1. GENERAL INFORMATION

Clinical Study Protocol

A Randomized, Open-Label, Single-Dose, Five-Period Crossover, Relative Bioavailability Study to Evaluate Cetirizine HCl Gummy 10 mg and Cetirizine HCl Oral Tablets 10 mg Administered in Healthy Adult Male and Female Subjects

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3. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Seattle Gummy Company	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:** **Volume:** **Reference:**	**(For National Authority Use Only)**
Name of Finished Product: Ceteric™ Allergy Gummy Regular		
Name of Active Ingredient: Cetirizine HCl		

Title: A Randomized, Open-Label, Single-Dose, Five-Period Crossover, Relative Bioavailability Study to Evaluate Cetirizine HCl Gummy 10 mg and Cetirizine HCl Oral Tablets 10 mg Administered in Healthy Adult Male and Female Subjects

Protocol Number: P001-2019

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Phase of Development: Phase 1

Objectives:

Primary:

- To determine the relative bioavailability of a single oral dose of cetirizine HCl Gummy 10 mg and cetirizine HCl oral tablets 10 mg administered under fasted conditions in healthy adult male and female subjects.

Secondary:

- To determine the relative bioavailability of a single oral dose of cetirizine HCl Gummy 10 mg administered under fasted and fed conditions in healthy adult male and female subjects;
- To determine the relative bioavailability of a single oral dose of cetirizine HCl Gummy 10 mg administered under fasted conditions with and without water in healthy adult male and female subjects;
- To determine the relative bioavailability of a single oral dose of cetirizine HCl Gummy 10 mg administered under fasted conditions and chewed or swallowed whole in healthy adult male and female subjects.

Test drug:

Ceteric™ Allergy Gummy Regular 10 mg (cetirizine HCl Gummy 10 mg), manufactured by Seattle Gummy Company, 108 First Avenue South, Suite 408, Seattle, WA 98104.

Reference drug:

Zyrtec® 10 mg tablets (cetirizine HCl oral tablets 10 mg), manufactured by Pfizer labs, New York, NY 10017.

Number of Subjects Planned:

Approximately 30 eligible subjects will be randomized and dosed such that at least 24 subjects complete all five periods. The selection of sample size is empirical. However, based on the reported approximate 10% intra-subject variability of the Reference Zyrtec®10 mg tablet, it's expected that 24 completed subjects should be adequate for evaluation of relative bioavailability and PK in this single dose, 5-period crossover study. Assuming up to a 20% dropout rate, 30 subjects will be randomized in the study.

Study Design and Methodology:

This is an open-label, single dose, randomized, five-period, crossover design study to evaluate the relative bioavailability of a single oral dose of cetirizine HCl Gummy 10 mg (Test) and cetirizine HCl oral tablets 10 mg (Zyrtec®, Reference) under fasted conditions in healthy adult male and female subjects, and the impact on the bioavailability of cetirizine HCl Gummy 10 mg when administered with food, when administered with or without water, and when chewed or swallowed whole.

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Following a screening period of up to 28 days, eligible subjects will be enrolled and randomized to receive study drug. Subjects will be confined to the Clinical Research Unit (CRU) for two overnight stays during each of the five study periods.

Eligible subjects will receive a single oral dose of one of five treatments (Treatments A, B, C, D or E) in five separate periods in a randomly assigned sequence, with each treatment separated by an approximate 5-day washout period. In each study period dosing will occur in the morning after an overnight fast of at least 10 hours.

All doses will be administered under fasted conditions except for Treatment C, when cetirizine HCl Gummy 10 mg will be administered after consumption of a high-calorie, high-fat breakfast.

All doses will be administered with approximately 240 mL of room temperature water except for Treatment D, when cetirizine HCl Gummy 10 mg dose will be administered without water.

All doses of cetirizine HCl Gummy 10 mg will be chewed before swallowing except for Treatment E, when subjects will be instructed to swallow the dose whole.

Treatment	Treatment Description
A	Test: Single oral dose of cetirizine HCl Gummy 10 mg, chewed, administered with approximately 240 mL of room temperature water, under fasted conditions
B	Reference: Single oral dose of cetirizine HCl oral tablets 10 mg, administered with approximately 240 mL of room temperature water, under fasted conditions
C	Test: Single oral dose of cetirizine HCl Gummy 10 mg, chewed, administered with approximately 240 mL of room temperature water, under fed conditions
D	Test: Single oral dose of cetirizine HCl Gummy 10 mg, chewed, administered with no water, under fasted conditions
E	Test: Single oral dose of cetirizine HCl Gummy 10 mg, swallowed whole, administered with approximately 240 mL of room temperature water, under fasted conditions

In each study period, confinement to the CRU will begin the day prior to dosing during each period and continue until after collection of the 36-h pharmacokinetic (PK) post-dose sample the evening of the day following dosing. Subjects will be discharged from the study after exit procedures are completed on Day 22 in Period 5, or after Early Termination.

Following an overnight fast of at least 10 hours, subjects will receive a single oral dose of their assigned study drug with approximately 240 mL of room temperature water (except when assigned to Treatment D) at approximately 0800 hours (±1 hour). Subjects assigned to Treatment C will consume a standardized high calorie, high fat breakfast within approximately 30 minutes prior to dosing.

During each of the five study periods, serial PK blood samples to measure plasma concentrations of cetirizine will be collected by direct venipuncture or by use of an indwelling cannula prior to dosing (up to 60 minutes prior to dosing), 10, 20 minutes post-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36 hours post-dose. Where PK sampling time points coincide with vital sign measurements, vital signs will be collected ±10 minutes of the scheduled time point, and PK samples will be collected at the scheduled time point.

Height and weight will be measured and body mass index (BMI) will be calculated at Screening. A full physical examination (PE) will be performed at Screening, and an abbreviated PE will be performed at the Study Exit/Early Termination Visit. Physical examinations may be repeated prior to study discharge as deemed necessary by the Investigator or in response to adverse events (AEs).

Demographic information, medical history, and concomitant medication use (prescribed and over-the-counter [OTC] medications, including vitamin/supplement use) will be obtained at the Screening

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Visit. A review of all medications will be repeated at each Check-in and at Study Exit/Early Termination. Subjects will be queried from Check-in for Period 1 through Study Exit/Early Termination as to any changes in their overall health, and all treatment-emergent adverse events (TEAE) will be captured and documented throughout the study from the time a subject receives the first dose of study drug until 7 days after the subject receives the last dose of study drug.

A resting (i.e. after at least 5 minutes rest in the supine position) 12-lead electrocardiogram (ECG) will be obtained at the Screening Visit. Electrocardiograms may be repeated at other times as deemed necessary by the Investigator or in response to AEs. Seated (i.e., after at least 3 minutes rest in the sitting position) vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR), respiration rate (RR) and oral temperature, will be measured at the Screening Visit, and seated SBP, DBP and pulse rate will be measured within 120 minutes prior to each dose and at approximately 1, 4, 8 and 10 hours post-dose in each study period and at Study Exit/Early Termination.

Clinical laboratory testing (chemistry, hematology, urinalysis) will be conducted at the Screening Visit and at Study Exit/Early Termination.

Serology testing (HIV 1/2 antibodies, Hepatitis B surface antigen, Hepatitis C antibody) will be performed at Screening only. All subjects will undergo urine drug and saliva alcohol testing at Screening and at each Check-in Visit. Female subjects will have a serum pregnancy test at Screening and a urine pregnancy test at each Check-in Visit. Postmenopausal females will have serum follicle-stimulating hormone (FSH) and estradiol levels measured at Screening to confirm postmenopausal status.

A total of approximately 420 mL (6 mL x 14 x 5 periods) of blood will be collected over the five study periods for determination of plasma cetirizine. Additionally, blood samples (approximately 35 mL) will be obtained at Screening and Discharge/Early Termination for chemistry, hematology and serology evaluations, for a total of approximately 455 mL of blood collected during the study.

Duration of Treatment:

Total length of study participation will be approximately 23 days (excluding up to 28 days of screening).

Selection of Subjects:

Inclusion Criteria:

1. Are capable of giving informed consent and complying with study procedures;
2. Male or female, 18 to 55 years of age, inclusive, at date of consent;
3. Body mass index (BMI) $\geq$ 18.0 to $\leq$ 32.0 kg/m^2 and total body weight > 50 kg (110 lbs.) at Screening;
4. All female subjects must have a negative pregnancy test at Screening and at each Check-in Visit; and one of the following:
    a. Using a medically acceptable form of birth control for at least 1 month prior to first dose [e.g., hormonal contraceptives (oral, patch, injectable or vaginal ring), intrauterine device, or a double barrier method (e.g., diaphragm, cervical cap, oral, patch or vaginal hormonal contraceptive, condom, spermicide, or sponge)]
    b. Documented as surgically sterile by hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/tubal occlusion) at least 6 months prior to the first dose;
    c. Postmenopausal (no menstruation for a minimum of 12 months and confirmed by FSH and estradiol at Screening);
5. Medically healthy based on medical history, vital sign measurements, clinical laboratory test results, and physical examination;
6. Non-smokers (including nicotine-containing products) for at least 6 continuous months prior to the first dose.
7. Be willing and able to consume all contents of the standardized high calorie, high fat breakfast within 30 minutes prior to dosing.

Exclusion Criteria:

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1. Females who are pregnant, lactating, or planning to become pregnant during the study;
2. Life-time history and/or recent evidence of alcohol or drug/substance abuse disorder;
3. Subjects with history of hypersensitivity to cetirizine or hydroxyzine, or any component of the test and reference formulations;
4. Subjects who test positive at Screening for human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), or Hepatitis C virus (HCV) antibody;
5. Subjects who test positive at Screening or at Check-in for alcohol and/or drugs of abuse;
6. Subjects who donated ≥ 500 mL of blood within 56 days prior to the first dose of study drug or ≥ 50 mL and ≤ 499 mL of blood within 30 days or plasma (e.g. plasmapheresis) within 14 days prior to the first dose of study drug;
7. Use of prescription or non-prescription drugs, dietary supplements, or herbal supplements at the time of Screening and within 14 days prior to the first dose of the study drug;
8. Subjects who have a history of difficulty in donating blood or difficulty with phlebotomy procedures, and poor venous access;
9. Subjects who have participated in another clinical trial within 30 days prior to the first study period;
10. Member or first-degree relative of study staff or the Sponsor directly involved in the study;
11. Any condition which in the opinion of Investigator would interfere with the subject's ability to provide informed consent, comply with study instructions, confound interpretation of study results, or endanger the subject if he or she took part in the trial.

Pharmacokinetic and Safety Variables

Pharmacokinetic:

Plasma concentrations of cetirizine will be measured and PK parameters, including C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el} and $t_{1/2}$, will be determined using non-compartmental analysis methods (Phoenix WinNonlin software, version 8.1 or higher, Certara USA Inc., Princeton, NJ).

Safety:

Safety will be based on the frequency of AEs and changes in vital signs, clinical laboratory assessments and PE findings.

Statistical Methods and Planned Analysis:

The primary PK endpoints will be maximum plasma cetirizine concentration (C_{max}), and area under the plasma drug concentration versus time curve calculated to the last measurable observation (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$).

The secondary PK endpoints will be time to C_{max} (T_{max}), elimination half-life ($t_{½}$) and terminal elimination rate constant (K_{el}).

The safety and tolerability of single 10 mg oral doses of cetirizine HCl, as assessed by incidence of TEAEs, study discontinuation information, laboratory test results, vital signs and PE findings will be secondary endpoints.

Relative Bioavailability Comparisons:

The following comparisons will be assessed:

Treatment A / Treatment B

The relative bioavailability of the Test formulation (cetirizine HCl Gummy 10 mg, chewed) administered with 240 mL room temperature water under fasted conditions will be compared to the Reference formulation (cetirizine HCl oral tablets 10 mg) administered with 240 mL room temperature water under fasted conditions;

Treatment A / Treatment C

The relative bioavailability of the Test formulation (cetirizine HCl Gummy 10 mg, chewed) administered with 240 mL room temperature water under fasted conditions will be compared to the Test formulation

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(cetirizine HCl Gummy 10 mg, chewed) administered with 240 mL room temperature water under fed conditions;

Treatment A / Treatment D

The relative bioavailability of the Test formulation (cetirizine HCl Gummy 10 mg, chewed) administered with 240 mL room temperature water under fasted conditions will be compared to the Test formulation (cetirizine HCl Gummy 10 mg, chewed) administered without 240 mL room temperature water under fasted conditions;

Treatment A / Treatment E

The relative bioavailability of the Test formulation (cetirizine HCl Gummy 10 mg, chewed) administered with 240 mL room temperature water under fasted conditions will be compared to the Test formulation (cetirizine HCl Gummy 10 mg, swallowed whole) administered with 240 mL room temperature water under fasted conditions.

For each of the comparisons, confidence intervals (CIs; 90%) will be constructed to test the two one-sided hypotheses at the $\alpha = 0.05$ level of significance for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Log-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ will be analyzed using an analysis of variance (ANOVA) model with fixed effects for treatment and sequence, and a random effect of subject nested in sequence.

The arithmetic means, geometric means, and ratio of the geometric means and 90% CIs on the ratios of each comparison will be displayed.

Nonparametric analyses of T_{max} and $t_{1/2}$ (between Test and Reference formulations) may be performed using Wilcoxon Signed Rank Test. The corresponding 95% CI for the difference in medians will be reported using Walsh Averages and 25th and 75th percentiles of the Wilcoxon Signed Rank Statistic Test.

Plots of mean concentrations of plasma cetirizine versus time will be generated for each treatment group. Individual concentrations versus time graphs will also be provided.

Statistical tables will be generated using SAS version 9.4 or higher.

Adverse events will be coded using a standardized Medical Dictionary for Regulatory Activities (MedDRA), Version 22,0 or higher. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Enhanced Dictionary (March 2019 or later). The proportion of subjects experiencing AEs will be summarized by treatment group. Tabulations will be prepared including all AEs and all AEs by relationship and severity. Adverse events resulting in early termination and events meeting regulatory criteria for seriousness will also be tabulated separately. By-subject listings of all safety data and concomitant medication use will be generated.