EOP2 = end of phase 2; DPARP = Division of Pulmonary, Allergy & Rheumatology Products; IND = investigational new drug; iPSP = initial pediatric study plan; IV = intravenous; OSE = Office of Surveillance and Epidemiology; PeRC = Pediatric Review Committee; PIND = pre-investigational new drug; PK = pharmacokinetic

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

An Office of Scientific Investigations inspection was not requested as there was only one small, single-dose, pivotal efficacy study, which did not warrant a consult.

4.2. Product Quality

With this application, the Applicant introduced a new formulation of cetirizine (IV solution). The data provided in the supplement support the conclusion that the proposed control strategy for the new presentation combined with in-process, release, and stability testing ensure process consistency and drug substance, formulated drug substance, and drug product with appropriate quality attributes. The Office of Pharmaceutical Quality recommends approval.

4.3. Clinical Microbiology

The Division of Microbiology Assessment recommends approval based on review of the Product Quality Microbiology and Sterility Assurance.

4.4. Devices and Companion Diagnostic Issues

No data regarding devices and companion diagnostic issues were submitted (nor required) as part of this supplementary application.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Introduction

A complete battery of nonclinical studies was conducted to support the oral route of administration for cetirizine HCl (10 mg/day) under NDA 019835. In support of the new IV route of administration for cetirizine HCl, three nonclinical studies were submitted: (1) "In Vitro Evaluation of the Influence of Cetirizine Injection (10 mg/mL) on Human Whole Blood Hemolysis and Plasma Flocculation (Study No. 600499);" (2) "Cetirizine Dihydrochloride: An Escalating Dose (phase 1) and 7-Day Repeat Dose (phase 2) IV Administration Toxicity Study in Sprague Dawley Rats (Study No. 72657);" and (3) "Cetirizine Dihydrochloride: A 14-Day IV Toxicity Study in Sprague Dawley Rats (Study No. 72658)." The in vitro hemolysis and plasma flocculation study in human whole blood with cetirizine and the 14-day toxicology study in rats with IV cetirizine were requested by the FDA at the time of the preinvestigational new drug (pre-IND) meeting (see meeting minutes dated March 24, 2010). Based on these study findings, NDA 211415 for IV cetirizine is recommended for approval from the nonclinical pharmacology and toxicology perspective. There are no outstanding nonclinical issues.

Brief Discussion of Nonclinical Findings

To support the safety of IV cetirizine for approval, the Applicant conducted a good laboratory practice (GLP) in vitro whole blood hemolysis and plasma flocculation study with cetirizine (Study No. 600499). Human whole blood from two males and two females was incubated for 24 hours at 37°C with vehicle/negative control (0.9% NaCl), hemolysis positive control (20% saponin), flocculation (turbidity) positive control (20% Intralipid®), or 10 mg/mL cetirizine injection (final concentrations of 0.01, 0.1, and 1 mg/mL). Under the conditions tested, cetirizine did not cause hemolysis or flocculation of human whole blood.

In addition, two toxicology studies in rats were conducted with IV cetirizine . In the first toxicology study, the Applicant conducted a four-phase non-GLP dose-range finding toxicity study (single ascending dose and 7-day repeat dose) with IV administration (tail vein or femoral vein) of cetirizine (dose levels from 1 to 100 mg/kg) to Sprague Dawley rats (Study No. 72657). In this study, mortality was seen with IV cetirizine dose levels ≥50 mg/kg. The maximum tolerated dose for a single IV dose of cetirizine was determined to be 35 mg/kg. Further, the Applicant chose the cetirizine dose levels of 6 mg/kg/day and 13 mg/kg/day for IV administration (via femoral vein) for the 14-day repeat-dose toxicology study in Sprague Dawley rats.

In the second toxicology study, the Applicant conducted a GLP 14-day repeat-dose IV toxicity study in Sprague Dawley rats with cetirizine at dose levels of 0.86, 6, and 13 mg/kg/day (about 0.8x, 6x, and 13x the clinical dose of 10 mg/day, respectively, for a 60-kg person on a mg/m^2 basis) (Study No. 72658). No dose-limiting toxicity or target organs of toxicity were identified

and the no observed adverse effect level (NOAEL) was 13 mg/kg/day (high-dose). The corresponding mean area under the concentration-time curve (AUC_{0-t}) and mean maximum concentration (C_{max}) on Day 14 were 29.783 mcg*hr/mL and 13.374 mcg/mL, respectively.

5.2. Referenced NDAs, BLAs, DMFs

- NDA 019835: Zyrtec® (cetirizine hydrochloride) by Johnson and Johnson Consumer Inc. McNeil Consumer Healthcare Division
- NDA 020346: Zyrtec® (cetirizine hydrochloride) by Johnson and Johnson Consumer Inc. McNeil Consumer Healthcare Division
- NDA 022064: Xyzal (levocetirizine dihydrochloride; active enantiomer of cetirizine) by Sanofi Aventis US LLC
- IND 107689: cetirizine hydrochloride by JDP Therapeutics Inc.
- DMF (b) (4): cetirizine dihydrochloride by (b) (4)
  - (b) (4) (manufacturer of drug substance cetirizine hydrochloride) provided a letter of authorization for cetirizine HCl in DMF (b) (4)

5.3. Drug

CAS Registry Number: 83881-52-1

Generic Name: cetirizine hydrochloride (cetirizine HCl)

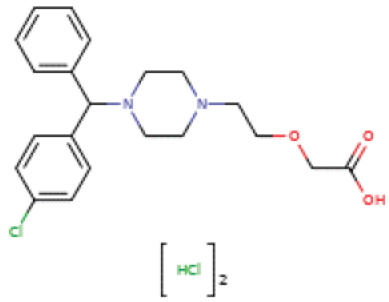
Code Name: CD/ZEN

Chemical Name: (+/-)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl]ethoxy] acetic acid, dihydrochloride

Molecular Formula: $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$

Molecular Weight: 461.8(b) (4)

Figure 1. Structure of Cetirizine Hydrochloride



Source: ChemIDplus, a TOXNET database

Pharmacologic Class: histamine-1 (H1) receptor antagonist

5.4. Drug Formulation

The cetirizine drug product is provided in a 2-mL size amber glass vial for single-use as a sterile, clear, colorless solution for injection. The cetirizine injection contains 10 mg/mL cetirizine as the active pharmaceutical ingredient and is formulated with 6.5 mg sodium chloride and sodium hydroxide and/or hydrochloric acid to adjust to pH (b) (4). See Table 5.

Table 5. Cetirizine Injection Qualitative and Quantitative Composition (Applicant's Table)

(b) (4) Drug Code	Ingredient	Quantity per mL	Function	Quality Standard
(b) (4)	Cetirizine HCl, USP	10.00 mg	API	USP
	Sodium Chloride, USP	6.50 mg	To adjust tonicity (b) (4)	USP
	Sodium Hydroxide, NF, (b) (4)	q.s.	To adjust pH	NF
	Acid, Hydrochloric, NF	q.s.	To adjust pH	NF
	Water for Injection, USP	(b) (4)		USP

Abbreviations: API = active pharmaceutical ingredient; NF = National Formulary; USP = United States Pharmacopeia; q.s. = *quantum satis*, the amount which is enough

Comments on Novel Excipients

The excipients in the cetirizine injection are all found in FDA approved IV drug products at comparable or greater doses. The recommended dosage for IV cetirizine injection is 10 mg to

be given once every 24 hours, as needed. Therefore, the total daily dose for sodium chloride will be 6.50 mg. There are no nonclinical concerns with the excipients.

Comments on Impurities/Degradants of Concern

Any individual unspecified impurity was controlled to no more than 0.10% and total impurities were controlled to no more than 0.3% per the active pharmaceutical ingredient specification. These specification limits cover any potential mutagenic impurities for the clinical maximum daily dose of 10 mg/day. Based on International Conference on Harmonisation (ICH) guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018), for an acute use product, the acceptable total daily intake for an individual impurity is 120 mcg/day. For a nonmutagenic impurity, based on the ICH guidance for industry *Q3A(R) Impurities in New Drug Substances* (June 2008), the total daily intake for an impurity is based on the qualification threshold of 0.15% or 1 mg/day intake (whichever is lower) for a maximum daily dose ≤2 g/day.

Elemental impurities for cetirizine were controlled within specification limits per the ICH guidance for industry *Q3D Elemental Impurities* (September 2015).

(b) (4) for cetirizine were controlled within specification limits per the guidance for industry (b) (4)

In consultation with the Quality Reviewer, there were no impurities/degradants of concern that required toxicological evaluation.

5.5. Pharmacology

No pharmacology studies were conducted in support of this 505(b)(2) NDA submission.

5.6. ADME/PK

No ADME/PK studies were conducted in support of this 505(b)(2) NDA submission.

5.7. Toxicology

5.7.1. General Toxicology

Study title/number: Cetirizine Dihydrochloride: A 14-Day Intravenous Toxicity Study in Sprague Dawley Rats (Study No. 72658)

Key Study Findings:

No dose-limiting or target organs of toxicity were identified.
NOAEL =13 mg/kg/day (high-dose)
Mean AUC_{0-t} on Day 14=29.783 mcg*hr/mL

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 6. Methods of 14-Day Intravenous Toxicity Study in Sprague Dawley Rats

Parameter	Details
Dose and frequency of dosing	0 (control; saline only), 0.86 (low-dose), 6 (mid-dose), and 13 (high-dose) mg/kg Administered once per day
Route of administration	IV administration to femoral vein over 2 minutes
Formulation/vehicle	0.9% Sodium Chloride for Injection, USP (Saline)
Species/strain	Rat/Sprague Dawley Crl:CD (SD)
Number/sex/group	Main toxicology study: 10 TK study: 3 (control) and 6 (low-dose, mid-dose, and high-dose)
Age	10 weeks of age at onset of treatment
Satellite groups/unique design	TK
Deviation from study protocol affecting interpretation of results	No

Abbreviations: IV = intravenous; TK = toxicokinetic; USP = United States Pharmacopeia

Table 7. Observations and Results: Changes From Control of 14-Day Intravenous Toxicity Study in Sprague Dawley Rats

Parameters	Major Findings
Mortality	There were no test article-related deaths during the study.
Clinical signs	There were no test article-related effects on clinical signs.
Body weights	There were no test article-related effects on body weights or body weight changes.
Hematology and Coagulation	A full battery of hematology and coagulation parameters was evaluated. There were no test article-related effects on hematology and coagulation parameters.
Clinical chemistry	A full battery of clinical chemistry parameters was evaluated. There were no test article-related effects on clinical chemistry parameters.
Urinalysis	A full battery of urinalysis parameters was evaluated. There were no test article-related effects on urinalysis parameters.
Gross pathology	Main study animals were euthanized on Day 15 and subjected to a full necropsy and gross pathology examination. There were no test article-related effects observed by gross pathology examination (i.e., no macroscopic observations).
Organ weights	There were no test article-related changes on organ weights.
Histopathology Adequate battery: Yes	A histopathological examination was performed on organs/tissues from all control and high-dose animals in the main study. Further, gross lesions from all animals were examined histologically. There were no test article-related effects observed by histopathology examination (i.e., no microscopic observations).

Parameters	Major Findings
Toxicokinetics	On Day 1 and Day 14, combined (males and females) mean AUC_{0-t} increased in a greater than dose-proportional manner between the low-dose and mid-dose and in an approximately dose-proportional manner between the mid-dose and high-dose. Mean AUC_{0-t} was greater for females than males at the mid-dose (12.316 vs. 3.504 mcg*hr/mL on Day 1 and 12.456 vs. 3.816 mcg*hr/mL on Day 14) and greater for males than females at the high-dose (28.682 vs. 16.287 mcg*hr/mL on Day 1 and 30.803 vs. 18.223 mcg*hr/mL). On Day 1 and Day 14, combined (males and females) mean C_{max} increased in an approximately dose-proportional manner between each dose level. Mean C_{max} was generally similar between males and females on Day 1 and Day 14. See Table 8.

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum concentration

Table 8. Summary of Toxicokinetic Parameters on Day 1 and Day 14 in a 14-Day IV Toxicity Study of Cetirizine in Sprague Dawley Rats

		Mean AUC_{0-t} (mcg*hr/mL)			Mean C_{max} (mcg/mL)		
	Dose (mg/kg/day)	Male	Female	Combined	Male	Female	Combined
Day 1	0.86	0.250	0.411	0.359	0.933	0.984	0.876
	6	3.504	12.316	8.396	7.257	8.162	7.709
	13	28.682	16.287	24.903	13.756	15.749	14.753
Day 14	0.86	0.219	0.336	0.289	1.024	0.789	0.865
	6	3.816	12.456	8.903	7.489	8.411	7.950
	13	30.803	18.223	29.873	13.643	13.105	13.374

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum concentration; IV = intravenous

General Toxicology; Additional Studies

The Applicant conducted a four-phase (i.e., phase 2, phase 2/2B, phase 3, and phase 4/4B) non-GLP dose-range finding toxicity study (single ascending dose and 7-day repeat dose) with IV administration of cetirizine to Sprague Dawley rats (Study No. 72657). Phase 1 included single ascending doses of cetirizine from 1 to 100 mg/kg given by IV administration to the tail vein of two animals/sex/group, in order to determine the maximum tolerated dose. Phase 1 animals were observed for 14 days after dosing and were then euthanized without further examination. Phase 2 included repeat-dose administration of 35 mg/kg cetirizine for 7 days to the tail vein of five animals/sex/group. Due to injection site swelling and necrosis after 3 days of repeat dosing, animals in phase 2 were euthanized without further examination. As such, phase 2B was conducted and included repeat-dose administration of 30 mg/kg cetirizine for 7 days to the tail vein of five animals/sex/group. At the end of the dosing period, surviving animals were euthanized, necropsied, and subjected to a gross examination. Phase 3 included repeat-dose administration of 30 mg/kg of the test article dose formulation (clinical formulation) for 7 days to the tail vein of five animals/sex/group. Due to injection site swelling and necrosis after 2 days of repeat dosing, animals in phase 3 were euthanized, necropsied, and subjected to gross examination on Day 3. Phase 4 included repeat-dose administration of 30 mg/kg of the test article dose formulation (clinical formulation) for 5 days to the femoral vein of two animals/sex/group, in order to determine the viability of using the femoral vein instead of the tail vein. At the end of the 5-day dosing period, animals were euthanized, necropsied, and

subjected to gross examination. Due to hematuria in phase 4, phase 4B included repeat-dose administration of 7 and 15 mg/kg of the test article dose formulation (clinical formulation) for 5 days to one animal/sex/group. The animals were monitored for clinical signs and hematuria. At the end of the 5-day dosing period, surviving animals were euthanized but not examined.

In phase 1, two of four animals in the single-dose 100 mg/kg cetirizine group (one of two males and one of two females) and three of four animals in the single-dose 50 mg/kg cetirizine group (two of two males and one of two females) were found dead immediately after dosing. Clinical signs in these groups included labored/decreased respiration, tremors, loss of coordination and limb function, and decreased activity.

In phase 2 (35 mg/kg cetirizine), all males (five of five) and all females (five of five) were sacrificed early due to injection site swelling and necrosis. In phase 2B (30 mg/kg cetirizine), there was no mortality, but clinical observations included injection site reactions (e.g., swelling, skin discoloration, lesions with discharge, and bruising). Related gross findings at the injection site included dark area associated with thickening and/or scab in 2 males/10 animals. Additional gross findings included enlargement of bronchial lymph node in 2/10 animals (1/5 males and 1/5 females).

In phase 3 (30 mg/kg cetirizine injection clinical formulation), all males (five of five) and all females (five of five) were sacrificed early (Day 3) due to injection site clinical signs (i.e., swelling, bruising, presence of liquid and discoloration indicating prenecrotic and necrotic tissue formation), which made further dosing difficult. Gross findings at the injection site consisted of dark focus/area/mottling in 8/10 animals, thickening in 6/10 animals, and scab in 1/10 animals. Additional gross findings included pale discoloration in the kidneys in 1 male/10 animals, mandibular lymph node enlargement in 3/10 animals (1/5 males and 2/5 females), mottled mediastinal lymph node in 1 male/10 animals, and mottled and enlarged popliteal lymph node in 1 female/10 animals.

In phase 4 (30 mg/kg cetirizine injection clinical formulation) there was no mortality, but clinical observations included red liquid in the cage tray and the urogenital area (hematuria) in all animals. In phase 4B, red liquid was noted in the cage tray of animals in the 15 mg/kg cetirizine injection clinical formulation group. There were no dosing site findings in phase 4/4B animals. Gross findings included dark focus in the lungs of two of four animals.

Based on these findings, the Applicant decided to proceed with dose levels of 6 mg/kg/day and 13 mg/kg/day in the 14-day repeat-dose toxicology study and to use the femoral vein for administration.

5.7.2. Genetic Toxicology

No genetic toxicology studies were conducted in support of this 505(b)(2) NDA submission.

5.7.3. Carcinogenicity

No carcinogenicity studies were conducted in support of this 505(b)(2) NDA submission.

5.7.4. Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were conducted in support of this 505(b)(2) NDA submission.

5.7.5. Other Toxicology Studies

The effect of cetirizine was examined in a GLP-compliant in vitro human whole blood hemolysis and plasma flocculation study (Study No. 600499). Whole blood was collected from two male and two female fasted adult humans (>18 years of age) and prepared in glass tubes according to Table 9 with the test article of cetirizine injection at 10 mg/mL stock concentration, the vehicle and negative control of 0.9% NaCl, the hemolysis positive control of 20% saponin, and the flocculation (turbidity) positive control of 20% Intralipid®. Each tube was mixed by inverting three times and incubated away from light for about 1 hour at 37°C. After incubation, whole blood samples were analyzed for hemoglobin (only Group 2, negative control of 0.9% NaCl) and hematocrit (except Group 4, 20% Intralipid®). Supernatant plasma (except Group 4, 20% Intralipid®) was analyzed for hemoglobin. Supernatant plasma was also analyzed for hemolytic (except Group 4, 20% Intralipid®) and turbidity (except Group 3, 20% saponin) indices.

Table 9. Control and Sample Preparation for In Vitro Evaluation of Cetirizine on Human Whole Blood Hemolysis and Plasma Flocculation (Applicant's Table)

Group ID	Control or Test Article	Cetirizine HCl Spiking Sol. (mL)	0.9% NaCl (mL)	20% Saponin (mL)	20% Intralipid® (mL)	Whole Blood (mL)	Cetirizine HCl Final Conc. (mg/mL)
1	Whole blood	-	-	-	-	2.0	0
2	0.9% NaCl	-	0.2	-	-	1.8	0
3	20% Saponin	-	-	0.2	-	1.8	0
4	20% Intralipid®	-	0.15	-	0.05	1.8	0
5	Cetirizine HCl 10 mg/mL	0.004	0.396	-	-	3.6	0.01
6	Cetirizine HCl 10 mg/mL	0.02	0.180	-	-	1.8	0.1
7	Cetirizine HCl 10 mg/mL	0.2	-		-	1.8	1

The mean results for in vitro evaluation of cetirizine (0.01, 0.1, or 1 mg/mL final concentrations) on male (n=2) and female (n=2) human whole blood hemolysis and plasma flocculation are shown in Table 10. Based on the data, cetirizine did not cause hemolysis or flocculation of human whole blood under the study conditions at the concentrations tested.

Table 10. Results for In Vitro Evaluation of Cetirizine on Human Whole Blood Hemolysis and Plasma Flocculation

Parameter	Group ID	Male Group Mean ± SD	Female Group Mean ± SD
Whole blood hemoglobin (g/dL)	2/Negative Control (0.9% NaCl)	13.5±0.4	12.3±1.1
Whole blood hematocrit (%)	1/Nonspiked Whole Blood	42.3±1.8	39.4±3.5
	2/Negative Control (0.9% NaCl)	38.7±0.1	35.0±2.5
	3/Positive Control (20% Saponin)	0.1±0.0	0.1±0.0
	5/Cetirizine: 0.01 mg/mL	37.4±1.8	35.9±3.5
	6/Cetirizine: 0.1 mg/mL	37.8±0.4	35.7±2.4
	7/Cetirizine: 1 mg/mL	38.0±0.2	34.6±3.4
Plasma hemoglobin conc. (g/dL)	1/Nonspiked Whole Blood	0.0±0.0	0.0±0.0
	2/Negative Control (0.9% NaCl)	0.0±0.0	0.0±0.0
	3/Positive Control (20% Saponin)	13.3±0.4	12.0±0.8
	5/Cetirizine: 0.01 mg/mL	0.0±0.0	0.0±0.0
	6/Cetirizine: 0.1 mg/mL	0.0±0.0	0.0±0.0
	7/Cetirizine: 1 mg/mL	0.0±0.0	0.0±0.0
Plasma hemolytic index (mg/dL)	1/Nonspiked Whole Blood	64±5	62±7
	2/Negative Control (0.9% NaCl)	52±0	37±4
	3/Positive Control (20% Saponin)	13970±1117	13440±1527
	5/Cetirizine: 0.01 mg/mL	16±1	14±1
	6/Cetirizine: 0.1 mg/mL	57±2	48±4
	7/Cetirizine: 1 mg/mL	66±7	109±5
Plasma hemolytic index (hemoglobin equivalent in g/dL)	1/Nonspiked Whole Blood	0.064±0.005	0.062±0.007
	2/Negative Control (0.9% NaCl)	0.052±0.000	0.037±0.004
	3/Positive Control (20% Saponin)	13.970±1.117	13.440±1.527
	5/Cetirizine: 0.01 mg/mL	0.016±0.001	0.014±0.001
	6/Cetirizine: 0.1 mg/mL	0.057±0.002	0.048±0.004
	7/Cetirizine: 1 mg/mL	0.066±0.007	0.109±0.005
Plasma hemolysis	1/Nonspiked Whole Blood	N for both	N for both
	2/Negative Control (0.9% NaCl)	N for both	N for both
	3/Positive Control (20% Saponin)	H^{+++} for both	H^{+++} for both
	5/Cetirizine: 0.01 mg/mL	N for both	N for both
	6/Cetirizine: 0.1 mg/mL	N for both	N for both
	7/Cetirizine: 1 mg/mL	N for both	H^{TR} for both
Hemolysis (%)	2/Negative Control (0.9% NaCl)	0.2±0.0	0.2±0.0
	3/Positive Control (20% Saponin)	98.1±0.5	97.9±1.6
	5/Cetirizine: 0.01 mg/mL	0.1±0.0	0.1±0.0
	6/Cetirizine: 0.1 mg/mL	0.3±0.1	0.3±0.1
	7/Cetirizine: 1 mg/mL	0.3±0.0	0.6±0.1
Visual plasma flocculation	1/Nonspiked Whole Blood	N for both	N for both
	2/Negative Control (0.9% NaCl)	N for both	N for both
	4/Positive Control (20% Intralipid®)	L^{+++} for both	L^{+++} for both
	5/Cetirizine: 0.01 mg/mL	N for both	N for both
	6/Cetirizine: 0.1 mg/mL	N for both	N for both
	7/Cetirizine: 1 mg/mL	N for both	N for both
Plasma turbidity index (660 nm/700 nm)	1/Nonspiked Whole Blood	11±8	7±0
	2/Negative Control (0.9% NaCl)	11±9	7±1
	4/Positive Control (20% Intralipid®)	79±56	89±10
	5/Cetirizine: 0.01 mg/mL	2±1	0±0
	6/Cetirizine: 0.1 mg/mL	1±1	1±1
	7/Cetirizine: 1 mg/mL	2±3	2±2

Abbreviations: Conc. = concentration; H+++ = severe (dark red corresponding to a hemoglobin concentration >0.5 g/dL and a hemolytic index >500); H^{TR} = trace of hemolysis; L+++ = severe flocculation (lactescent); N = no hemolysis observed (corresponding to hemoglobin <0.2 g/dL and a hemolytic index <200); NaCl = sodium chloride; SD = standard deviation

5.8. Exposure Margins

The maximum recommended human dose of IV cetirizine is 10 mg/day. A four-period, four-sequence crossover study in 24 healthy volunteers compared the PK of cetirizine 10 mg and 5 mg by IV injection over a period of 1 to 1.5 minutes and 10 mg by intramuscular injection to cetirizine 10 mg oral tablet. From this study, the $AUC_{0\text{-}inf}$ was 2746 ng*hr/mL for the cetirizine 10 mg IV injection. The mean C_{max} for the 10 mg IV cetirizine was 1344 ng/mL.

A GLP 14-day repeat-dose IV toxicity study in Sprague Dawley rats with cetirizine (Study No. 72658) was the pivotal toxicology to support marketing approval of IV cetirizine. The mean $AUC_{0\text{-}t}$ and mean C_{max} on Day 14 at the NOAEL (13 mg/kg/day high-dose) were 29.783 mcg*hr/mL (equivalent to 29783 ng*hr/mL) and 13.374 mcg/mL (equivalent to 13374 ng/mL), respectively.

The AUC and C_{max} at the rat NOAEL are about 11-fold and 10-fold higher, respectively, than the clinical AUC and C_{max} at the maximum recommended human dose. See Table 11.

Table 11. Animal to Human Exposure Margins for IV Cetirizine Based on AUC and C_{max} for the Proposed Clinical Dose

		TK/PK Parameters		Animal to Human Exposure Margins	
Parameter	**NOAEL (mg/kg/day)**	**AUC (ng*hr/mL)**	**C_{max} (ng/mL)**	**Based on AUC**	**Based on C_{max}**
14-day repeat-dose IV in rat (Study No. 72658)	13 mg/kg/day (high-dose)	29783[1]	13374[1]	-	-
Human	-	2746[2]	1344[2]	10.8x	9.95x

[1] Mean $AUC_{0\text{-}t}$ and mean C_{max} from the 14-day rat study are each combined for males and females.
[2] Mean clinical $AUC_{0\text{-}inf}$ and C_{max} at the maximum recommended human dose of 10 mg/day IV cetirizine are from a four-period, four-sequence crossover study in 24 healthy volunteers comparing the PK of cetirizine 10 mg and 5 mg by IV injection over a period of 1 to 1.5 minutes and 10 mg by intramuscular injection to cetirizine 10 mg oral tablet.
Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; IV = intravenous; NOAEL = no observed adverse effect level; PK = pharmacokinetic; TK = toxicokinetic

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant, JDP Therapeutics, Inc., has submitted NDA 211415 for cetirizine hydrochloride (HCl) 10 mg/mL solution for IV injection for the treatment of acute urticaria in adults and children 6 months of age and older. The proposed dosing regimen for IV cetirizine is once every 24 hours on an as-needed basis.

Cetirizine is a second-generation histamine-1 (H_1) receptor antagonist that selectively inhibits peripheral H_1-receptors. The clinical development program included a phase 1 relative bioavailability (BA) study in healthy adult subjects (Trial CTN-P0-741/ETTAU-01) and one pivotal efficacy and safety trial (ETTAU-03) in adult patients with acute urticaria.

6.2. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted under NDA 211415. This NDA is recommended for Approval from a clinical pharmacology perspective for the treatment of acute urticaria in adults and children 6 months of age and older.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The following are the major clinical pharmacology findings from the current review:

(1) Following single-dose administration in healthy adult subjects (18 years of age and older), the 90% confidence interval (CI) for the test/reference (T/R) geometric mean ratio (GMR) of 10 mg IV cetirizine (proposed product, T) and Zyrtec® 10-mg tablet (reference product, R) for systemic exposure (area under the curve (AUC)) was within the bioequivalence limits of 80 to 125%. Therefore, some relevant information for cetirizine, including pharmacokinetics (PK), drug interaction, and others, could rely on the approved U.S. labeling for Zyrtec® tablets (NDA 019835). However, peak concentration (geometric mean C_{max}) was 3.71-fold higher for the IV cetirizine drug product compared to Zyrtec® tablet (Study ETTAU-01). No serious adverse events or deaths were reported in this trial. The safety of the proposed product was also assessed in one pivotal trial (ETTAU-03) in adult subjects with acute urticaria (See Section 8 for details). Additionally, safety of higher than approved oral doses of cetirizine (i.e., up to 60 mg) have been assessed previously in adult subjects.

(2) The systemic exposure (AUC) of cetirizine in pediatric patients with acute urticaria 6 months to less than 17 years of age is expected to be comparable to that in patients 18 years and older with the proposed dosing regimen, so the efficacy of cetirizine in pediatric patients could be extrapolated from efficacy in patients 18 years of age and older.

(3) The proposed drug product is expected to result in higher peak concentration (C_{max}) of cetirizine following IV administration of the proposed product compared to the approved oral doses of cetirizine at the same nominal dose in children (6 months to 11 years of age)

and adolescents (≥12 to 17 years of age). Safety data are available to support approval of the proposed product in the pediatric population (refer to Section 9 and OSE review archived July 5, 2019 for further details).

(4) No dose adjustment for IV cetirizine is recommended in adults, adolescents, and children 6 to 11 years of age with renal and/or hepatic impairment. Due to absence of PK and safety information for IV cetirizine below 6 years of age and that the prescribing information for the listed drug (Zyrtec®) reports that oral cetirizine is not recommended in pediatric patients less than 6 years of age with impaired renal or hepatic function, the same recommendation will apply for IV cetirizine. A cautionary language to monitor for antihistaminic side effects will be proposed in the prescribing information.

(5) The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and analytical sites for the relative BA study (ETTAU-01), and they declined to inspect both sites based on past inspection history.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The following dosing regimen of IV cetirizine HCl is recommended for adults and children 6 months of age and older.

Table 12. Recommended Dosing Regimen of IV Cetirizine HCl

Age Group	Dosage Regimen
Adults and adolescents 12 years of age and older	10 mg
Children 6 to 11 years of age	5 mg or 10 mg, depending on symptom severity
Children 6 months to 5 years of age	2.5 mg

Cetirizine is to be administered intravenously once every 24 hours on an as-needed basis.

Therapeutic Individualization

No dose adjustment is recommended in adults, adolescents, and children 6 to 11 years of age with renal impairment and/or hepatic impairment. This patient population should be monitored for antihistaminic side effects of cetirizine. Refer to Section 6.3.2 for details.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Cetirizine, an antihistamine, is a H_1-receptor antagonist with its principal effects mediated via selective inhibition of peripheral H_1-receptors. Linear PK was observed for oral doses ranging from 5 mg to 60 mg. In a mass balance study in healthy subjects, 70% of the administered radioactivity was recovered in urine and 10% in feces. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The terminal half-life ($t_{1/2}$) of cetirizine in healthy subjects is 8.3 hours with an apparent total body clearance of approximately 53 mL/min.

The clinical development program included one phase 1 crossover relative BA study in healthy adult subjects (ETTAU-01) and one pivotal phase 3 efficacy study (ETTAU-03) in adult patients with acute urticaria. Refer to Section 8 for details on Study ETTAU-03. Study ETTAU-01 was a phase 1, randomized, single-dose, laboratory-blinded, four-period, four-sequence, crossover study in healthy adult male and female subjects to assess the relative BA of i) cetirizine 10 mg IV relative to Zyrtec® 10-mg tablets (fasting condition), ii) cetirizine 10 mg intramuscular (IM) relative to Zyrtec® 10-mg tablets (fasting condition), and iii) cetirizine 10 mg IM relative to cetirizine 10 mg IV (fasting condition), and to assess dose proportionality between cetirizine 5 mg and 10 mg IV (fasting condition). Given that the Applicant is seeking approval of IV cetirizine, the study results pertaining to IV cetirizine and Zyrtec® tablet (listed drug) are discussed in this review.

Study ETTAU-01 evaluated the relative BA of IV cetirizine to Zyrtec® tablet following a 10 mg single-dose in healthy adult subjects. The 90% CI for the T/R GMR for AUC was within 80 to 125%, however a 3.71-fold higher geometric mean C_{max} was observed for IV cetirizine compared to Zyrtec® tablets. The Applicant conducted a pivotal phase 3 study to support the efficacy and safety of the proposed drug product in adult patients with acute urticaria. Additionally, based on the prescribing information of the listed drug, Zyrtec® tablet (NDA 019835), doses up to 60 mg per day for a 1-week dosing duration have been studied previously in adult subjects in a thorough QT (TQT) study. Given the linear PK for orally administered cetirizine (for oral doses 5 mg to 60 mg), the 60 mg Zyrtec® oral dose in the TQT study would result in peak concentrations (C_{max}) that are higher compared to that observed following IV cetirizine HCl 10 mg.

The proposed doses for IV cetirizine in children (6 months to 11 years of age) and adolescents (≥12 to 17 years of age) are the same as the approved doses for Zyrtec® in the respective age groups. In-line with the observed comparable cetirizine exposure at the recommended doses across different age groups with Zyrtec® (prescribing information), the systemic exposure (AUC) of cetirizine in pediatric patients is expected to be comparable to that in patients 18 years and older with the proposed dosing regimen. Thus, the efficacy of cetirizine in pediatric patients could be extrapolated from efficacy in patients 18 years of age and older based on comparable cetirizine exposure. Given the different routes of administration, the peak concentration of cetirizine is expected to be higher for IV cetirizine relative to Zyrtec®. The Applicant assumes that the fold-increase in C_{max} relative to Zyrtec® in children (6 months to 11 years of age) will the same as that in adults; no observed PK data are available to support this assumption. Safety data are available to support the expected higher C_{max} in the proposed pediatric population (refer to Section 8 and OSE review archived July 5, 2019 for further details).

The PK of IV cetirizine is expected to be similar between adolescents (≥12 to 17 years of age) and adults; this is further supported by the same dose approved for Zyrtec® tablets in the adolescent and adult population. Safety data are available to support the higher geometric mean C_{max} (3.71-fold increase compared to Zyrtec® tablets) expected in adolescents (refer to Section 8 and OSE review archived July 5, 2019 for further details).

No renal and/or hepatic impairment studies were conducted in the IV cetirizine development program. Cetirizine is primarily cleared via the renal route and metabolized to a limited extent by oxidative O-dealkylation (Zyrtec® package insert). For treatment of acute urticaria, IV cetirizine is intended to be administered as a single dose, and a second dose can be administered at 24 hours post first-dose on an as-needed basis (given the short elimination $t_{1/2}$ of IV cetirizine, little to no accumulation is expected at 24 hours postdose). Per the guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* (March 2010) and *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003), a renal/hepatic impairment study is not required for drugs intended for single-dose administration, as is generally the case for the proposed drug product. Therefore, no dose adjustment for IV cetirizine is recommended in adults, adolescents, and children 6 to 11 years of age with renal and/or hepatic impairment. A cautionary language to monitor for antihistaminic side effects will be proposed in the prescribing information.

6.3.2. Clinical Pharmacology Questions

Describe the relevant regulatory history for the review of this 505 (b)(2) NDA

The regulatory interactions with the Agency during the clinical development program for IV cetirizine are listed in Section 3 of the review. Key regulatory interactions with the Agency relevant to clinical pharmacology are outlined below:

- End-of-phase 2 meeting (EOP2, IND 107689, dated March 18, 2015): At the EOP2 meeting it was agreed that a TQT study was not needed and that the primary endpoint in Study ETTAU-03 will be patient rated pruritis score change at 2 hours and physician score will be a secondary endpoint.
- Agreed initial pediatric study plan (iPSP, IND 107689, dated November 18, 2015): The agreed iPSP reports that the approval of IV cetirizine in children (6 months to 11 years of age) and adolescents (≥12 to 17 years of age) will be based on IV cetirizine data in adults and previous findings of safety and efficacy of cetirizine oral products in children aged 6 months and above, and that pediatric PK studies (to support safety and dose) and pediatric efficacy studies are not planned to be conducted.

  The justification for not conducting a pediatric PK study are:

  – There is sufficient knowledge of efficacious dose based on the Zyrtec® program which can be extrapolated to IV cetirizine given the comparable systemic exposure (AUC) between IV cetirizine and Zyrtec® tablets observed in adult subjects.
  – There is sufficient pediatric PK data for Zyrtec®.
  – The known adult PK relationship between IV cetirizine and Zyrtec® tablets can be extrapolated to the pediatric population.
  – The observed safety of IV cetirizine and the potential lack of impact of higher C_{max} on the safety profile of cetirizine in adults and pediatrics.

What are the clinical studies submitted under this NDA?

The clinical studies conducted in the IV cetirizine development program are presented in Table 13. Studies ETTAU-01 and ETTAU-03 are reviewed under the current NDA.

Table 13. Overview of Clinical Studies in the IV Cetirizine Clinical Development Program

Study	Design/Objectives	Patient Population	Dosing Regimen
ETTAU-01 (CTN-P0-741) pivotal phase 1	Randomized, single-center, laboratory-blinded, four-period, four-sequence, crossover study under fasting state Objectives: To assess the PK, safety, tolerability of cetirizine 5 mg and 10 mg IV and cetirizine 10 mg IM in comparison to Zyrtec® 10-mg tablet	Healthy male and female subjects (n=24, enrolled); at least 18 years of age	Cetirizine 10 mg/mL injection, 5 mg IV single-dose Cetirizine HCl 10 mg/mL injection, 10 mg IV single-dose Cetirizine HCl 10 mg/mL injection, 10 mg IM single-dose Zyrtec® (cetirizine) tablet, 10 mg single-dose
CTN-P1-571 (ETTAU-01P) Pilot phase 1	Single-center, 2-way crossover study Objectives: To assess safety, tolerability, and PK	Healthy subjects (n=4)	Cetirizine HCl 10 mg/mL injection, 10 mg IM, short needle Cetirizine HCl 10 mg/mL injection, 10 mg IM, long needle
ETTAU-03 pivotal phase 3	Randomized, multicenter, parallel-group, double-blind, active-controlled study Primary Objective: Established noninferiority of cetirizine injection with diphenhydramine injection in reducing patient-reported pruritus severity score at 2 hours after treatment of acute urticaria	Male and female patients with a diagnosis of acute urticaria (n=262, enrolled); 18 years of age or older	Cetirizine HCl 10 mg/mL injection, 10 mg IV single-dose Diphenhydramine 50 mg/mL injection (Benadryl® or generic equivalent), 50 mg IV single-dose
CTN-P4-427 (ETTAU-02) pilot phase 3	Randomized, multicenter, parallel-group, double-blind study Primary Endpoints: Extent of urticaria/erythema score (physician assessment), physician pruritus severity score, patient pruritus severity score	Male and female patients with a diagnosis of acute urticaria (n=33, enrolled); 18 years of age or older	Cetirizine HCl 10 mg/mL injection, 10 mg IV single-dose Diphenhydramine 50 mg/mL injection (Benadryl® or generic equivalent), 50 mg IV single-dose

Source: Information collated from Module 5.2 Tabular Listing of All Clinical Studies on Cetirizine Injection and Clinical Study Reports for Study CTN-P0-741, Study ETTAU-03, and Study ETTAU-02
Abbreviations: IM = intramuscular; IV = intravenous; PK = pharmacokinetic

Was the to-be-marketed cetirizine IV injection used in Studies ETTAU-01 and ETTAU-03?

The to-be-marketed drug product of cetirizine HCl injection 10 mg/mL was used in the relative BA study (ETTAU-01) and the pivotal phase 3 study (ETTAU-03). Cetirizine HCl injection 10 mg/mL is a sterile, clear, colorless, nonpyrogenic, preservative-free isotonic solution. The drug

product solution is presented in a 2 mL size amber glass vial for single-use. The composition of cetirizine HCl injection 10 mg/mL is presented in Table 14.

Table 14. Composition of Cetirizine HCl Injection 10 mg/mL

(b) (4) Drug Code	Ingredient	Quantity per mL	Function	Quality Standard
(b) (4)	Cetirizine HCl, USP	10.00 mg	API	USP
	Sodium Chloride, USP	6.50 mg	To adjust tonicity (b) (4)	USP
	Sodium Hydroxide, NF, (b) (4)	q.s.	To adjust pH	NF
	Acid, Hydrochloric, NF	q.s.	To adjust pH	NF
	Water for Injection, USP	(b) (4)		USP

Source: Module 2.3.P Quality Overall Summary Drug Product
Abbreviations: API = active pharmaceutical ingredient; NF = National Formulary; USP = United States Pharmacopeia; q.s. = *quantum satis*, the amount which is enough

What are the findings from OSIS inspection?

OSIS inspection was requested for the clinical and analytical sites for the relative BA study (ETTAU-01). OSIS declined to conduct on-site inspection for both sites since the clinical and analytical sites were inspected in (b) (4) which falls within the surveillance interval (refer to OSIS review archived February 21, 2019).

Is the proposed dosing regimen appropriate for the patient population for which the indication is being sought?

The proposed IV dosing regimen of 10 mg once every 24 hours on an as-needed basis in adults (18 years of age and older) for the treatment of acute urticaria is reasonable from a clinical pharmacology perspective. The clinical development program did not include any dose-ranging studies, and the efficacy and safety of the proposed drug product is supported by a single pivotal phase 3 study (ETTAU-03). As noted previously, the geometric mean C_{max} of the proposed cetirizine HCl IV dose (10 mg) is 3.71-fold higher compared to the approved adult dose of the listed drug (Zyrtec® tablet; 10 mg cetirizine HCl). Based on the prescribing information of the listed drug, doses of up to 60 mg per day for 1 week have been studied previously in adult subjects. Briefly, healthy adult subjects were administered Zyrtec® doses of up to 60 mg per day for 1-week duration in a TQT study. The administered dose is 6 times the maximum approved dose for Zyrtec® in adults (10 mg per day). Linear PK for cetirizine is observed for oral doses ranging from 5 mg to 60 mg. The Zyrtec® 60-mg dose in the TQT study would result in a higher C_{max} than that observed following administration of IV cetirizine HCl 10 mg.

For children (6 months to 11 years of age) and adolescents (≥12 to 17 years of age), the proposed IV cetirizine dosing regimens are acceptable and safety data are available to support the expected higher peak concentrations following IV cetirizine in this population.

Per the Agreed iPSP, the approval of IV cetirizine in children 6 months to 17 years of age will be based on efficacy extrapolation and safety/PK extrapolation from the Applicant's adult studies for IV cetirizine and Zyrtec® adult/pediatric data. The phase 1 relative BA study (ETTAU-01) in healthy adult subjects showed that the systemic exposure (AUC) was comparable following single dose administration of 10 mg IV cetirizine HCl and Zyrtec® 10-mg tablet; however, the peak concentration (geometric mean C_{max}) was 3.71-fold higher for IV route compared to the oral route of administration. The proposed doses of IV cetirizine in the pediatric population (6 months to 17 years) are the same as the approved doses for Zyrtec® in the respective age groups. Zyrtec® is available as tablet and syrup dosage forms; refer to Table 15 for the dosage forms available for different age groups. Per the Zyrtec® package insert, comparable BA was observed for the tablet and syrup dosage forms. For Zyrtec®, the cetirizine systemic exposure in the pediatric population at the approved doses is comparable to the exposure at the approved dose in adults. Therefore, the systemic exposure (AUC) of IV cetirizine in pediatric patients is also expected to be comparable to that in patients 18 years and older with the proposed dosing regimen.

Table 15. Age Groups and Available Zyrtec® Dosage Forms

Age Group	Zyrtec® Dosage Forms
Adults and adolescents 12 years of age and older	Tablet, Syrup
Children 6 to 11 years of age	Tablet, Syrup
Children 2 to 5 years of age	Syrup
Children 6 months to less than 2 years of age	Syrup

Adults 18 Years of Age and Older

For Study ETTAU-01, the relative BA in the fasted state between IV cetirizine HCl and Zyrtec® tablet following a 10 mg single-dose in healthy adult subjects is presented in Table 16. The 90% CI for the T/R GMR for AUC was within the bioequivalence limits of 80 to 125%. The geometric mean C_{max} was 3.71-fold higher for IV cetirizine compared to Zyrtec® tablet at the same dose. This observed difference in PK parameter between the proposed drug product and Zyrtec® tablet can be attributed to the different routes of administration of cetirizine, i.e., IV versus oral. These relative BA results were confirmed by in-house analysis conducted by the Reviewer.

Table 16. Comparison of Geometric Mean Pharmacokinetic Parameters: IV Cetirizine HCl 10 mg (Treatment-D) vs. Zyrtec® 10-mg tablet (Treatment-A) (Study ETTAU-01, n=24)

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TREATMENT-D (TEST)	TREATMENT-A (REFERENCE)		LOWER	UPPER
C_{max}	29.2	1162.16	312.63	371.73	323.87	426.67
AUC_{0-t}	10.9	2590.61	2516.03	102.96	97.71	108.50
AUC_{inf}	10.9	2693.51	2617.06	102.92	97.68	108.44

* units are ng/mL for C_{max} and ng·H/mL for AUC_{inf}
Last blood draw: 36hr, $AUC_{0-t} = AUC_{0-36hr}$
Source: Results based on an ANOVA model with treatment, period, sequence as fixed effects and subject effect (nested within sequence) as a random effect.
Source: January 16, 2019 ORIG-1/Clinical Pharmacology/Response to Information Request - Module 5.3.1.2 Study CTN-P0-741, PK Summary Revised per FDA IR dated January 11, 2019; Module 5.3.1.2 Clinical Study Report No. CTN-P0-741
Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum concentration

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No dosage adjustment for IV cetirizine is recommended in adults, adolescents, and children 6 to 11 years of age with renal and/or hepatic impairment. These patients should be monitored for antihistaminic side effects. The prescribing information for the listed drug (Zyrtec®) reports that oral cetirizine is not recommended in pediatric patients less than 6 years of age with impaired renal or hepatic function. The same recommendation will apply for IV cetirizine.

Cetirizine is primarily cleared via the renal route and is metabolized to a limited extent by oxidative O-dealkylation (Zyrtec® package insert). The prescribing information of the listed drug (Zyrtec®) reports on the impact of renal and hepatic impairment on the PK of oral cetirizine, and based on these results, a dose reduction of oral cetirizine is recommended in adults, adolescents , and children 6 to 11 years of age with renal and hepatic impairment for the indication of chronic urticaria. (b) (4) unlike Zyrtec®, IV cetirizine is proposed to be used in an acute setting (i.e., treatment of acute urticaria). Based on the reasons outlined in the subsequent paragraphs, a dose reduction of IV cetirizine in adults, adolescents, and children 6 to 11 years of age with renal and hepatic impairment is not recommended.

No renal and/or hepatic impairment studies were conducted in the IV cetirizine development program. The *Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling* (March 2010) and *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003) guidances indicate that renal and hepatic impairment is not likely to alter PK enough to justify dosage adjustment for drugs intended for single-dose administration, and therefore omits the need for a dedicated renal/hepatic impairment study in this scenario. IV cetirizine is intended to be administered as a single-dose for the treatment of acute urticaria, and if needed for further symptomatic relief, another dose can be given in 24 hours. Given the

elimination $t_{1/2}$ of IV cetirizine is 7.7 hours, little to no accumulation of the drug is expected at 24 hours postdose.

Additionally, it should be noted that the clinical development program for this NDA did not include any dose-ranging studies, and a single IV dose of 10 mg cetirizine HCl was evaluated in the pivotal phase 3 study (ETTAU-03). In the phase 3 study (ETTAU-03) for IV cetirizine in patients with acute urticaria, the primary efficacy endpoint was the 2-hour patient-rated pruritus severity score reduction/change from baseline. Since the primary efficacy endpoint was measured at 2 hours postdose in the phase 3 study, the impact of C_{max} of cetirizine on the primary efficacy endpoint cannot be ruled out. Given that the impact of reducing the IV dose on the efficacy of cetirizine for treatment of acute urticaria in adults, adolescents, and children 6 to 11 years of age is not known, no dose adjustment for IV cetirizine is recommend in patients with renal and/or hepatic impairment.

Is the bioanalytical method properly validated to measure cetirizine concentration in plasma samples?

The bioanalytical method used for quantification of cetirizine in human plasma was a reversed-phase high performance liquid chromatography with triple quadrupole mass spectrometry detection. Method validation (validation report number: CTN-V4-056 (Revision 5 (R5))) and sample analysis supporting the relative BA clinical study (analytical report number CTN-P0-741) were in-line with the Agency's recommendations outlined in the guidance for industry *Bioanalytical Method Validation* (May 2018), and all acceptance criteria as specified in the guidance were met. The validation summary of the bioanalytical method used to measure cetirizine in human plasma is presented in Table 17.

Table 17. Validation Summary of Bioanalytical Method

Validation Report	**Validation of a HPLC Method Using MS/MS Detection for the Determination of Cetirizine in Human Plasma CTN-V4-056 (R5)**
Matrix (anticoagulant)	Human plasma (K_2EDTA)
Injection volume	15 µL
Analytical method/detection	Liquid-liquid extraction; Reversed-phase HPLC with MS/MS detection
Internal standard	(b) (4)
Validated range	2 ng/mL to 500 ng/mL
Calibration model	Linear regression
Weighting factor	$1/x^2$
Quantitation method	Peak area ratio
Sensitivity	2 ng/mL (lower limit of quantitation)
Interassay accuracy (%Bias)	101% to 106%
Interassay precision (%CV)	≤9.2%
Dilution linearity	10,000 ng/mL diluted 50-fold
Selectivity	No significant matrix effect was observed
Effect of hemolyzed and lipemic plasma	No significant interference from hemolyzed or lipemic plasma
Concomitant drug interference	No interference was observed with the tested concomitant drugs
Extraction efficiency	64% to 66%

Validation Report	Validation of a HPLC Method Using MS/MS Detection for the Determination of Cetirizine in Human Plasma CTN-V4-056 (R5)
Freeze-thaw matrix stability	4 cycles at -20°C
Frozen matrix stability	283 days at -20°C
Ambient matrix stability	26.5 hours at 22°C
Studies	ETTAU-01

Source: May 1, 2019 ORIG-1/Multiple Categories/Subcategories Module 1.11.3 Response to IR dated April 24, 2019 – Clinical Pharmacology and Module 5.3.1.4 CTN-P0-741: Appendix 1 – Validation Report CTN-V4-056 (R5)
Abbreviations: CV = coefficient of variation; HPLC = high performance liquid chromatography; MS/MS = tandem mass spectrometry

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 18. Table of Clinical Studies

Trial Name Dates	Trial Design/Duration	Regimen/ Schedule/ Route	#	Population	Primary Endpoints	No. of Centers/Countries
ETTAU-01 (CTN-PO-741) 4/12/2011- 5/25/2011	SC, R, laboratory-blinded, four-period, four-sequence, crossover design 24 days	10 mg tablet 10 mg IM 5 mg IV 10 mg IV	6 6 6 6	Adult healthy volunteers	- Safety, tolerability, and PK	1 site - Canada
ETTAU-02 (CTN-P4-427) 3/27/2013- 12/12/2014	MC, P, R, DB pilot study SD with follow-up at 24 hours	SD cetirizine 10 mg IV SD diphenhydramine 50 mg IV	16 17	Patients 18 years of age and older with acute urticaria	- Extent of urticaria/ erythema score (physician assessment) - Physician pruritus severity score - Patient pruritus severity score	1 site - Canada
ETTAU-03 3/2/2017- 4/14/2018	MC, P, R, DB, NI for primary endpoint, superiority for secondary endpoints pivotal phase 3 SD with follow-up at 24 and 48 hours	SD cetirizine 10 mg IV SD diphenhydramine 50 mg IV	127 135	Patients 18 years of age and older with acute urticaria	- Patient-reported pruritus severity score at 2 hours after treatment of acute urticaria.	19 sites – United States (17), Canada (2)

Abbreviations: SC = single center; R = randomized; SD = single dose; MC = multicenter; P = parallel; NI = noninferiority; DB = double-blinded; IM = intramuscular; IV = intravenous; PK = pharmacokinetics

Source: Information collated from Module 5.2 Tabular Listing of All Clinical Studies on Cetirizine Injection and Clinical Study Reports for Study CTN-P0-741, Study ETTAU-02, and Study ETTAU-03

7.2. Review Strategy

The clinical review was conducted by one primary clinical reviewer and one statistical reviewer. The Applicant submitted data from three studies (ETTAU-01, ETTAU-02, and ETTAU-03). ETTAU-01 is a single center, randomized, four-period, four-sequence, crossover design to assess safety, tolerability, and PK in 24 healthy adult volunteers. Study ETTAU-02 is a double-blind, randomized, pilot study in 33 adults with acute urticaria comparing IV cetirizine to IV diphenhydramine to inform the noninferiority margin to be used in the subsequent study, ETTAU-03. Study ETTAU-03 is a parallel, noninferiority efficacy study comparing IV cetirizine to IV diphenhydramine in 262 adults with acute urticaria. The efficacy review focuses on Trial ETTAU-03 as this trial was powered to assess the non-inferiority of IV cetirizine compared to IV diphenhydramine.

Data sources in this electronic submission included protocols, clinical study reports, narratives, and SAS transport datasets in legacy format.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy: ETTAU-03

8.1.1. Trial Design

Trial Design

Trial ETTAU-03, conducted between March 2, 2017, and April 14, 2018, was a multicenter, parallel group, randomized, double-blind, active-controlled, phase 3 study in adults with acute urticaria designed to evaluate noninferiority comparing cetirizine injection 10 mg to diphenhydramine injection (Benadryl or generic equivalent), 50 mg, for the treatment of acute urticaria.

Subjects were recruited from emergency departments, hospitals, allergy clinics or urgent care centers with acute urticaria, or developed acute urticaria following allergen challenge at an allergy clinic. Subjects were randomized 1:1 to receive a single dose of 10 mg IV cetirizine or 50 mg of IV diphenhydramine. Safety was monitored through the reporting of adverse events for up to 28 days following treatment and by monitoring vital signs at planned intervals from admission into the treating facility until readiness for discharge. Subjects were contacted by phone 24 and 48 hours post discharge 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 19.

Table 19. ETTAU-03 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

Abbreviations: Q&A = question and answer.

[1] Assessed only by the doctor.
[2] Assessed by the doctor and the subject.
Source: Excerpted from the Statistical Analysis Plan for Study ETTAU-03 (page 9)

8.1.2. Study Population

Key Inclusion Criteria

- Adult male and female subjects aged 18 years or older
- Diagnosis of acute urticaria who needed treatment with an antihistamine to alleviate their symptoms
- Patient-rate pruritus severity score ≥1

Key exclusion criteria:

- Receipt of an investigational drug or device within the past 30 days.
- Subjects with conditions where antihistamine use is contraindicated (e.g., narrow angle glaucoma, symptomatic prostatic hypertrophy).
- Subjects who received any antihistamine (H1 antagonist) within the past 2 hours, regardless of route of administration, an H2 antagonist within the past 2 hours, doxepin within 2 hours, Epinephrine within the past 20 minutes, or steroids (oral, IV, IM, or inhalational routes) within the past 4 hours.
- Anaphylaxis (if subjects presented with acute urticaria combined with anaphylaxis, after anaphylaxis symptoms resolved, these subjects could be included in the study as long as urticaria was still present).
- Known allergy to hydroxyzine, cetirizine, levocetirizine, or diphenhydramine
- Subjects on concomitant p-glycoprotein inhibitors
- Subjects who had an acute allergic reaction to a medication that they were taking (e.g. antibiotics, NSAIDs, etc.) and who could not stop the medication.
- Subjects who based on their medical history or in the opinion of the Investigator, had chronic urticaria, hereditary angioedema, urticaria refractory to antihistamines, or a dermatological disease that interfered with the evaluation of a therapeutic response.

The following medications were prohibited: any antihistamine (H1 or H2 antagonist) or doxepin given 2 hours prior to enrollment, epinephrine administered 20 minutes prior to enrollment, steroids (oral, IV, IM, or inhalational routes) within the past 4 hours, and p-glycoprotein inhibitors.

8.1.3. Analysis Populations

- Intent-to-treat population (ITT): Included 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 noninferiority analyses were performed on the ITT population with subjects grouped by the treatment they were randomized to receive.
- Safety population: Included any subjects in the ITT population who actually received a blinded study drug, regardless of whether or not they completed all assessments, withdrew, or were discontinued by the Investigator. All safety summaries were performed on the safety population with subjects grouped by the treatment they actually received.
- Per protocol (PP) population: Included subjects in the safety population who completed all necessary assessments without any incidence that would potentially affect the ability to objectively assess treatment response (e.g., discontinuation, protocol deviation, etc.).

8.1.4. Primary Endpoint

The primary objective of this study was to establish the noninferiority of cetirizine injection with respect to diphenhydramine injection in reducing patient-reported pruritus severity score at 2 hours after treatment of acute urticaria.

The primary clinical efficacy outcome measure was the 2-hour patient-rated pruritus severity score reduction/change from baseline, compared between the two treatment groups (cetirizine injection, 10 mg, and diphenhydramine injection, 50 mg). The patient-rated pruritus severity score scales from 0 (none) to 3 (severe). Patients were asked "How severely are your hives itching at the moment?" and scored as follows:

0 = none

1 = mild (minimal awareness, easily tolerated)

2 = moderate (definite awareness, quite bothersome)

3 = severe (difficult to tolerate).

Subjects remained in the treatment center at least until the 1-hour assessment, after which they could be discharged at the physician's discretion provided that the following criteria were met:

1. Symptoms of the acute allergic reaction were treated based on Investigator/designee's opinion
    a. Patients were assessed by their treating physician as being "effectively treated," based on their improvement in urticaria and pruritus symptoms and rescue medication use. Administration of rescue medications was investigator determined. Physicians recorded the % of body area with urticaria (0 = none, 1 = mild (< 25% body coverage), 2 = moderate (25-50% body coverage), 3 = severe/intense (> 50% body coverage) and intensity of redness (0 = none, 1 = mild (light pink), 2 = moderate (pink), 3 (severe/intense (red)). Patients were required to have a score of 0 for % of body area with urticaria if discharged 1 hour or 2 hours post treatment.
2. Subject was alert enough (sedation score = 0) to understand discharge instructions.
    a. Patients were asked "How drowsy do you feel at the moment?" and asked to rate their sedation as follows: 0 = none (not drowsy at all), 1 = mild (slightly drowsy), 2 = moderate (quite drowsy), and 3 = severe (extremely drowsy).
3. Based on the Investigator's judgement, the subject was fit to be discharged.

8.1.5. Secondary Efficacy Endpoints

The following key secondary efficacy endpoints were intended to support the primary analysis findings and were assessed for each subject:

(1) Return to treatment center: The number and proportion of subjects who returned to a treatment center for additional treatment of their urticaria was summarized by response (YES, NO, UNKNOWN) for each follow-up time and by treatment group

(2) Time spent at treatment center: The average time spent (time in hour from treatment administration to "readiness for discharge") in a treatment center (for the initial treatment)

The following other secondary clinical or efficacy measures were assessed for each subject:

(1) Pruritus treatment success (percent of subjects), defined as a patient who had a pruritus severity score reduction of at least 1 unit for the 2-hour patient-rated pruritus severity score from baseline (D2) compared between the two treatment groups

(2) Patient-rated pruritus severity score reduction/change from baseline at 1 hour and at "time of discharge" (D1 and D3)

(3) Sedation scores, at baseline, 1 hour, and/or 2 hours, and/or "readiness for discharge"

(4) Physician-rated extent of urticaria/erythema scores and their reduction/change from baseline at 1 hour, 2 hours, and "time of discharge"

(5) Use of rescue medication (e.g., epinephrine, bronchodilators, steroids, etc.) and the reasons for the use of rescue drugs

(6) 'Effectively treated' based on investigator's opinion of Yes or No

(7) Symptom recurrence and additional symptom occurrence within approximately 24 to 48 hours after subject discharge from treatment center

(8) The need for prescribed medication within approximately 24 to 48 hours after discharge

(9) The need for additional medication, including any over-the-counter medications, within approximately 24 to 48 hours after discharge

(10) Ability to return to normal activity after discharge

8.1.6. Statistical Analysis Plan

Determination of Sample Size

Assuming the diphenhydramine-treated group respond similarly to ETTAU-02 results, the common standard deviation was expected to be around 1.22. A sample size of 127 subjects per arm (total 254) would be needed to provide 90% statistical power to determine that cetirizine injection will be noninferior to diphenhydramine injection. The sample size was calculated based on the assumption of -0.5 as the noninferiority limit of the difference, using one-sided test at alpha =0.025 with an expected common SD =1.22. Sample size estimation was performed using NQUERY Advisor (v7, Statistical Solutions, Ltd) method for two-group t-test of equivalence in means.

Primary Efficacy Analysis Model

The purpose of this study was to determine if the effectiveness of cetirizine injection, 10 mg/mL, was noninferior to the effectiveness of diphenhydramine injection, 50 mg/mL for the mean change from baseline of the 2-hour patient-rated pruritus score.

In calculating the noninferiority (NI) margin, the effect of diphenhydramine injection based on patient-recorded pruritus score in comparison to placebo is unknown. The Agency proposed an NI margin of -0.5, and the Applicant accepted the margin, evaluating the diphenhydramine effect in Study ETTAU-02, assuming that if subjects with urticaria left untreated, there would be no spontaneous resolution within 2 hours of emergency department/clinic admission. The mean change in the pruritus score at 2 hours from baseline in Study ETTAU-02 was -1.65 (SD =1.22) for the diphenhydramine-treated group with a 95% CI of -2.11, -1.18. The NI margin of -0.5 would preserve 60% clinical fraction of the diphenhydramine response from the upper bound -1.18 of the 95% CI.

The null hypothesis was that cetirizine injection was inferior to diphenhydramine injection if the difference was less than or equal to -0.5 at a two-sided 5% Type I error rate. The null hypothesis was stated as:

H_0: $D2_{diph} - D2_{cet} \leq -0.5$,
where D2 was the change from baseline of the 2-hour patient-rated severity of pruritus for each treatment.

The alternative hypothesis to be tested was:

H_1: $D2_{diph} - D2_{cet} > -0.5$.

The Applicant planned to calculate the point estimate of the treatment difference and its 95% CI using a generalized linear mixed-effects model to adjust for any heterogeneity of treatment variance or imbalance in number of subjects in each treatment, and to adequately model the resulting ordinal outcome of D2. The model was also to be adjusted for site and site by treatment interaction and any baseline characteristics, such as age or gender, deemed likely to influence model variance.

If the null hypothesis was rejected in favor of the alternative, and the treatment difference was greater than zero, then the alternative hypothesis was to be further refined in a stepwise manner (i.e., only after rejecting the null hypothesis for noninferiority) to test for superiority of cetirizine injection over diphenhydramine injection as:

H_2: $D2_{diph} - D2_{cet} > 0$.

Secondary Efficacy Analysis Model

The number and proportion of subjects who returned to a treatment center for additional treatment of their urticaria were summarized by response (YES, NO, UNKNOWN) for each follow-up time and by treatment group. The difference in treatments was tested using Fisher's two-sided exact test.

The average time spent in the treatment center was tested for treatment differences using the same model as proposed for the primary endpoint.

Multiplicity

There were two outcome measures that were key in supporting the efficacy claim, the need to return to a treatment center after study discharge and time spent at the treatment center (time from treatment administration to "readiness of discharge"). The Applicant planned to use Holm-Bonferroni method of rejecting individual hypotheses to control family-wise error rate.

Missing Data Handling

The primary analysis was performed on the ITT population with last observation carried forward (LOCF) used to impute 2-hour scores if subjects were discharged prior to the 2-hour assessment.

If the investigator determined that the subject was physically and mentally fit to be discharged from the center, the discharge could have occurred any time after the 1-hour assessment if the symptom score had reached zero at 1 hour postinjection. Therefore, assessments of pruritus, extent of urticaria, and sedation for subjects discharged prior to the 2-hour assessment were to be carried forward from the last recorded score to 2 hours and beyond.

In addition, subjects may have received rescue medication at any time after study drug administration and prior to "readiness for discharge" if the attending physician deemed it necessary. In the event that a rescue medication was used prior to the 1-hour assessment, patient-rated pruritus severity score reduction/change from baseline at 1 hour was set to zero for that subject. Otherwise, if rescue drug was given, then the last observation prior to rescue was carried forward to all subsequent assessments, including the 2-hour and "readiness for discharge" assessment.

Subgroup Analysis

No subgroup analyses were planned.

All statistical analyses and summaries were performed using SAS for UNIX, Version 9.4 or later (SAS Institute, Cary, NC). All continuous variables, except where specified, were summarized with descriptive statistics (the number of subjects assessed [N], the number of nonmissing values/valid cases [n], mean, standard deviation [SD], median, minimum, and maximum), and all categorical variables were to be summarized with frequency counts and percentages, by treatment group. The denominator for each percentage includes the number of subjects within the population of the treatment arm (unless specified). The assumed overall type I error rate/significance level for the primary efficacy outcome was 5%, two-sided, unless otherwise specified. Two-sided confidence limits were to be evaluated at 95%; p-values from the inferential tests comparing specific cohorts or subgroups were compared to 0.05.

Protocol Amendments

The phase 3 clinical study protocol was revised on May 1, 2015, in order to incorporate the Agency's comments from the EOP2 meeting on March 18, 2015. The primary endpoint of the two treatment group comparison of composite score reduction of acute urticaria symptoms at various time points compared to baseline was changed to patient rated pruritus severity score 2 hours postdose. Additionally, the agency advised that secondary endpoints should include: extent of urticaria/erythema, time to discharge, patient-based sedation score, and rescue medications used. A protocol amendment was later finalized on October 5, 2016. The following changes were incorporated:

- The statistical section was revised to match the statistical analysis plan, since the statistical analysis plan proposed LOCF of the last prerescue scores and of the predischarge scores (if discharged at less than 2 hours) for subjects' 2-hour score.
- The protocol was revised to add the option of early discharge (between 1 hour and 2 hours)
- The 24-hour follow-up is revised to state, "site staff will telephone them at approximately the same time or the next convenient time (e.g., if a patient is discharged at 3 am, the site staff will telephone the patient at 8 a.m.) the following day."

Additionally, an updated phase 3 clinical protocol #ETTAU-03, version January 9, 2017, incorporated the following changes: "the need to return to treatment center after study discharge (i.e., second visit within 24 hours after discharge)" was moved to key secondary endpoints and "sedation score" was moved to other endpoints. The rationale for this change is that the shorter time to discharge seen in the pilot study was attributed to cetirizine's less sedating feature compared to diphenhydramine, and therefore, there is no need to analyze sedation again under key secondary endpoints. Instead, the Applicant proposed to evaluate the frequency of return after discharge in the key secondary endpoints section. The revised version now includes the need to return to the treatment center after study discharge as well as time to discharge.

8.1.7. Study Results

Compliance With Good Clinical Practices

The Applicant states that this trial was conducted in accordance with generally accepted standards of good clinical practice as well as all applicable federal, state and local laws, rules and regulations.

Financial Disclosure

The Applicant adequately disclosed financial interests and arrangements with clinical investigators. There were no investigators with disclosable financial interest that may have impacted the conduct of the trials submitted. Financial disclosure details are shown in Section 15.2.

8.1.7.1. Disposition

Table 20 details the total number of all randomized subjects and Table 21 details the disposition of all randomized subjects. Overall, the completion rate was similar across the two groups with 98% completion rate in the diphenhydramine group and 97% completion rate in the cetirizine group (Table 21). There were three patients in each study arm who discontinued study treatment prematurely and were lost to follow-up (Table 21). There was one additional patient from the cetirizine injection group who discontinued study treatment prematurely; however, the reason is listed as "other" (Table 21).

Table 20. ETTAU-03 Data Sets Analyzed (All Randomized Subjects)

	Diphenhydramine Injection N=135 (%)	Cetirizine Injection N=127 (%)	Overall N=262 (%)
ITT population	135 (100)	127 (100)	262 (100)
PP population	130 (96)	121 (95)	251 (96)
Safety population	135 (100)	127 (100)	262 (100)

Data shown are n (%). All percentages are based on N; %=100 x n/N, where n = number of treated subjects in specific category.
Abbreviations: ITT = intent-to-treat; PP = per protocol

Source: FDA Statistical Reviewer

Table 21. ETTAU-03 Subject Dispositions (All Randomized Subjects)

	Diphenhydramine Injection N=135 (%)	Cetirizine Injection N=127 (%)	Overall N=262 (%)
Randomized	135 (100)	127 (100)	262 (100)
Completed the study	132 (98)	123 (97)	255 (97)
Discontinued study treatment prematurely	3 (2)	4 (3)	7 ()
Primary reason for discontinuation			
Lost to follow-up	3 (2)	3 (2)	6 (2)
Other	0	1 (1)	1 (< 1)

Data shown are n (%). All percentages are based on N; %=100 x n/N, where n = number of treated subjects in specific category.

Source: FDA Statistical Reviewer

The primary endpoint was measured at 2 hours post-administration of drug; however, the primary analysis was completed for the ITT population with LOCF for patients who were discharged prior to the 2-hour assessment. If the investigator determined that the subject was both physically and mentally fit to be discharged, the discharge could occur any time after the 1-hour assessment so long as the symptom score reached zero at 1 hour postinjection. Please refer to Section 8.3 for further discussion about patient disposition.

In the event that a patient required a rescue medication prior to the 1-hour assessment, the patient-rated pruritus severity score reduction/change from baseline at 1 hour was set to zero for that subject.

Otherwise, if rescue drug was given, then the last observation prior to rescue was carried forward to all subsequent assessments, including the 2-hour, and "readiness for discharge" assessment. A total of 37 (27%) subjects in the diphenhydramine group and 19 (15%) subjects

in the cetirizine group used at least one additional drug at least once. Drugs administered included: calcium chloride, dexamethasone, dimenhydrinate, diphenhydramine, epinephrine, famotidine, hydrocortisone, hydroxyzine, ketorolac, lorazepam, methylprednisolone, ondansetron, potassium, prednisone, ranitidine, sodium chloride, and sodium lactate. A total of 4 subjects received epinephrine (1 in the cetirizine group and 3 in the diphenhydramine group). The most commonly administered drugs included: steroids (dexamethasone, methylprednisolone, and prednisone), diphenhydramine, and famotidine.

8.1.7.2. Protocol Violations/Deviations

There were a total of 11 protocol violations for study ETTAU-03. The study subjects were excluded for the following reasons:

- H1 antagonist given within 2 hours (n=1)
- Wrong disease (n=3)
- Received about half of the required dose as mistakenly shared the same treatment vial with another subject (n=2)
- Wrong disease and H2 antagonist given within 2 hours (n=1)
- Baseline vital signs done after infusion and timing of baseline pruritis assessment could not be confirmed (n=4)

No other major protocol deviations were identified in this study.

8.1.7.3. Demographic Characteristics

Demographics of subjects in the cetirizine injection group and diphenhydramine injection group were generally similar. The majority of subjects in this study were white (48%) and female (63%) with a mean (SD) age of 39 (16) years with range from 18 to 92 years. There was a slightly lower population of female subjects in the cetirizine injection treatment group than in the diphenhydramine injection treatment group (61% versus 65%). See Table 22 for full demographics details.

Table 22. ETTAU-03 Demographic Characteristics (ITT Population)

Characteristic	Diphenhydramine Injection N=135	Cetirizine Injection N=127	Overall N=262
Age, years			
Mean (SD)	39 (16)	39 (16)	39 (16)
Median (min, max)	37 (18, 87)	36 (18, 92)	37 (18, 92)
Age group (years), n (%)			
Age ≥65	9 (7)	9 (7)	18 (7)
Age <65	126 (93)	118 (93)	244 (93)
Sex, n (%)			
Male	47 (35)	50 (39)	97 (37)
Female	88 (65)	77 (61)	165 (63)

Characteristic	Diphenhydramine Injection N=135	Cetirizine Injection N=127	Overall N=262
Race, n (%)			
Asian	5 (4)	4 (3)	9 (3)
Black	44 (33)	41 (32)	85 (32)
Hispanic	21 (16)	14 (11)	35 (13)
Native Hawaiian	0 (0)	1 (1)	1 (0.4)
Other	3 (2)	2 (2)	5 (2)
White	62 (46)	64 (50)	126 (48)
White, Hispanic or Latino	0 (0)	1 (1)	1 (0.4)
Country, n (%)			
United States	114 (84)	106 (84)	220 (84)
Canada	21 (16)	21 (16)	42 (16)

All percentages are based on N% =100 x n/N, where n = number of treated subjects in specific category.
Abbreviations: ITT = intent-to-treat; Max = maximum; Min = minimum; SD = standard deviation
Source: FDA Statistical Reviewer

8.1.7.4. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Table 23 summarizes participant atopic baseline characteristics. A total of 10 subjects had a prior history of anaphylaxis which was either attributed to a medication, food, insect sting, or combination. Of note, three subjects (2%) in the IV cetirizine group and one (1%) patient in the diphenhydramine IV group had a prior history of urticaria.

Table 23. ETTAU-03 Participant Baseline Characteristics

Participant Characteristic	IV Diphenhydramine n (%) N =135	IV Cetirizine n (%) N =127	Total n (%) N = 262
Drug hypersensitivity	37 (27)	42 (33)	79 (30)
Food allergy	14 (10)	13 (10)	27 (10)
Seasonal allergy	8 (6)	16 (13)	24 (9)
Asthma	21 (16)	10 (8)	31 (12)
Asthma exercise induced	0 (0)	1 (1)	1 (< 1)
Rash	9 (7)	7 (6)	16 (6)
Urticaria	1 (1)	3 (2)	4 (2)
Dermatitis contact	4 (3)	2 (2)	6 (2)
Eczema	5 (4)	1 (1)	6 (2)
Anaphylaxis	5 (4)	5 (4)	10 (4)

Abbreviation: IV = intravenous
Source: Clinical Reviewer generated JMP analysis. ADSL, ADMH, TRT01A vs. Dictionary-Derived Term. Multiple occurrences for unique subject ID not counted. Anaphylaxis data from ADSL, ADMH.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects received their treatment in the treatment center (e.g. emergency departments, hospitals, allergy clinics or urgent care centers).

Subjects could also receive rescue therapy for acute urticaria. A total of 19 (15%) patients in the cetirizine group and 37 (27%) patients in the diphenhydramine group received rescue therapy. Medications administered included: calcium chloride, dexamethasone, dimenhydrinate, diphenhydramine, epinephrine, famotidine, hydroxyzine, ketorolac, lorazepam, methylprednisolone, ondansetron, potassium, prednisone, ranitidine, sodium chloride, and

sodium lactate. Complete details regarding the rescue medication administered are included in Table 24.

Table 24: Subjects Receiving Rescue Medications At Least Once

Rescue Medication	Diphenhydramine Injection N=135 n (%)	Cetirizine Injection N=127 n (%)	All Subjects N=262 n (%)
Calcium chloride; Potassium; Sodium Lactate	2 (2)	0	2 (1)
Dexamethasone	12 (9)	7 (6)	19 (7)
Dimenhydrinate	0	1 (1)	1 (0.4)
Diphenhydramine	10 (7)	6 (5)	16 (6)
Epinephrine	3 (2)	1 (1)	4 (2)
Famotidine	9 (7)	6 (5)	15 (6)
Hydrocortisone	1 (1)	0	1 (0.4)
Hydroxyzine	2 (2)	0	2 (1)
Ketorolac	1 (1)	0	1 (0.4)
Lorazepam	1 (1)	0	1 (0.4)
Methylprednisolone	9 (7)	2 (2)	11 (4)
Ondansetron	2 (2)	0	2 (1)
Prednisone	9 (7)	6 (5)	13 (5)
Ranitidine	1 (1)	1 (1)	1 (0.4)
Sodium Chloride	1 (1)	0	1 (0.4)

Source: ETTAU-03 CSR Table 14.2.5; Modified by Clinical Reviewer

8.1.7.5. Primary Endpoint

The primary efficacy endpoint was the change from baseline in patient-rated pruritus score assessed 2 hours post-treatment administration for the ITT population (analysis results are in Table 25). The mean (SD) change from baseline in patient-rated pruritus severity score on a scale of 0 - 3 was -1.61 (0.94) for cetirizine-treated subjects and -1.50 (0.98) for diphenhydramine-treated subjects. The least squares estimated treatment difference was 0.06 (95% CI = -0.281, 0.40; p=0.74). Since the lower bound of the 95% CI for the treatment difference, -0.281, was greater than-0.5, effectiveness of cetirizine injection was demonstrated to be noninferior to the effectiveness of diphenhydramine injection. However, because the lower bound was not greater than 0 and the p-value for the treatment difference was not smaller than 0.05, cetirizine injection has not demonstrated superiority to diphenhydramine injection.

Table 25. ETTAU-03 Summary of Change from Baseline in Patient-Rated Pruritus Score at 2 Hours (Using LOCF; ITT Population)

	Diphenhydramine Injection N=135	Cetirizine Injection N=127	Adjusted Treatment Difference* (95% CI)	P-Value
Mean (SD)	-1.50 (0.98)	-1.61 (0.94)	0.06 (-0.28, 0.40)	0.74
Median (min, max)	-2.0 (-3.0, 1.0)	-2.0 (-3.0, -1.0)		

* The treatment difference, 95% CI, and p-value were calculated from a generalized linear mixed-effects model consisting of the change from baseline at 2 hrs as the dependent variable and site, treatment, and an interaction of site and treatment as fixed effects. Investigator sites with no subjects in one of the two treatment groups were pooled to be included in the model. Specifically, site 2 was pooled with site 1, and site 20 was pooled with site 7.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; Max = maximum; Min = minimum; SD = standard deviation.

Source: FDA Statistical Reviewer

Similar results hold for the PP population in terms of noninferiority and superiority conclusions of the primary efficacy endpoint (Table 26).

Table 26. ETTAU-03 Change from Baseline in Patient-Rated Pruritus Score at 2 Hours (Using LOCF; PP Population)

	Diphenhydramine Injection N=130	Cetirizine Injection N=121	Adjusted Treatment Difference* (95% CI)	P-Value
Mean (SD)	-1.50 (0.99)	-1.66 (0.92)	0.10 (-0.25, 0.45)	0.58
Median (min, max)	-2.0 (-3.0, 1.0)	-2.0 (-3.0, -1.0)		

* The treatment difference, 95% CI, and p-value were calculated from a generalized linear mixed-effects model consisting of the change from baseline at 2 hrs as the dependent variable and site, treatment, and an interaction of site and treatment as fixed effects. Investigator sites with no subjects in one of the two treatment groups were pooled to be included in the model. Specifically, site 2 was pooled with site 1, and site 20 was pooled with site 7.
Abbreviations: CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; PP = per protocol; SD = standard deviation.

Source: FDA Statistical Reviewer

8.1.7.6. Secondary and Other Relevant Endpoints

Need to Return to the Treatment Center

Fewer subjects who were treated with cetirizine injection compared to those treated with diphenhydramine injection returned to the treatment center compared to those treated with diphenhydramine injection (p=0.02 for the ITT population; p=0.01 for the PP population), as shown in Table 27.

Table 27. ETTAU-03 Returned to Treatment Center (ITT Population)

	Diphenhydramine Injection N=135	Cetirizine Injection N=127	P-Value
No	116 (85.93)	120 (94.49)	
Yes	19 (14.07)	7 (5.51)	0.02

Treatment center = emergency department or clinic, after study discharge.
Data shown are n (%) or p-value. All percentages are based on N% =100 x n/N, where n = number of treated subjects in specific category.
Abbreviation: ITT = intent-to-treat
Source: FDA Statistical Reviewer

Time Spent in the Treatment Center

Subjects treated with cetirizine injection compared to those treated with diphenhydramine injection had stays that were 22 minutes shorter, based on the ITT population (p=0.07), and 27 minutes shorter based on the PP population analysis (p=0.002), as shown in Table 28.

Table 28. ETTAU-03 Time (Hours) Spent at Treatment Center (ITT Population)

	Diphenhydramine Injection N=135	Cetirizine Injection N=127	Adjusted Treatment Difference (95% CI)	P-Value
n*	133	120		
Mean (SD)	2.07 (1.11)	1.71 (0.87)	0.32 (-0.03, 0.67)	0.07
Median (min, max)	2.02 (0.9, 6.1)	1.42 (0.5, 7.2)		

* Nine patients had no record of discharge time or were admitted for further observations.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; Max = maximum; Min = minimum; SD = standard deviation.

Source: FDA Statistical Reviewer

Pruritus Treatment Success

Patient-rated pruritus severity scores were assessed at baseline, 1 hour, and/or 2 hours, and/or "readiness for discharge" in the ITT population. Patient pruritus severity scores decreased during the study from baseline and were similar between both treatment groups. Mean scores and mean change from baseline were additionally similar between treatment groups with the largest treatment differences noted at the 2-hour assessment, as shown in Table 29.

Table 29. ETTAU-03 Physician-Rate Urticaria/Erythema Scores by Visit (ITT Population)

	Diphenhydramine Injection N=135	Cetirizine Injection N=127	Adjusted Treatment Difference (95% CI)	P-Value
1-hour assessment				
Mean (SD)	1.42 (0.64)	1.27 (0.68)	0.292 (0.06, 0.53)	0.04
Min, Max	0.0, 3.0	0.0, 3.0	0.29 (0.06, 0.53)	
2-hour assessment				
Mean (SD)	1.33 (0.68)	1.19 (0.70)	0.268 (0.03, 0.50)	0.03
Min, Max	0.0, 3.0	0.0, 3.0	0.27 (0.03, 0.50)	
Discharge assessment				
Mean (SD)	1.33 (0.68)	1.17 (0.70)	0.292 (0.06, 0.53)	0.02
Min, Max	0.0, 3.0	0.0, 3.0	0.29 (0.06, 0.53)	

Abbreviations: ITT = intent-to-treat; Max = maximum; Min = minimum; SD = standard deviation.
Source: FDA Statistical Reviewer

Urticaria/Erythema Scores

Physician-rated urticaria/erythema scores were assessed at baseline, 1 hour, and/or 2 hours, and/or "readiness for discharge" in the ITT population. Lower scores indicate a decrease in physician-rated urticaria/erythema scores or no or milder urticaria/erythema. Mean physician-rated urticaria/erythema scores were statistically significant and lower in subjects treated with cetirizine injection compared to diphenhydramine injection at the 1-hour, 2-hour, and discharge assessments (nominal p=0.04, 0.03, 0.02, respectively).

Subject Condition During 24 and 48 Hours After Discharge

A summary of conditions that ranged from recurrence of allergic symptoms to need for medication prescription after discharge were obtained at 24 and 48 hours after discharge in the ITT population. Cetirizine-treated subjects experienced lower rates of recurrence of allergic symptoms when compared to the diphenhydramine injection group as reported at 24 and 48 hours post discharge. Overall the proportion of subjects who needed to use medication prescribed to them at discharge was similar between both groups; however, the proportion of subjects who did not need a prescription at discharge was lower in the cetirizine treatment group. Additionally, fewer cetirizine-treated subjects needed any additional medication at 24 hours and 48 hours post discharge or returned to a treatment center (Table 27). Subjects in the cetirizine group additionally spent less time in the treatment center (Table 28).

Additional Analyses Conducted on the Individual Trial

Traditional and Bayesian Shrinkage Subgroup Analysis

Although subgroup analysis was not planned by the Applicant, we conducted the subgroup analysis to gain insight into the level of consistency or heterogeneity of the treatment effect across subgroups. The analysis was performed using the Applicant's prespecified analysis method. The subgroups were described as follows:

- Sex (Female, Male)
- Race (African-American, White, Hispanic/Latino, Others)
- Region (United States, Canada)

We also determined shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model. Shrinkage estimates use more information and are more precise, closer to the true subgroup treatment effects than the sample estimates.

In traditional subgroup analyses, there were some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size or large variability for some subgroups. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. With a shrinkage method, sample estimate is "shrunk" towards the overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage).

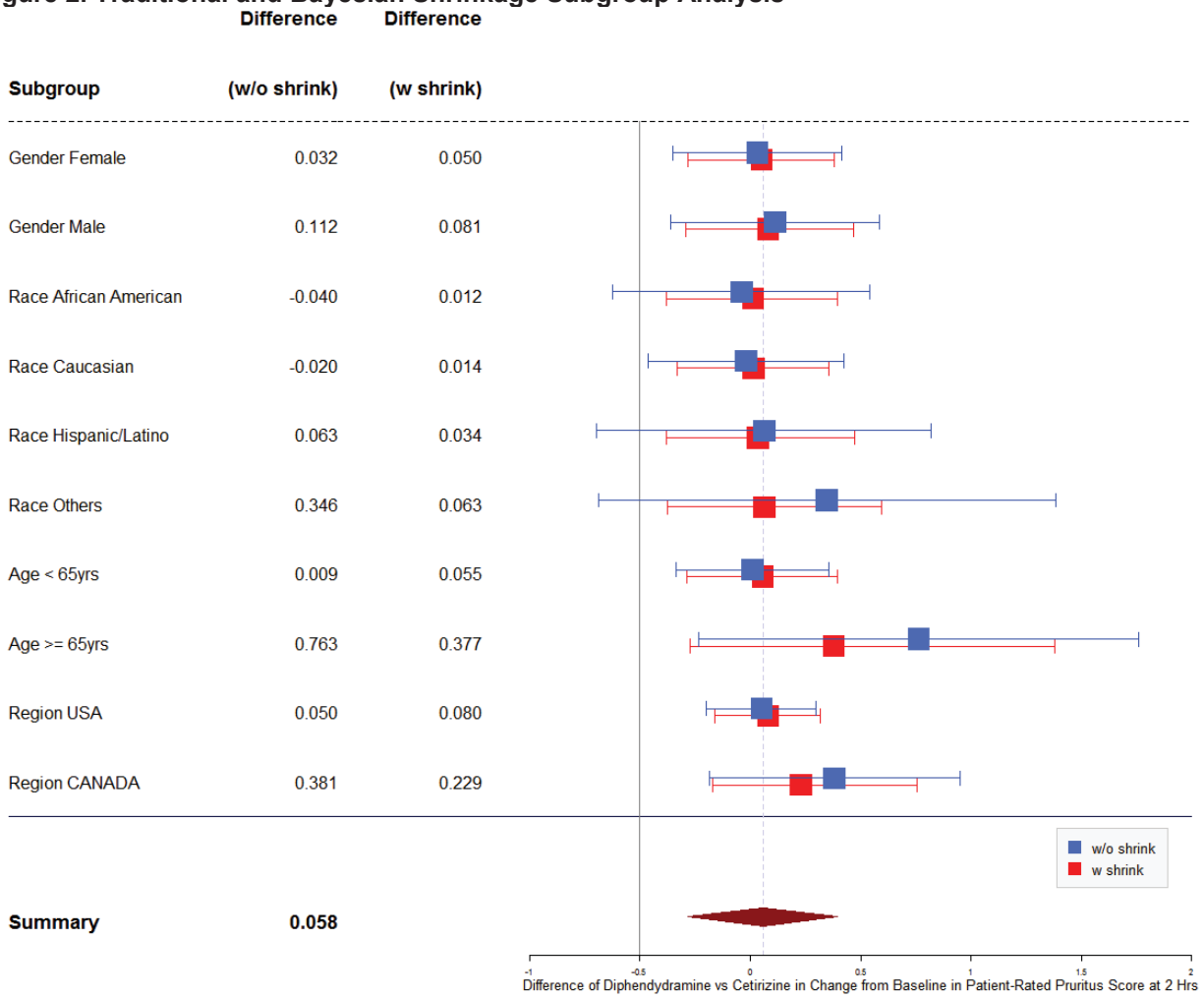
The Bayesian hierarchical model was used in this review as a shrinkage method with sample estimates from the traditional subgroup analysis with the same flat prior to derive shrinkage estimates for all subgroups and assumptions as followings:

Y_i: the observed sample estimate of treatment effect in a subgroup level i (i =1,2, …, total number of subgroups), assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$ with $\mu \sim N(0, c^2)$, $1/\tau^2 \sim$ Gamma (0.001, 0.001) (noted as "shrinkage," c from patient-level standard deviation)

Shrunken estimates and 95% credible interval (equivalent to confidence interval of sample estimate) are calculated and depicted in the forest plot.

Figure 2. Traditional and Bayesian Shrinkage Subgroup Analysis



Examining Figure 2, we conclude that:

- In general, the effect of cetirizine did not show clinically meaningful differences in noninferiority across the examined subgroups
- Among race subgroups, African-American, Hispanic/Latino and Others did not demonstrate noninferiority potentially due to the small sample size in traditional subgroup analysis (without shrink)
- All the subgroup means from the Bayesian shrinkage subgroup analysis shrunk to the overall mean
- All the 95% credible intervals of subgroup mean from Bayesian shrinkage subgroup analyses were narrower than the sample estimates' 95% confidence intervals
- The Bayesian shrinkage subgroup analysis produced more accurate subgroup means and their credible intervals, making all the subgroup lower bounds lie above the NI margin of -0.5

8.1.8. Integrated Assessment of Effectiveness

Cetirizine injection was found to be noninferior to diphenhydramine injection for the primary endpoint of the mean change from baseline in patient-rated pruritus at the 2-hour assessment in the ITT population. The key secondary endpoints of the number of patients returning to any emergency department or clinical and time spent in the treatment center also favored treatment with cetirizine.

The recommended dosage regimen is once every 24 hours as needed for acute urticaria. Although the trials were single-dose trials, this dosage regimen is supported as this is an IV product that will be administered in a healthcare setting and is therefore unlikely to be dosed chronically. Moreover, acute urticaria by definition is a self-limited condition.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant submitted safety data from Trial ETTAU-03 to support the use of IV cetirizine for treatment of acute urticaria once every 24 hours as needed for acute urticaria in adults and children 6 months of age and older. Although Trial ETTAU-03 also provided the largest safety database for review, Trial ETTAU-02, a pilot study in 33 adults, also contributed safety data and will be briefly discussed.

No pediatric clinical studies were conducted. Pediatric safety is supported by the oral cetirizine pediatric studies down to 6 months of age. Cmax is expected to be higher than oral cetirizine in pediatric subjects based on the adult PK data with IV cetirizine and PK data with oral cetirizine in children down to 6 months of age demonstrating a linear PK. Safety data for the higher Cmax in pediatric patients is supported by overdose cases identified in the FDA Adverse Event Reporting System (FAERS) which include sufficient exposures to cover the IV Cmax in this age group. Details and findings from this consult can be found in Section 9 of this review.

8.2.2. Review of the Safety Database

8.2.3. Overall Exposure

The size of the database and exposure are adequate for review. A total of 295 patients are included in the Applicant's overall safety database (ETTAU-02 and ETTAU-03 trials) of whom 143 received one dose of IV cetirizine. No differences in baseline demographics are seen between treatment groups. The safety data provided from the ETTAU-03 does not include postmarketing reports and only includes safety events reported during and up to 48 hours after subjects were involved in the ETTAU-03 trial.

8.2.4. Population Characteristics

See Section 8.1.7.

8.2.5. Adequacy of the Safety Database

The safety database of 127 adults treated with a single-dose of IV cetirizine in Trial ETTAU-03 is adequate to assess the safety of IV cetirizine for use to treat acute urticaria, supported by the safety data from oral cetirizine.

8.2.6. Adequacy of Applicant's Clinical Safety Assessments

The safety database is of sufficient size to assess the safety of the proposed IV cetirizine. The single-dose study design is adequate to assess the safety of IV cetirizine for the treatment of acute urticaria, as acute urticaria is a self-limited disease, therefore this product will not be administered chronically. Additionally, given that the studies highlighted in this review focuses on single-dosing of IV cetirizine, we are also using known safety data from oral cetirizine.

Issues Regarding Data Integrity and Submission Quality

No data quality issues as they relate to safety were identified in the review of this NDA.

Categorization of Adverse Events

The Applicant provided accurate definitions of AEs and serious AEs in the protocols. Adverse events were monitored throughout trial ETTAU-03, from signing of informed consent until up to 28 days following treatments and by monitoring vital signs at planned intervals from admission into the treating facility until readiness for discharge. AEs with onset after the start of study drug were summarized and grouped by Medical Dictionary for Regulatory Affairs (Version 21.0) system organ class and specific adverse event. The severity of an AE was classified according to the following terms:

Mild: Symptom was manifested but was tolerated
Moderate: Normal activity affected
Severe: Severe effect or inability to work necessitating discontinuation of study medication

Routine Clinical Tests

Routine laboratory values were not collected as a part of the ETTAU-03 trial protocol. Results of routine tests, such as vital signs, are presented separately in sections below.

8.2.7. Safety Results

8.2.7.1. Deaths

There were no deaths reported in either treatment arm (diphenhydramine injection or cetirizine injection).

8.2.7.2. Serious Adverse Events

There was one serious adverse event (SAE) in the diphenhydramine injection treatment arm. The subject was a 65 year-old African-American female enrolled in study ETTAU-03. The subject

had an episode of mild urticaria on (b) (6), at (b) (6) and received her first dose of diphenhydramine injection on (b) (6), between (b) (6). While there were no signs of anaphylaxis during screening and enrollment, the subject experienced nausea, vomiting, and was found to have bradycardia (heart rate of 45, systolic blood pressure of 104, diastolic blood pressure of 61) although no time is given for the onset of these symptoms. The subject was treated with epinephrine (3 mg IM), Solu-Medrol IV (125 mg), Pepcid (20 mg by mouth), famotidine (20 mg PO), prednisone (40 mg PO), diphenhydramine (25 mg PO), Benadryl (25 mg IV), and lactated Ringer's (1L). The subject stabilized with treatment and maintained her blood pressure without any further anaphylactic symptoms. The subject was treated with lactated Ringer's (2L) prior to discharge and was prescribed prednisone, Pepcid, Benadryl, and an EpiPen (dosage unknown). The subject was discharged from the hospital on (b) (6), at which time the SAE was considered recovering/resolving. The subject completed the study on (b) (6).Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts and/or discontinuation due to adverse effects.

8.2.7.3. Significant Adverse Events

There were no significant adverse events.

8.2.7.4. Treatment-Emergent Adverse Events and Adverse Reactions

There were a total of 24 adverse events reported in the diphenhydramine injection group and a total of 7 adverse events reported in the cetirizine injection group. The most common adverse events in the diphenhydramine group were dizziness (4%), nausea (3%), pyrexia (2%), burning sensation (2%), and urticaria (2%) which is consistent with the known safety profile of diphenhydramine. None of these adverse events occurred in the IV cetirizine treatment group. Single adverse events of bradycardia, injection site pain, vomiting, anaphylactic reaction (outline in Section 8.2.7.2 SAEs), erythema, and pruritus were also reported in the diphenhydramine group, but not in the IV cetirizine group. The cetirizine group overall had fewer adverse events reported with the following AEs occurring with an incidence of 1%: dyspepsia, feeling hot, dysgeusia, headache, paresthesia, presyncope, and hyperhidrosis. Dysgeusia and headache occurred as singular events in both treatment groups. Adverse events are summarized in Table 30.

Table 30. Study ETTAU-03 Common Adverse Events

	Diphenhydramine Injection N=135 n (%)	Cetirizine Injection N=127 n (%)	All Subjects N=262 n (%)
No. with any adverse event	24 (18%)	7 (6%)	31 (12%)
		No. Adverse Events	
Cardiac disorders			
Bradycardia	1 (1%)	0	1 (<1%)
Gastrointestinal disorders			
Dyspepsia	0	1 (1%)	1 (<1%)
Nausea	4 (3%)	0	4 (2%)
Vomiting	1 (1%)	0	1 (<1%)

	Diphenhydramine Injection N=135 n (%)	Cetirizine Injection N=127 n (%)	All Subjects N=262 n (%)
General disorders & administration site conditions			
Feeling hot	0	1(1%)	1 (<1%)
Injection site pain	1 (1%)	0	1 (<1%)
Pyrexia	2 (2%)	0	2 (1%)
Immune system disorders			
Anaphylactic reaction	1 (1%)	0	1 (<1%)
Nervous system disorders			
Burning sensation	2 (2%)	0	2 (1%)
Dizziness	6 (4%)	0	6 (2%)
Dysgeusia	1 (1%)	1 (1%)	2 (1%)
Headache	1 (1%)	1 (1%)	2 (1%)
Paresthesia	0	1 (1%)	1 (<1%)
Presyncope	0	1 (1%)	1 (<1%)
Skin and subcutaneous tissue disorders			
Erythema	1 (1%)	0	1 (<1%)
Hyperhidrosis	0	1 (1%)	1 (<1%)
Pruritus	1 (1%)	0	1 (<1%)
Urticaria	2 (2%)	0	2 (1%)

Source: CSR ETTAU-03 Table 14.3.1 pg. 54 and Table 14.3.2 pg. 55 verified by Reviewer in JMP

Laboratory Findings

Not applicable for this study.

Vital Signs

Vitals signs including sitting systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate, were collected for each subject upon arrival at the treatment center, at baseline (prior to treatment administration), at 1 hour and/or 2 hours post-treatment, and at the time of discharge (where obtained). There were no safety concerns with respect to vital signs and in general, vital signs were consistent between treatment groups and within normal ranges.

8.2.8. Analysis of Submission-Specific Safety Issues

Antihistamines are known to cause sedation; however first generation antihistamines such as diphenhydramine are associated with higher rates of sedation compared to second generation antihistamines such as cetirizine(American Academy of Allergy Asthma & Immunology 2019).

Subject-rated sedation scores were assessed at baseline, 1 hour, and/or 2 hours, and/or “readiness for discharge” in the ITT population. Over the first hour after treatment, sedation scores increased in both treatment groups and then declined over the second hour with cetirizine-treated subjects returning to baseline sedation by 2 hours. The sedation score increase in the cetirizine injection group was significantly smaller than that observed in the

diphenhydramine injection group during the study. Table 31 details subject-rated sedation score by visit.

Table 31. Summary of Subject-Rated Sedation Score by Visit (ITT Population)

	Diphenhydramine Injection (N = 135)	Cetirizine Injection (N = 127)	p-value[1]
Baseline Assessment: Mean (SD)	0.39 (0.76)	0.39 (0.67)	0.56
1 Hr Assessment: Mean (SD)	1.10 (0.98)	0.62 (0.85)	0.02
1 Hr Change from Baseline: Mean (SD)	0.70 (0.92)	0.24 (0.79)	<0.01
2 Hr Assessment: Mean (SD)	0.88 (0.96)	0.46 (0.72)	0.08
2 Hr Change from Baseline Mean (SD)	0.49 (0.92)	0.08 (0.81)	0.03

Abbreviations: Hr = hour; SD = standard deviation.
Source: ETTAU-03 CSR Table 10, pg 47; modified by Clinical Reviewer

8.2.9. Safety Analyses by Demographic Subgroups

As this was a single-dose study with a small number of adverse reactions, there were not enough events to analyze by demographic subgroup.

8.2.10. Specific Safety Studies/Clinical Trials

8.2.10.1. Trial ETTAU-02

Trial ETTAU-02 was a multi-center, single-dose, parallel group, randomized, double-blind pilot trial of cetirizine injection 10 mg/mL versus diphenhydramine injection 50 mg/mL in 33 adults who presented with acute urticaria to hospital Emergency Departments, allergy clinics or Urgent Care Centers. Trial ETTAU-02 trial ran from 3/27/2013 to 12/12/2014 at eight clinical sites. Trial ETTAU-02 was of similar design as Trial ETTAU-03.

8.2.10.1.1. Objectives

Primary

- Describe the recruitment of patients with acute urticaria who presented to hospital emergency departments, urgent care centers and allergy clinics in a blinded clinical study comparing two IV antihistamines (diphenhydramine and cetirizine)
- Document the timing and compliance with proposed outcome measures
- Document the responses captured by the proposed primary outcome measures for IV diphenhydramine and IV cetirizine

- Document and review the conduct of various study procedures, e.g. technique for blinding study medication administration, patient follow-up at approximate 24 hours, and use of the Source Document and/or electronic data capture system.

Secondary:

Documenting AEs and SAEs in each study group,

Describe the amount of time spent in the treating center prior to discharge, to document the percentage of patients requiring rescue medication, to describe the reasons for the use of rescue drugs, and to complete a statistical calculation to project sample size for future studies.

8.2.10.1.2. Study population

Key Inclusion Criteria

- Adult male and female subjects aged 18 years or older
- Diagnosis of acute urticaria who needed treatment with an antihistamine to alleviate their symptoms
- Patient-rate pruritus severity score ≥1
- Extent of Urticaria/Erythema Score ≥ 1

Key exclusion criteria:

- Receipt of an investigational drug or device within the past 30 days.
- Subjects with conditions where antihistamine use is contraindicated (e.g., narrow angle glaucoma, symptomatic prostatic hypertrophy).
- Subjects who received any antihistamine (H1 antagonist) within the past 2 hours, regardless of route of administration, an H2 antagonist within the past 2 hours, doxepin within 12 hours, epinephrine within the past 30 minutes, or steroids (oral, IV, IM, or inhalational routes) within the past 12 hours.
- Anaphylaxis (if subjects presented with acute urticaria combined with anaphylaxis, after anaphylaxis symptoms resolved, these subjects could be included in the study as long as urticaria was still present).
- Known allergy to hydroxyzine, cetirizine, levocetirizine, or diphenhydramine
- Subjects on concomitant p-glycoprotein inhibitors
- Subjects who had an acute allergic reaction to a medication that they were taking (e.g. antibiotics, NSAIDs, etc.) and who could not stop the medication.
- Subjects who based on their medical history or in the opinion of the Investigator, had chronic urticaria, hereditary angioedema, urticaria refractory to antihistamines, or a dermatological disease that interfered with the evaluation of a therapeutic response.

The following medications were prohibited: any antihistamine (H1 or H2 antagonist) given 12 hours prior to enrollment or doxepin given 12 hours prior to enrollment, epinephrine administered 30 minutes prior to enrollment, steroids (oral, IV, IM, or inhalational routes) within the past 12 hours, and p-glycoprotein inhibitors.

8.2.10.1.3. Safety results

A total of 33 subjects were enrolled, 17 subjects received diphenhydramine and 16 subjects received cetirizine injection.

No deaths, SAEs, or AEs leading to discontinuation were reported for any of the subjects enrolled in this study. A total of 6 subjects (18%) reported a total of 13 AEs during this study. Four of the 17 (24%) subjects who received diphenhydramine injection reported 11 AEs, of which the most common AEs included: dizziness, drowsiness, and sedation. Two of the 16 (13%) subjects who received cetirizine injection reported AEs which included: burning sensation after study drug administration and constipation. Two of 17 (12%) subjects in the diphenhydramine group were determined to require rescue medication by a physician. Rescue medications used included: prednisone and ranitidine for one subject and solumedrol and ranitidine for the other. One of 16 (6%) subjects in the cetirizine group required rescue medication, which included epinephrine and solumedrol. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Given the known safety profile of oral cetirizine and the short-term use of this product, carcinogenicity or tumor development was not assessed.

Human Reproduction and Pregnancy

There were no cases of pregnancy reported.

Pediatrics and Assessment of Effects on Growth

Pediatric safety for oral cetirizine is discussed here. Effects on growth was not assessed as this is not a chronically administered therapy.

No pediatric clinical studies were conducted with IV cetirizine. Pediatric safety is supported by the oral cetirizine pediatric studies down to 6 months of age. Per the prescribing information for Zyrtec® (revised August 2003), 4-week, placebo-controlled trials were conducted in 376 subjects 6 to 11 years of age, dosed with 5 or 10 mg a day, and 168 subjects 2-5 years of age (dosed 0.2-0.4 mg/kg). Placebo-controlled, 18-month trials were conducted in 399 subjects 12 to 24 months (dosed 0.25 mg/kg twice daily) and 7-day trials were conducted in 42 subjects 6 to 11 month olds dosed 0.25 mg/kg twice daily. In subjects 6 to 11 years of age, the most common adverse events occurring with a frequency of ≥ 2% and more frequently than placebo were headache, pharyngitis, abdominal pain, coughing, somnolence, diarrhea, epistaxis, bronchospasm, nausea, and vomiting. The safety profile for subjects 2 to 5 years of age was similar to subjects 6 to 11 year old of age. In subjects 6 to 24 months of age, the incidence of adverse reactions was similar in the cetirizine group compared to placebo.

The Cmax is expected to be higher than oral cetirizine in pediatric subjects based on the adult PK data with IV cetirizine and PK data with oral cetirizine in children down to 6 months of age demonstrating a linear PK. Safety data for the higher Cmax in pediatric patients is supported by

overdose cases identified in the FDA Adverse Event Reporting System (FAERS) which include sufficient exposures to cover the IV Cmax in this age group. Details and findings from this consult can be found in Section 9 of this review.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Information from adult and pediatric overdose cases will be included in the prescribing information (Overdosage Section). Details for the overdose cases are given in Section 9 of this review.

IV cetirizine is indicated for acute use in a healthcare facility under the supervision of healthcare providers, and therefore overdose, drug abuse potential, withdrawal, and rebound are not applicable to this NDA application.

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No post-market data is available for IV cetirizine; however the Zyrtec® prescribing information (Revised August 2003) includes the following adverse events: anaphylaxis, cholestasis, glomerulonephritis, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, thrombocytopenia, aggressive reaction and convulsions.

Expectations on Safety in the Postmarket Setting

There is an expectation that safety continues to be monitored in the postmarket setting.

8.2.12. Integrated Assessment of Safety

The safety analysis of IV cetirizine is primarily based on Trial ETTAU-03, which included 262 adults with acute urticaria who were randomized to receive a single-dose of IV cetirizine or IV diphenhydramine, with adverse events assessed up to 28 days post-dose. A smaller pilot study (ETTAU-02) of similar design in 33 adults with acute urticaria, also provided supportive safety. The safety profile for Trial ETTAU-02 was generally consistent with Trial ETTAU-3 and did not identify any new safety concerns. Single-dose studies were considered appropriate as the primary safety evaluation, as acute urticaria is a self-limiting disease and IV cetirizine will be given in a supervised medical setting and not administered chronically.

In Trial ETTAU-03 no deaths, or adverse events leading to discontinuation were reported. One SAE of anaphylaxis was reported in the diphenhydramine treatment group. Common AEs reported in subjects receiving IV diphenhydramine included dizziness (4%), nausea (3%), pyrexia (2%), burning sensation (2%), and urticaria (2%). None of these adverse events occurred in the IV cetirizine treatment group. Single adverse events of bradycardia, injection site pain, vomiting, erythema, and pruritus were also reported in the diphenhydramine group, but not in the IV cetirizine group. Common AEs for IV cetirizine occurring with an incidence of less than 1%

included dyspepsia, feeling hot, dysgeusia, headache, paresthesia, presyncope, and hyperhidrosis. Dysgeusia and headache occurred as singular events in both treatment groups.

As sedation is a known adverse reaction for both diphenhydramine (first-generation anti-histamine) and oral cetirizine (second-generation antihistamine), but thought to be decreased for cetirizine, sedation was prospectively assessed using a subject-rate sedation score. Although sedation was not specifically reported as an adverse event in any treatment group, subjects in the IV cetirizine treatment group reported less sedation at all timepoints compared to subjects treated with IV diphenhydramine.

As the IV cetirizine development program was based on single-dose studies, the safety evaluation for IV cetirizine also relies on the known safety profile of oral cetirizine. The most common adverse side effects (incidence equal to or greater than 2%) with use of oral cetirizine are somnolence, fatigue, dry mouth, pharyngitis, and dizziness.

Moreover, as the peak concentration (C_{max}) for IV cetirizine was shown to be increased by 3.7 fold in healthy adults in Trial ETTAU-01 compared to oral cetirizine, the safety of oral cetirizine that would result in higher peak concentrations was also relied upon. In the prescribing information of the listed drug, Zyrtec® tablet (NDA 019835), doses up to 60 mg per day for a 1-week dosing duration were studied previously in adult subjects in a thorough QT (TQT) study. Given the linear PK for orally administered cetirizine (for oral doses 5 mg to 60 mg), the 60 mg Zyrtec® oral dose in the TQT study would result in peak concentrations (C_{max}) that are higher compared to that observed following IV cetirizine 10 mg.

As no pediatric clinical studies were conducted with IV cetirizine, pediatric safety is supported by the oral cetirizine (Zyrtec®) pediatric studies down to 6 months of age as the proposed doses for IV cetirizine in children (6 months to 11 years of age) and adolescents (≥12 to 17 years of age) are the same as the approved doses for Zyrtec® in the respective age groups. Per the prescribing information for Zyrtec® (revised August 2003), in subjects 6 to 11 years of age, the most common adverse events occurring with a frequency of ≥ 2% and more frequently than placebo were headache, pharyngitis, abdominal pain, coughing, somnolence, diarrhea, epistaxis, bronchospasm, nausea, and vomiting. The safety profile for subjects 2 to 5 years of age was similar to subjects 6 to 11 year old of age. In subjects 6 to 24 months of age, the incidence of adverse reactions was similar in the cetirizine group compared to placebo.

Cmax is expected to be higher than oral cetirizine in pediatric subjects based on the adult PK data with IV cetirizine and PK data with oral cetirizine in children down to 6 months of age demonstrating a linear PK. Safety data for the higher Cmax in pediatric patients is supported by overdose cases identified in the FDA Adverse Event Reporting System (FAERS) which include sufficient exposures to cover the IV Cmax in this age group. Pediatric overdose cases involved patients 18 months to 15 years of age receiving oral cetirizine hydrochloride doses of 90 mg to 300 mg (9 to 72 times the maximum age recommended dose) without other drug exposures. The adverse reactions reported included: somnolence, difficulty walking, agitation/irritability, hard to swallow/articulate clearly, tachycardia, vomiting, mydriasis, elevated creatinine phosphokinase.

8.3. Statistical Issues

During the review, we identified the following issues in Study ETTAU-03:

1) High rate of LOCF imputations for primary endpoint

The primary analysis was performed on the ITT population with the LOCF imputation method used to impute 2-hour scores if subjects were discharged prior to that assessment. There were mainly two reasons for the early discharge. If rescue occurred prior to the 2-hour assessment, then the last recorded assessment prior to rescue was carried forward. The "readiness of discharge" could have occurred any time after the 1-hour assessment if the symptom score had reached zero at 1 hour postinjection. Due to the nature of this study, the large amount of missing data at 2 hours was expected, as shown in the Applicant's pilot study (ETTAU-02). The Applicant prespecified LOCF method as the primary method to handle this high missing data. Almost 60% of the 2-hour scores was imputed with LOCF (Table 32). The Agency raised concerns regarding the high imputation rate and whether the LOCF method is reliable under the setting. In this study, subjects presented to emergency departments, hospitals, allergy clinics, or urgent care centers with acute urticaria, and efficacy measures were assessed at 1 hour and/or 2 hours after the injection. Due to the short time interval and onetime injection (treatment), it was likely that the last observation before the "readiness of discharge" (good outcome) or rescue (bad outcome) was not much different from 2-hour score (if measured). Thus, the LOCF imputation here is not likely creating a biased conclusion of efficacy, although the single imputation might underestimate the variability. But a control-based multiple imputation might give a bias toward no difference, which would also be concerning. Table 32

Table 32. ETTAU-03 Frequency of LOCF for Pruritus Score at 2 Hours Assessment (All Randomized Subjects)

LOCF	Diphenhydramine Injection N=135	Cetirizine Injection N=127	Overall N=262
No	57 (42)	49 (39)	106 (41)
Yes	78 (58)	78 (61)	156 (60)
Reasons for LOCF			
Rescue	27 (35)	16 (21)	43 (28)
Early discharge without rescue	51 (65)	62 (80)	113 (72)

Abbreviation: LOCF = last observation carried forward

Source: FDA Statistical Reviewer

As per clinical reviewers' request, we ran a sensitivity analysis on 1-hour score data, presuming that 1-hour scores are "cleaner" data since they had more actual data points compared to 2-hour scores. The result showed that cetirizine injection was noninferior to diphenhydramine using NI margin of -0.5. (results not shown)

2) Estimand and estimator

We defined the primary estimand and estimator for Study ETTAU-03.

Estimand:

(1) Population of interest: Male or female subjects, 18 years of age or older, with a diagnosis of acute urticaria who needed treatment with antihistamine to alleviate their symptoms, with a patient-rated pruritus severity score ≥1
(2) Variable of interest: 2-hour patient-rated pruritus severity score change from baseline
(3) Population-level summary for the endpoint: Difference between variable means between cetirizine injection, 10 mg, and diphenhydramine injection, 50 mg
(4) How potential intercurrent events are reflected:
    a. Rescue medication: the patients who had rescue would be considered treatment failures (composite strategy)
    b. "Readiness for discharge": the patients who were discharged before the primary endpoint time of 2 hours, due to the investigator determined that the patients were physically and mentally fit to be discharged, would be considered treatment success (composite strategy)

In the context of the estimand defined by us, there are two potential intercurrent events: rescue medication and "readiness for discharge" prior to 2 hours assessment. The rescue medication use is considered as "treatment failure" and "readiness for discharge" as "treatment success." Both intercurrent events were handled with a composite strategy where intercurrent event is taken to be a component of the variable of interest.
The method of estimation (estimator) specified the LOCF method to reflect the missing measurements after the intercurrent events. The LOCF method was based on logical rules that the use of rescue indicates that the assigned treatment is not working, resulting in a bad score prior to the rescue, which makes the use of LOCF of the bad score in the estimation sound reasonable. Regarding "readiness for discharge," the event is a good outcome indicating urticarial symptoms are pretty much gone, so staying for next assessment is not necessary. Again, LOCF of the good score measured prior to discharge sounds reasonable.

The Agency considers the above defined estimand clinically acceptable, and the LOCF imputation method is acceptable strategy to deal with missing data after rescue and "readiness for discharge."

3) Early rescued patients

There were six patients who were rescued within 15 minutes after drug administration. According to the Applicant, any such patients should have been withdrawn from the study because he/she should have been excluded during screening. However, for those patients, the baseline score was carried forward to the 2-hour assessment and their

data were still incorporated in the primary analysis. We ran the analysis excluding the early rescued patients, and the result (95% CI lower bound: -0.2821) was very similar to the primary analysis result (95% CI lower bound:-0.2811).

4) Ad hoc primary analysis model

The Applicant changed their statistical model, and added unplanned covariate for the primary endpoint evaluation. The Applicant stated that a random effects model, where site was considered a random factor, fit better than the prespecified model based on smaller Akaike's information criterion scores. Thus, the primary and key secondary analyses were performed using this better fitting model on the ITT population. Furthermore, they stated the baseline pruritus score was found to be a significant covariate, and added it in the changed statistical model.
Note that these justifications are vague, and the change has been made after efficacy data were observed. Technically, this is an ad hoc analysis (statistical analysis that was not prespecified) and the Agency does not consider it when evaluating the evidence of efficacy.

The ad hoc analysis alters the overall study results. For example, time spent at the treatment center is statistically different between two treatment groups (p-value: 0.0052; original p-value: 0.0703) in the ad hoc analysis. It also affects lower bound of 95% CI of difference between treatments in the primary endpoint, leading to a stronger tendency of noninferiority. For this reason, we rather consider the ad hoc results provided by the Applicant as supportive analyses.

5) Key secondary analysis results and multiplicity adjustment

In the key secondary efficacy evaluations, fewer subjects who were treated with cetirizine injection returned to the treatment center compared to those treated with diphenhydramine injection (p-value: 0.023, ITT population). Also, subjects treated with cetirizine injection compared to those treated with diphenhydramine injection had stays that were 22 minutes shorter (p-value: 0.07, ITT population). (b) (4) .
Furthermore, the multiplicity adjustment for overall testing of hypotheses proposed by the Applicant is not clear. They controlled family-wise error rate on key secondary endpoints only. One acceptable way to control type I error is a sequential testing procedure in the following order:

(1) noninferiority on the primary endpoint
(2) superiority on the primary endpoint
(3) superiority on the first key secondary endpoint
(4) superiority on the second key secondary endpoint

(b) (4)

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8.4. Conclusions and Recommendations

JDP Therapeutics submitted a 505(b)(2) NDA for cetirizine hydrochloride (HCl) 10 mg/mL solution for IV injection for the treatment of acute urticaria in adults and children 6 months of age and older.

The Applicant provides data from clinical trials (ETTAU-01, ETTAU-02, and ETTAU-03) to support this new dosage form, route of administration and indication. Trial ETTAU-01 is a safety, tolerability, and PK in 24 healthy adult volunteers. Trials ETTAU-02 and ETTAU-03 are double-blind, randomized, active-controlled trials in adults with acute urticaria comparing IV cetirizine to IV diphenhydramine. Trial ETTAU-02 enrolled 33 adults and informed the noninferiority margin to be used subsequently in ETTAU-03. Trial ETTAU-03 enrolled 262 adults provided the pivotal efficacy data as it was powered to assess the non-inferiority of IV cetirizine compared to IV diphenhydramine; based on a pre-specified agreed upon non-inferiority margin.

Cetirizine injection was found to be noninferior to diphenhydramine injection for the primary endpoint of the mean change from baseline in patient-rated pruritus at the 2-hour assessment in the ITT population. Supportive key secondary endpoints of clinical significance included that fewer subjects in the cetirizine group required return for further treatment compared to subjects treated with diphenhydramine injection. Additionally, subjects treated with cetirizine injection also spent less time at the treatment facility than subjects treated with diphenhydramine injection.

Efficacy in children < 18 years of age is extrapolated from adult studies of IV cetirizine data based on the similar clinical presentation of both adult and pediatric acute urticaria, consistency in therapeutic approach, mechanism of action, relevance of the clinical endpoints for both efficacy and safety, and PK showing similar oral cetirizine exposure for the recommended doses across different age groups.

The recommended dosage regimen is once every 24 hours as needed for acute urticaria. Although the trials were single-dose trials, this dosage regimen is supported as this is an IV product that will be administered in a healthcare setting and is therefore unlikely to be dosed chronically. Moreover, acute urticaria is a self-limiting condition.

A review of the safety data did not identify any new safety concerns and was generally similar to the known safety profile of oral cetirizine. Safety for the increased Cmax in adults for IV cetirizine was further supported by an oral cetirizine through QT trial which included doses with higher peak concentrations than what was observed for IV cetirizine. Pediatric safety is supported by oral cetirizine pediatric studies down to 6 months and overdose cases identified in the FDA Adverse Event Reporting System (FAERS) that included doses that would result in higher peak concentrations than what would be expected with IV cetirizine.

Considering the demonstrated efficacy and safety, the risk-benefit assessment is favorable and supports approval of cetirizine hydrochloride (HCl) 10 mg/mL solution for IV injection for the treatment of acute urticaria in adults and children 6 months of age and older.

The recommended action is Approval.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held to discuss the results of this pediatric program.

DPV-I was consulted to analyze postmarketing data for oral cetirizine to provide additional safety support for the pediatric population. The Cmax is expected to be higher than oral cetirizine in pediatric subjects based on the adult PK data with IV cetirizine and PK data with oral cetirizine in children down to 6 months of age demonstrating a linear PK. DPV-1 was consulted to identify overdoses cases in the FDA Adverse Event Reporting System (FAERS) and published literature which include sufficient exposures to cover the IV Cmax in this age group to provide safety data for the higher Cmax in pediatric patients.

DPV-I analyzed all pediatric and adult cases reporting administration of a onetime dose of greater than 60 mg of cetirizine. This dose cut-off was chosen based on the 60 mg Zyrtec® TQT study dose which would result in higher peak concentrations (C_{max}) than IV cetirizine 10 mg.

In FAERS 87 cases were included in the case series describing supratherapeutic cetirizine exposures. Less than half (45%, 39/87) of the cases involved exposure to cetirizine only. Approximately one-third (24/87) of the cases involved pediatric patients less than 18 years of age. Pediatric patients 0 to <12 years of age mostly ingested cetirizine only (10/13), whereas most of the children >12 years of age ingested multiple substances including cetirizine (10/11).

Adult overdose cases involved patients 18 to 81 years of age receiving oral cetirizine hydrochloride doses of 70 mg to 800 mg (7 to 80 times the maximum recommended dosage of 10 mg/day in adults). In subjects with exposure to cetirizine only, the most commonly reported adverse reactions in patients were somnolence and fatigue. Other reported adverse reactions included tachycardia, abdominal pain, nausea, and vomiting. Pediatric overdose cases involved patients 18 months to 15 years of age receiving oral cetirizine hydrochloride doses of 90 mg to 300 mg (9 to 72 times the maximum age recommended dose) without other drug exposures. The adverse reactions reported included: somnolence, difficulty walking, agitation/irritability, hard to swallow/articulate clearly, tachycardia, vomiting, mydriasis, elevated creatinine phosphokinase.

There were 3 cases of death in adults; however these were in the setting of polysubstance use and were attributed to underlying disease or other drug exposures.

The National Poison Data System search yielded 5,471 reports. Drowsiness and lethargy (47%), known adverse events with cetirizine, were the most frequently reported clinical effects related to cetirizine single exposures in pediatric patients in the National Poison Data System database.

Overall, DPV-I did not identify any new patterns of unexpected events with supratherapeutic cetirizine exposures in pediatric patients. The most frequently reported events including lethargy and somnolence were based on the known safety profile of cetirizine at approved doses. Additional details can be found in the DPV-I consult review.

10. Pediatrics

The Application proposes for the approval of IV cetirizine for treatment of acute urticaria down to 6 months of age. A waiver was requested for subjects less than 6 months of age since necessary studies are impossible or highly impractical. The Division agrees with this waiver, but finds that the more appropriate rationale is that the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. Generally, infants are treated with oral antihistamines, even in an acute care setting, due to challenges with placing IVs in infants.

The Pediatric Review Committee discussed this NDA on August 28, 2019 and agreed with the waiver in children less than 6 months of age. The PeRC was also in agreement with the plan to extrapolate efficacy for subjects 6 months to less than 18 years of age and rely on oral cetirizine pediatric safety, including the over dose cases to provide safety data for the higher peak concentrations (Cmax) expected with IV cetirizine compared to the pediatric doses approved for oral cetirizine. The PeRC also agreed to inclusion of the overdose cases in the prescribing information.

11. Labeling Recommendations

11.1. Trade Name

Proprietary name requests	Jan 9, 2018 & Aug 17, 2018	Tradename (b) (4) rejected (1/2018) and Tradename (b) (4) rejected (8/2018)
Accepted name	Jan 2019	Tradename QUZYTTIR accepted

11.2. Reliance on Other Approved Product Labels

JPD Therapeutics relied upon Zyrtec syrup product (NDA 020346) and Xyzal (NDA 22064 (tablet) and NDA 22157 (oral solution)) to inform the labeling for IV cetirizine. The tablet form prescription label of Zyrtec could not be relied upon as the over-the-counter (OTC) tablet labeling supersedes the prescription tablet labeling. There are no longer any prescription cetirizine tablet products listed in the Orange Book. The last approved version of the Zyrtec label is from 2003, and includes both tablet and syrup dosage forms. At the time of the full prescription to OTC switch, the combined label was not updated. The Zyrtec syrup NDA was withdrawn in 2016, therefore labeling can no longer be updated to remove the tablet information from the prescription label. It appears that an Abbreviated New Drug Application (ANDA) labeling referencing Zyrtec syrup includes PK information comparing the tablet and syrup (which is now referred to as a solution), which supports the position that the PK information is relevant to the Zyrtec syrup prescription labeling and would have been retained even if the product labeling had been updated appropriately after the full prescription to OTC switch.

11.3. Labeling

Recommendations from labeling consultants in OPDP were incorporated into the final label. Patient labeling was not consulted as there was no patient information labeling as this product is proposed to be used by a healthcare practitioner. The Division of Pediatrics and Maternal Health (DPMH) and the Office of Surveillance and Epidemiology (OSE) also reviewed the label and suggested changes to Section 8.4 and 10, respectively. Changes are described in Table 33 that are reflective of the final QUZYTTIR label received on October 2, 2019.

Table 33. Cetirizine IV Prescribing Information

Section	Proposed Labeling	Approved Labeling	Rationale
Highlights: Product Name	"QUZYTTIR is an H1 receptor antagonist indicated for the treatment of acute urticaria…"	"H1 receptor antagonist" was changed to "histamine-1 (H1) receptor antagonist"	Corresponds to the FDA established pharmacologic class text phrase for cetirizine.
Highlights: Product Name	Initial U.S. Approval: 199 (b) (4)	Initial U.S. Approval: 1995	Cetirizine, as a new molecular entity, was first approved in 1995 under NDA 019835
Highlights: Dosage and Administration	6 months (b) (4) to 5 years: 2.5 mg	6 months to 5 years: 2.5 mg	(b) (4)
Highlights: Dosage Forms and Strengths	(b) (4)	"Injection: 10 mg/mL single-use vial"	Based on the UPS <1121>the correct term is injection

Section	Proposed Labeling	Approved Labeling	Rationale
Highlights: Contraindications	"Known hypersensitivity to cetirizine, levocetirizine, or hydroxyzine."	"Known hypersensitivity to cetirizine or any of its ingredients, levocetirizine, or hydroxyzine."	Revised to account for hypersensitivity to other ingredients"
Highlights: Adverse Reactions	"The most common adverse reactions (incidence greater than 2%) are (b) (4) s, headache, (b) (4) (6)"	"The most common adverse reactions (incidence less than 1%) with QUZYTTIR are dysgeusia, headache, paresthesia, presyncope, dyspepsia, feeling hot, and hyperhidrosis. Most common adverse reactions (incidence equal to or greater than 2%) with use of oral cetirizine are somnolence, fatigue, dry mouth, pharyngitis, and dizziness. (6)"	Updated to include most common adverse reactions for QUZYTTIR and clarified the common AEs for oral cetirizine.
(b) (4)	Removed		(b) (4)
6	(b) (4)	Created separate headings for oral and IV cetirizine. Added incidence rates of common AEs from Zyrtec® prescribing information. (b) (4)	For clarity
6.1 Clinical Trials Experience	(b) (4)	Removed AE and sedation table and replaced with text. Included IV cetirizine AEs in text.	We separated ETTAU-02 from ETTAU-03 as ETTAU-03 is the pivotal study and ETTAU-02 is considered supportive.
Section 7		Added "possible that larger theophylline doses could have a greater effect"	Included additional drug interaction

Section	Proposed Labeling	Approved Labeling	Rationale
Section 8.1 and 8.2		Additional detail added for nonclinical studies, based on general text and cetirizine data in the Zyrtec® label (revised label was approved on October 8, 2003) as well as the current Xyzal (levocetirizine dihydrochloride) label. Exposure margins were updated.	The Xyzal label was updated on April 2, 2019 to comply with the PLLR format, and a consult was requested to the DPMH. Exposure margins between animal data and clinical doses are based on mg/m^2 and 60 kg human weight.
Section 8.4 Pediatric Use		Revised to note that efficacy "down to 6 months of age is based on extrapolation of the efficacy of QUZYTTIR in adults with this condition and the likelihood that the disease course, pathophysiology and the drug's effect are similar between these two populations." Discussed details of safety of QUZYTTIR	Revised to comment that efficacy is supported by extrapolation from adult studies. Safety relied on oral cetirizine safety and the increased Cmax of IV supported by FAERS overdose cases with oral cetirizine which resulted in a higher exposure than the predicted Cmax with IV. The reliance of FAERS overdoses was reasonable given the context of use (acute condition in a medically supervised setting).
8.5 Geriatric Use	(b) (4)	"In clinical trials with QUZYTTIR, 18 patients were 65 years and older, and 6 patients were 75 years and older…"	Updated numbers for geriatric use with intravenous cetirizine based on data from the ETTAU-03 study.
8.6 and 8.7 Hepatic and Renal Impairment			The impact of organ impairment following IV administration of the proposed product is unknown. Additionally, due to lack of exposure-response data, the impact of C_{max} and AUC on the efficacy endpoint is unknown. Therefore, we recommend not to dose adjust for organ impairment and monitor patients for antihistaminic side effects.
Section 10 Overdosage	(b) (4)	Updated to include summary of additional adult and pediatric overdose cases.	Expanded this section to include adult and pediatric cases of overdose with oral cetirizine to further support safety. Reviewed by OSE.

Section	Proposed Labeling	Approved Labeling	Rationale
Section 11 Description	"H1 receptor antagonist"	"H1 receptor antagonist" was changed to "histamine-1 (H1) receptor antagonist"	Corresponds to the FDA established pharmacologic class text phrase for cetirizine.
Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Based on text in Zyrtec® label	Additional detail added for nonclinical studies, based on general text and cetirizine data in the Zyrtec® label (revised label was approved on October 8, 2003) as well as the current Xyzal (levocetirizine dihydrochloride) label.	Consistent with text from Xyzal label.

(b) (4)

Section	Proposed Labeling	Approved Labeling	Rationale
Section 14 Clinical Studies		Modified to focus on pivotal study (ETTAU-03) as ETTAU-02 was considered supportive.	For clarity
		(b) (4)	
Section 17 Patient Counseling Information	(b) (4)	Removed last paragraph	This section focused on major risk of the drug, therefore (b) (4) do not need to be included here. See guidance for industry *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2014) and 21 CFR 201.57(c)(18)

Abbreviations: AUC = area under the concentration-time curve; CFR = code of federal regulations; C_{max} = maximum concentration; FAERS = FDA Adverse Event Reporting System; IV = intravenous; DPMH = Division of Pediatric and Maternal Health; PLLR = Pregnancy and Lactation Labeling Rule

12. Risk Evaluation and Mitigation Strategies

Given the favorable safety profile of IV cetirizine there are no additional risk management strategies required.

13. Postmarketing Requirements and Commitment

No postmarketing requirements or postmarketing commitments were requested.

14. Division Director (or designated authority, clinical) Comments

The Applicant, JDP Therapeutics, has submitted a 505(b)(2) new drug application (NDA) for cetirizine hydrochloride (HCl) 10 mg/mL solution for intravenous (IV) injection for the treatment of acute urticaria in adults and children 6 months of age and older. This NDA presents a new dosage form, route of administration and indication for cetirizine, a second-generation histamine-1 (H1) receptor antagonist. The proposed dosing is: 2.5 mg (6 months to 5 years of age), 5 mg or 10 mg (6 to 11 years of age), and 10 mg (12 years of age and older). The proposed dosing regimen is once every 24 hours as needed for acute urticaria. As part of the 505(b)(2) regulatory pathway, the Applicant has referenced both oral cetirizine (Zyrtec®) and oral levocetirizine (Xyzal).

To support the proposed indication, the Applicant has provided data from three clinical trials (ETTAU-01, ETTAU-02, and ETTAU-03) to support this new dosage form, route of administration and indication. ETTAU-01 was a safety, tolerability, and PK trial in 24 healthy adult volunteers. ETTAU-02 and ETTAU-03 were double-blind, randomized, active-controlled trials in adults with acute urticaria comparing IV cetirizine to IV diphenhydramine. Trial ETTAU-02 enrolled 33 adults and was used to inform the non-inferiority margin for future studies. Trial ETTAU-03 was the pivotal efficacy/study to support the proposed indication.

Trial ETTAU-03 enrolled 262 adults and provided the pivotal efficacy data, as it was powered to assess the non-inferiority of IV cetirizine compared to IV diphenhydramine (based on the NI margin from ETTAU-02). The primary efficacy endpoint was the change from baseline in patient-rated pruritus score assessed 2 hours post-treatment administration. The mean (SD) change from baseline in patient-rated pruritus severity score on a scale of 0 to 3 was -1.61 (0.94) for cetirizine-treated subjects and -1.50 (0.98) for diphenhydramine-treated subjects. The least squares estimated treatment difference was 0.06 (95% CI = -0.281, 0.396; p=0.74). Since the lower bound of the 95% CI for the treatment difference, -0.28, was greater than -0.5 (predetermined NI margin), effectiveness of cetirizine injection was demonstrated to be noninferior to diphenhydramine injection. The key secondary endpoints also favored treatment with cetirizine.

No new safety concerns were identified compared to the well-known safety profile of oral cetirizine. Common AEs for IV cetirizine occurring with an incidence of less than 1% included dyspepsia, feeling hot, dysgeusia, headache, paresthesia, presyncope, and hyperhidrosis. Sedation was also lower for IV cetirizine compared to IV diphenhydramine.

From a pharmacokinetics (PK) perspective, following single-dose administration in healthy adult subjects, the 90% confidence interval (CI) for the geometric mean ratio (GMR) of 10 mg IV cetirizine and Zyrtec® 10-mg tablet for systemic exposure (AUC) was within the bioequivalence limits of 80% to 125%. Establishment of bioequivalence allows for reliance on some relevant information from oral cetirizine, via the 505(b)(2) regulatory pathway. While no pediatric PK studies were conducted, due to the linear/dose proportional PK characteristics, the systemic exposure (AUC) of IV cetirizine is expected to be comparable to that in adult patients. Therefore, efficacy in children < 18 years of age can appropriately be extrapolated from adequate, well-controlled adult studies of IV cetirizine data based on the similar clinical presentation of both adult and pediatric acute urticaria, consistency in therapeutic approach, mechanism of action, relevance of the clinical endpoints for both efficacy and safety, and PK showing similar oral cetirizine exposure for the recommended doses across different age groups.

While AUC is comparable between oral and IV cetirizine, peak concentration (geometric mean C_{max}), as would be expected, was 3.71-fold higher for the IV cetirizine drug product compared to Zyrtec® tablet. To provide support for the safety of the higher Cmax in adults, the safety of IV cetirizine was assessed in study ETTAU-03. Additionally, safety of higher than approved oral doses of cetirizine which would be expected to result in a higher C_{max} (i.e., up to 60 mg in a thorough QT study) have been assessed previously in adult subjects.

IV cetirizine was not studied in pediatric patients (6 months to 17 years of age). In terms of AUC, safety of IV cetirizine in pediatric patients down to 6 months of age is supported by data from oral cetirizine. However, to support the safety of the higher Cmax, we identified accidental overdose cases in pediatric patients in the FDA Adverse Event Reporting System

(FAERS). These overdose cases include sufficient exposures to cover the IV Cmax in this age group. While this is an atypical approach to address this issue, given the well-established safety profile of oral cetirizine, the availability of overdose data, the use of IV cetirizine in a limited (single-dose/24 hours) manner for acute treatment, and administration in a monitored setting, I agree with the assessment of the review team that the safety data is appropriate to cover the higher Cmax in pediatric patients.

Overall, the data submitted by the Applicant supports a favorable benefit-risk assessment for the use of IV cetirizine for the treatment of acute urticaria in patients aged 6 months or older. There are currently no approved therapies for the indication of acute urticaria. At this time, standard of care for the treatment of acute urticaria consists of diphenhydramine, and other antihistamines, with or without steroids. This application presents the first therapy approved specifically for acute urticaria. While cetirizine is available in different formulations, this application represents the first formulation for parenteral administration, and represents a meaningful addition to the treatment armamentarium for acute urticaria. I agree with the assessments of the different review disciplines. Labeling has been discussed and agreed upon with the Applicant. The regulatory action for this new drug application is *Approval.*

15. Appendices

15.1. References

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): ETTAU-03

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 21		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MIYA O PATERNITI
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