TITLE PAGE

Protocol Title: A single centre, single dose, open-label, randomized, 2-part, 2-way crossover study to determine the bioequivalence of levocetirizine oral disintegrating tablet given with water and without water compared to levocetirizine immediate release tablet in healthy Japanese male subjects

Protocol Number: 204706

Compound Number: Levocetirizine

Study Phase: I

Short Title: Bioequivalence study between levocetirizine oral disintegrating tablet and levocetirizine immediate release tablet

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): Not applicable

Approval Date: 1-AUG-2018

SPONSOR SIGNATORY:

Kosuke Kozaiwa, VP & Board of Director, Vice Head, Japan Development, GlaxoSmithKline K.K.	**Date**

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	1-AUG-2018	2018N360906_02
Amendment 1	25-MAY-2018	2018N360906_01
Original Protocol	20-APR-2018	2018N360906_00

Amendment 1: 1-AUG-2018

Overall Rationale for the Amendment: for conducting the add-on subject study of Part 2

Section # and Name	Description of Change	Brief Rationale
1.1.Synopsis	To include the additional information of Part 2	In order to conduct the add-on study for Part 2
2.2.Background	To include the additional information of Part 2	In order to conduct the add-on study for Part 2
4.1.Overall Design	To include the additional information of Part 2	In order to conduct the add-on study for Part 2
9.2.3.Sample Size Re-estimation or Adjustment	To include the additional information of Part 2	In order to conduct the add-on study for Part 2

Amendment 1: 25-MAY-2018

Overall Rationale for the Amendment: Description maintenance

Section # and Name	Description of Change	Brief Rationale
9.1.Statistical Hypotheses	Description maintenance	In order to ensure consistency with statements in the statistical analysis plan
9.4.1.PK Analyses	Description maintenance	In order to ensure consistency with statements in the statistical analysis plan

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A single centre, single dose, open-label, randomized, 2-part, 2-way crossover study to determine the bioequivalence of levocetirizine oral disintegrating tablet given with water and without water compared to levocetirizine immediate release tablet in healthy Japanese male subjects

Short Title: Bioequivalence study between levocetirizine oral disintegrating tablet and levocetirizine immediate release tablet

Rationale: As a new dosage form of levocetirizine hydrochloride (hereafter levocetirizine) oral disintegrating tablet (ODT) is being developed for the purpose of boosting convenience and compliance for patients with allergic disease. The primary objective of this study is to evaluate the bioequivalence between levocetirizine ODT and levocetirizine immediate release tablet (IRT) in healthy Japanese male subjects.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence between levocetirizine ODT 5 mg (Test product) and levocetirizine IRT 5 mg (Reference product) in healthy Japanese male subjects.	• Plasma pharmacokinetic (PK) parameters of levocetirizine: AUC(0-t) and Cmax
Secondary	
• To assess the safety and tolerability following a single dose of levocetirizine 5 mg when given as levocetirizine ODT and levocetirizine IRT in healthy Japanese male subjects.	• Safety: Adverse events (AEs), changes from baseline in clinical laboratory tests, vital signs (blood pressure, pulse rate and body temperature), and 12-lead electrocardiogram (ECG) • Plasma PK parameters of levocetirizine: AUC(0-inf), tmax, t1/2, %AUCex, CL/F, Vz/F, kel and MRT
Exploratory	
• To evaluate the palatability of levocetirizine ODT.	• Palatability Questionnaire

Overall Design: This will be a single centre, single dose, open-label, randomized, 2-way crossover study in healthy Japanese male subjects. This study consists of two parts: Part 1 compares bioavailability of levocetirizine ODT and levocetirizine IRT taken with water in the fasted state, Part 2 compares bioavailability of levocetirizine ODT without water and levocetirizine IRT with water in the fasted state.

In both parts (Part 1 and Part 2), subjects will have a screening visit within 30 days prior to the first dose of study intervention, two-way crossover intervention periods, and a follow-up 5-7 days after the last dose. All subjects will be housed in the clinical research unit from Day -1 to 48 hours post-dose of each period for assessments.

In both parts (Part 1 and Part 2), a total number of 24 subjects will be equally divided into two groups (12 subjects in each group). All subjects will receive a single dose of levocetirizine 5 mg after an overnight fast (at least 10 hours) during the intervention period. Subjects will be administered one intervention of either levocetirizine ODT 5 mg or levocetirizine IRT 5 mg in Period 1 and then receive the alternate intervention in Period 2. There will be a washout period of at least 5 days between these periods.

Disclosure Statement: This is an open-label, 2-part, 2-way crossover study.

Number of Participants:

Sufficient subjects will be randomized such that 24 evaluable subjects complete both Part 1 and Part 2. There will be a total of 48 subjects in the 2 study parts. The definition of study complete is described in Section 4.4.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

If bioequivalence could not be demonstrated in Part 1 and/or Part 2 because of an insufficient number of subjects, an add-on subject study was to be performed with 12 (6 subjects in each group) or more subjects per part using the same methodology and according to the Japanese Guideline for Bioequivalence Studies of Generic Products [Japanese BE guideline, 2012].

Analyses of the Part 2 results indicated that BE was not demonstrated. Considering the possibility noted in the protocol of adding further subjects to meet the BE criteria, , an add-on study with the same design as Part 2 will be performed. An additional 24 subjects (12 subjects in each group) will be studied to increase the number of subjects to be included in the BE assessment.

Intervention Groups and Duration:

Subjects will participate either in Part 1 or Part 2, and receive the study interventions shown below.

Part 1 (Dosing of levocetirizine ODT with water)

- Single dose of levocetirizine ODT 5 mg x 1 with 150 mL of water in the fasted state

- Single dose of levocetirizine IRT 5 mg x 1 with 150 mL of water in the fasted state

Group	n	Period 1	Period 2
A	12	Levocetirizine IRT 5 mg (with water)	Levocetirizine ODT 5 mg (with water)
B	12	Levocetirizine ODT 5 mg (with water)	Levocetirizine IRT 5 mg (with water)

Part 2 (Dosing of levocetirizine ODT without water)

- Single dose of levocetirizine ODT 5 mg x 1 without water in the fasted state NOTE: ODT is placed on the subject's tongue, infiltrated with saliva, collapsed gently with the tongue, then swallowed with saliva without water.

- Single dose of levocetirizine IRT 5 mg x 1 with 150 mL of water in the fasted state

Group	n	Period 1	Period 2
C	12	Levocetirizine IRT 5 mg (with water)	Levocetirizine ODT 5 mg (without water)
D	12	Levocetirizine ODT 5 mg (without water)	Levocetirizine IRT 5 mg (with water)

Blood sampling for pharmacokinetic (PK) analysis will be performed prior to dosing and until 48 hours post-dose during each intervention period. The duration of each subject's participation in each part will be approximately 7 weeks from screening to follow-up.

A palatability questionnaire will be administered to each subject following dosing of ODT treatments only.

Data Monitoring Committee: No

1.2. Schedule of Activities (SoA)

Procedure	Screening[2]	Part 1 and Part 2 Intervention period (Period 1 and Period 2)																	Follow-up[3]
		Day -1	Day 1													Day 2		Day 3	
			Pre dose	0 h	0.25 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	9 h	12 h	16 h	24 h	36 h	48 h	
Informed consent	X																		
Admission to unit		X																	
Height, Weight, Body mass index (BMI)	X																		
Physical examination	X	X	X				X									X		X	X
Serology test	X																		
Clinical laboratory test[1]	X		X															X	X
Urine drug screen	X																		
12-lead ECG	X		X				X											X	X
Vital signs	X		X				X									X		X	X
PK blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study intervention				X															
Palatability questionnaire[4]				X															
AEs				←														→	
Discharge from unit																		X	

1. Clinical laboratory test: haematology, clinical chemistry, and urinalysis
2. Screening: up to 30 days prior to Day 1 of Period 1
3. Follow-up: 5-7 days post dose of Period 2
4. Palatability questionnaire will be administered to each subject within 10 minutes following dosing of ODT treatments only

2. INTRODUCTION

Levocetirizine is one of the two enantiomers (*R*-enantiomer: levocetirizine, *S*-enantiomer: dextrocetirizine) of racemic cetirizine hydrochloride (hereafter cetirizine). Levocetirizine has high affinity and selective antagonistic activity against histamine H1 receptors that is 30-fold higher than that of dextrocetirizine [Yanai, 2011], and as an active component of cetirizine, exerts an inhibitory effect on eosinophil chemotaxis with negligible penetration into the central nervous system (CNS) due to a hydrophilic group. In view of these characteristics, levocetirizine is classified as a second generation antihistamine and considered to be a highly useful drug in the treatment of allergic diseases.

2.1. Study Rationale

The primary objective of this study is to evaluate the bioequivalence between levocetirizine ODT and levocetirizine IRT in healthy Japanese male subjects.

2.2. Background

In Japan, levocetirizine IRT (brand name: Xyzal® Tablets 5 mg) has been approved since October 2010 for the indications of allergic rhinitis, urticaria, eczema/dermatitis group, prurigo and cutaneous pruritus and used in adults and children aged between 7 and 15 years. In addition, levocetirizine syrup (brand name: Xyzal® Syrup 0.05%) has been approved since January 2014 to be used in children aged on or over 6 months and under 7 years, on or over 7 and under 15 years and adults for the same indications.

As a new dosage form of levocetirizine, the ODT is being developed for the purpose of boosting convenience and compliance for patients with allergic disease.

To date, two clinical pharmacology studies comparing the same dose of levocetirizine contained in different formulations were conducted in healthy Japanese male subjects, confirming that levocetirizine exposure in plasma was equivalent between formulations when given as levocetirizine IRT 5 mg and as cetirizine IRT 10 mg [Ino, 2010], and when given as levocetirizine oral solution 5 mg and as cetirizine dry syrup 10 mg [Ino, 2014]. In the safety endpoints of both studies, no adverse events (AEs) were reported, and no clinically significant abnormalities were observed for the results of the following examinations: vital signs, 12-lead electrocardiogram ECG), or clinical laboratory tests. Additional information can be found in the Xyzal® package inserts and the Japanese Drug Interview Form.

Bioequivalence between levocetirizine ODT and levocetirizine IRT was evaluated in 48 healthy Japanese male subjects (Part 1; 24 subjects, Part 2; 24 subjects) during May to June 2018, and statistical analyses were initially completed for Part 2. In Part 2, 23 subjects completed the study and one subject withdrew from the study for personal reasons. While no adverse event was reported after dosing of levocetirizine IRT, 5 adverse events were reported in 4 subjects who received levocetirizine ODT; Diarrhoea, Tonsillitis, Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased and Neck pain. ALT increased and AST increased, which were observed in one subject, were considered to be related to the study treatment by the investigator. Intensity

of tonsillitis was moderate, and intensity of the remaining AEs was mild. As BE was not demonstrated in Part 2, considering the possibility of adding further subjects to meet the BE criteria, an add-on study with the same design as Part 2 will be performed. An additional 24 subjects (12 subjects in each group).will be studied to increase the number of subjects to be included in the BE assessment.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs associated with levocetirizine may be found in the Xyzal® package insert and Japanese Drug Interview Form.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., Levocetirizine]		
Shock, Anaphylaxis	Adverse reaction reports related to shock and anaphylaxis have been issued overseas and these events are also described in the Company Core Safety Information (CCSI).	To ensure subjects' safety during this study, safety monitoring will be performed as described in Section 8.1. The study is being run at a clinical pharmacology unit which has all relevant emergency services available.
Convulsion	Adverse reaction reports related to convulsion have been issued overseas and this event is also described in the CCSI.	To ensure subjects' safety during this study, safety monitoring will be performed as described in Section 8.1. The study is being run at a clinical pharmacology unit which has all relevant emergency services available.
Hepatic dysfunction, Jaundice	Adverse reaction reports related to hepatic dysfunction and jaundice have been issued overseas and these events are also described in the CCSI.	Safety, and pre-defined stopping criteria are included in Section 7.1. To ensure subjects' safety during this study, safety monitoring will be performed as described in Section 8.1. Subjects will not be discharged from the unit until the Investigator has reviewed all the available safety data.
Thrombocytopenia	Adverse reaction reports related to thrombocytopenia have been issued overseas.	To ensure subjects' safety during this study, safety monitoring will be performed as

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		described in Section 8.1. Subjects will not be discharged from the unit until the Investigator has reviewed all the available safety data.

2.3.2. Benefit Assessment

This study is being conducted in healthy Japanese male subjects with no significant medical history. Subjects will not receive benefit from participation in this study.

2.3.3. Overall Benefit: Risk Conclusion

Pre-clinical and clinical data to date do not indicate that single dose levocetirizine at the exposure planned for this study is associated with excessive risks.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence between levocetirizine ODT 5 mg (Test product) and levocetirizine IRT 5 mg (Reference product) in healthy Japanese male subjects.	• Plasma PK parameters of levocetirizine: AUC(0-t) and Cmax
Secondary	
• To assess the safety and tolerability following a single dose of levocetirizine 5 mg when given as levocetirizine ODT and levocetirizine IRT in healthy Japanese male subjects.	• Safety: AEs, changes from baseline in clinical laboratory tests, vital signs (blood pressure, pulse rate and body temperature), and 12-lead ECG • Plasma PK parameters of levocetirizine: AUC(0-inf), tmax, t1/2, %AUCex, CL/F, Vz/F, kel and MRT
Exploratory	
• To evaluate the palatability of levocetirizine ODT.	• Palatability Questionnaire

4. STUDY DESIGN

4.1. Overall Design

This will be a single centre, single dose, open-label, randomized, 2-way crossover study in healthy Japanese male subjects. This study consists of two parts: Part 1 compares bioavailability of levocetirizine ODT and levocetirizine IRT taken with water in the fasted state, Part 2 compares bioavailability of levocetirizine ODT without water and levocetirizine IRT with water in the fasted state.

In both parts (Part 1 and Part 2), subjects will have a screening visit within 30 days prior to the first dose of study intervention, two-way crossover intervention periods with at least a 5-day washout period, and a follow-up visit 5-7 days after the last dose. All subjects will be housed in the clinical research unit from Day -1 to 48 hours post-dose of each period for assessments.

In both parts (Part 1 and Part 2), a total number of 24 subjects will be equally divided into two groups (12 subjects in each group) and will be randomized in a 1:1 ratio (to one of two groups in each part). Subjects will only participate in either Part 1 or Part 2. All subjects will receive a single dose of levocetirizine 5 mg after an overnight fast (at least 10 hours) during the intervention period as shown below.

Part 1 (Dosing of levocetirizine ODT with water)

- Single dose of levocetirizine ODT 5 mg x 1 with 150 mL of water in the fasted state
- Single dose of levocetirizine IRT 5 mg x 1 with 150 mL of water in the fasted state

Group	n	Period 1	Period 2
A	12	Levocetirizine IRT 5 mg (with water)	Levocetirizine ODT 5 mg (with water)
B	12	Levocetirizine ODT 5 mg (with water)	Levocetirizine IRT 5 mg (with water)

Part 2 (Dosing of levocetirizine ODT without water)

- Single dose of levocetirizine ODT 5 mg x 1 without water in the fasted state
  NOTE: ODT is placed on the subject's tongue, infiltrated with saliva, collapsed gently with the tongue, then swallowed with saliva without water.
- Single dose of levocetirizine IRT 5 mg x 1 with 150 mL of water in the fasted state

Group	n	Period 1	Period 2
C	12	Levocetirizine IRT 5 mg (with water)	Levocetirizine ODT 5 mg (without water)

D	12	Levocetirizine ODT 5 mg (without water)	Levocetirizine IRT 5 mg (with water)

Blood sampling for PK analysis will be performed prior to dosing and until 48 hours post-dose during each intervention period. The duration of each subject's participation in each part will be approximately 7 weeks from screening to follow-up.

A palatability questionnaire will be administered to each subject following dosing of ODT treatments only.

Sufficient subjects will be randomized such that 24 evaluable subjects complete both Part 1 and Part 2. There will be a total of 48 subjects in the 2 study parts. The definition of the study complete is described in the Section 4.4.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

If bioequivalence could not be demonstrated in Part 1 and/or Part 2 because of an insufficient number of subjects, an add-on subject study was to be performed with 12 (6 subjects in each group) or more subjects per part using the same methodology and according to the Japanese BE guideline.

Initial analyses demonstrated that BE was not demonstrated in Part 2. Considering the possibility noted in the protocol of adding further subjects to meet the BE criteria, an add-on study with the same design as Part 2 will be performed. An additional 24 subjects (12 subjects in each group) will be studied to increase the number of subjects to be included in the BE assessment.

4.2. Scientific Rationale for Study Design

This study is a 2-way crossover study to demonstrate the bioequivalence of levocetirizine following single oral doses of levocetirizine ODT 5 mg and levocetirizine IRT 5 mg in healthy Japanese male subjects.

Aligned to the Japanese BE guideline, this study is single dose and study interventions will be given to healthy subjects with 150 mL of water after fasting for at least 10 hours. Fasting lasts for at least 4 hours post-dose.

Current Japanese approval reviews of ODTs require that the bioequivalence studies are conducted both with and without water being given with the ODT. Therefore this study evaluates single doses of levocetirizine ODT administered with water (Part 1) and without water (Part 2).

In previous studies in healthy Japanese, the terminal phase t1/2 of levocetirizine reported was approximately 8 hours subjects [Ino, 2010, Ino, 2014]. Therefore, it was decided to

continue observation/examination of subjects for up to 48 hours after each dose of study intervention, to set the washout periods to be ≥5 days, and to set the follow-up visit to be at 5-7 days after the dose in Period 2 of both Part 1 and Part 2.

4.3. Justification for Dose

Levocetirizine IRT and dry syrup has been approved and marketed in Japan. The recommended single dosage for Japanese adults is levocetirizine 5 mg (as levocetirizine hydrochloride), though this dosage may be increased up to 10 mg/day. The Japanese BE guideline generally recommends that one dose unit or a clinical usual dose should be employed. Thus, 5 mg was the dose of levocetirizine ODT and levocetirizine IRT selected for evaluation in this study.

4.4. End of Study Definition

A participant is considered to have completed the study if he has completed all phases of the study including the last follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 20 to 55 years of age inclusive, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Japanese participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring

Weight

3. Body weight of ≥50 kg and body mass index (BMI) within the range of ≥18.5 and <25.0 kg/m^2

Sex

4. Male

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period and until the completion of follow-ups:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
    - Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
    - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

Tobacco

5. Participants must be non-smokers

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data
2. Abnormal blood pressure as determined by the investigator
3. History of allergic rhinitis

4. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
5. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
7. QT interval correction (QTc) >450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF) machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the participant from the trial.

Prior/Concomitant Therapy

8. Past or intended use of over-the-counter or prescription medication including vitamins, diet supplements (including St. John's wort), herbal medications within 14 days prior to first dosing or 5 half-lives (whichever is longer). Specific medications listed in Section 6.5 may be allowed

Prior/Concurrent Clinical Study Experience

9. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day
10. Current enrolment or past participation within 4 months prior to the first dosing day in this or any other clinical study involving an investigational study intervention or any other type of medical research (except for the participants with no study intervention administered during any of those enrolment or participation)

Diagnostic Assessments

11. The participant with positive serological test for syphilis (Rapid Plasma Reagin [RPR] and Treponema pallidum [TP] antibody tests), Human immunodeficiency virus (HIV) Antigen/Antibody, Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV) antibody, or Human T-cell lymphotropic virus type 1 (HTLV-1) antibody at screening
12. Positive pre-study drug screen

Other Exclusions

13. Regular moderate alcohol consumption within 6 months prior to the study participation defined as:

    - An average weekly intake of >14 units for males. One unit is equivalent to 360 mL of beer, 150 mL of wine or 45 mL of 80 proof distilled of spirits.

14. Smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening
15. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates participation in the study
16. History of donation of blood or blood products ≥400 mL within 3 months or ≥200 mL within 1 month prior to the first dosing day

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study intervention until after collection of the final PK sample.
- Subjects will refrain from any food and drink (except water) at least 10 hours before dosing and 4 hours after dosing.
- No water is allowed until 2 hours after dosing, water is allowed ad libitum at all other times.

5.3.2. Caffeine, Alcohol and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- During each dosing session participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from screening until after the final follow-up visit.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the clinical studies (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

ARM Name	Reference formulation	Test formulation
Intervention Name	Levocetirizine IRT 5 mg	Levocetirizine ODT 5 mg
Dose Formulation	Film-coated Tablets	Oral Disintegrating Tablets
Unit Dose Strength(s)	5 mg	5 mg
Dosage Level(s)	5 mg of single dose Part 1: with 150 mL water Part 2: with 150 mL water	5 mg of single dose Part 1: with 150 mL water Part 2: without water
Route of Administration	Oral	Oral
Sourcing	GSK	Zensei Pharmaceutical Co., Ltd.
Packaging and Labelling	Study Intervention will be provided in container. Each container will be labelled as required per country requirement.	Study Intervention will be provided in container. Each container will be labelled as required per country requirement.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual (SRM).

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open label study. Subjects will be assigned to one of two groups in each part in accordance with the randomization schedule generated by the Biomedical Data Science Department at GSK, prior to the start of the study.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

6.6. Dose Modification

This protocol allows no dose modification.

6.7. Method of Treatment Assignment

Subjects will be assigned to one of two groups in each part, in accordance with the randomization schedule generated by Biomedical Data Sciences Department at GSK, using validated internal software prior to the start of the study.

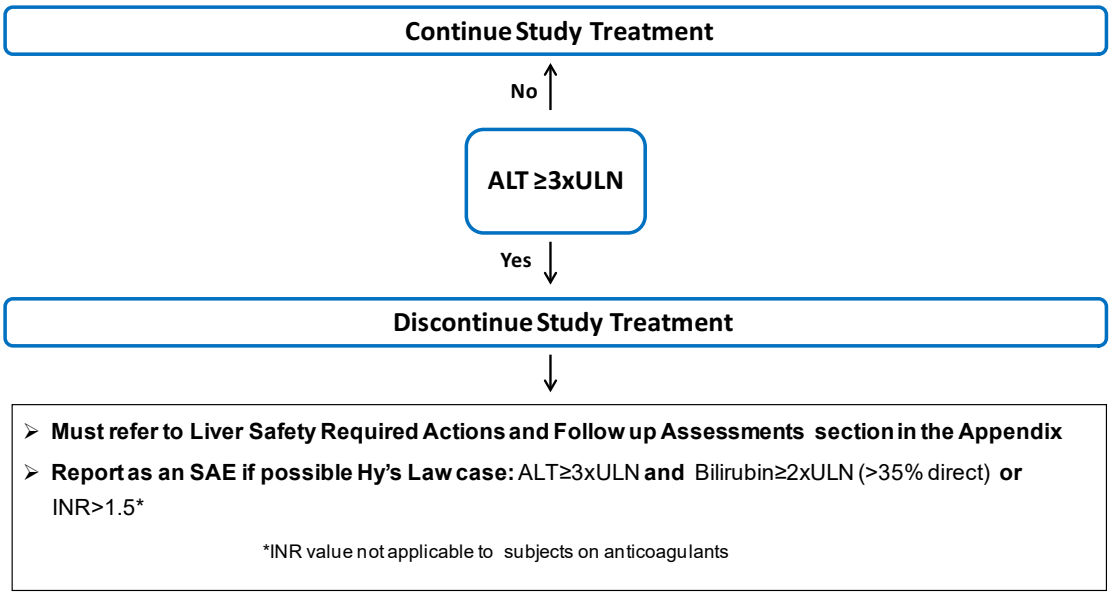
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

7.1.1. Liver Chemistry Stopping Criteria

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: INR = international normalized ratio.

Liver Safety Required Actions and Follow-up Assessments Section can be found in Appendix 5.

7.1.2. QTc Stopping Criteria

If the single QTc value meets either bulleted criterion, the additional double QTc values should be obtained over a brief (e.g., 5-10 minute) recording period. A subject that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study intervention.

- QTcF >500 msec

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 400 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.2).

8.1.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded at the Screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.1.2. Vital Signs

- Axillary temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

8.1.3. ECG

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF. Refer to Section 7.1 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

8.1.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the Case Report Form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.2).

8.2. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the subject to discontinue the study intervention (see Section 7).

8.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.2). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, or invasive tests) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.2).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- All AEs related to Levocetirizine IRT 5 mg will be recorded and reported to the sponsor within 24 hours as indicated in Section 10.3.4.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.2.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure (IB) and will notify the IRB, if appropriate according to local requirements.

8.2.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3. Treatment of Overdose

For this study, any dose of levocetirizine greater than 5 mg within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for AE/SAE and laboratory abnormalities until levocetirizine can no longer be detected systemically (at least 14 days).
3. Obtain a plasma sample for PK analysis within 14 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.4. Pharmacokinetics

- Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of levocetirizine at the times specified in the SoA (Section 1.2)
- The actual date and time (24 h clock time) of each sample will be recorded.
- Instructions for the collection and handling of biological samples will be provided by the sponsor.

8.5. Palatability Assessment

A palatability questionnaire will be administered to each subject within 10 minutes following dosing of ODT treatments only, see Appendix 6. Subjects will be given the questionnaire to read prior to receiving the ODT.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This study is designed to test the bioequivalence of levocetirizine ODT 5 mg (with water or without water) relative to levocetirizine IRT 5 mg.

The null hypothesis is that the true ratio of the geometric mean of the levocetirizine ODT 5mg (μ_{test}) to the geometric mean of the levocetirizine IRT 5mg (μ_{ref}), μ_{test}/μ_{ref}, for each primary PK endpoint (AUC(0-t) and Cmax of levocetirizine), is either less than or equal to 0.80 or greater than or equal to 1.25. The alternative hypothesis is that the true ratio of the test treatment geometric mean to the reference treatment geometric mean is greater than 0.80 and less than 1.25.

Symbolically, this is expressed as follows:

H_0: $\mu_{test}/\mu_{ref} \leq 0.80$ or $\mu_{test}/\mu_{ref} \geq 1.25$,

i.e., treatments are not bioequivalent.

Versus

H_1: $0.80 < \mu_{test}/\mu_{ref} < 1.25$,

i.e., treatments are bioequivalent.

These hypotheses will be considered for levocetirizine ODT 5 mg with water or without water separately, relative to levocetirizine IRT 5 mg.

For each PK parameters, designated as a primary endpoint (AUC(0-t) and Cmax), a two one-sided t-test (TOST) procedure [Schuirmann, 1987] with $\alpha = 0.05$ for each one-sided test will be used to test this set of hypotheses. This is equivalent to requiring that a 90% interval for the true ratio of levocetirizine ODT 5 mg to levocetirizine IRT 5 mg geometric means (μ_{test}/μ_{ref}) falls entirely within the range of 0.80 to 1.25. A judgment by 90% confidence interval (CI) will be conducted in this study.

However, even though the confidence interval is not in the above range, test products are accepted as bioequivalent, if the geometric means (μtest/μref) falls within a range of 0.90 to 1.11., which is in line with the Japanese BE GL.

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

Sample size calculation is based on the within-subject estimates of variability (CVw%). CVw% of about 6% and 11% for AUC(0-48) and Cmax were observed, respectively, in a previous study in healthy Japanese male subjects (LOC116459).

Assuming CVw% of 22% (double of 11%) conservatively, it is estimated that sample size of 23 subjects will provide at least 90% power to demonstrate bioequivalence in each part. Considering the treatment assignment, a total of 24 healthy Japanese male subjects will be enrolled in each part of this study. This calculation is based on TOST procedure with each type 1 error rate of 5% and assumes a true ratio of 1.00. This procedure is corresponding to acceptance criteria for 90% CI.

9.2.2. Sample Size Sensitivity

Some sample size sensitivity calculations have been performed to assess robustness of sample size with deviations in the assumptions.

Powers by changing assumptions in case of a sample size of 24 subjects are shown below.

Geometric means ratio	Within-subject CVw%			
	17%	20%	23%	26%
0.95	96.2%	89.6%	80.7%	70.4%
1.00	99.5%	96.7%	90.2%	80.0%
1.05	96.6%	90.3%	81.6%	71.3%

9.2.3. Sample Size Re-estimation or Adjustment

Sample size re-estimation will not to be conducted in this study. However, after completing the study, if bioequivalence could not be demonstrated in Part 1 and/or Part 2 because of an insufficient number of subjects, following the Japanese BE guideline, an add-on subject study could be performed in the same manner using not less than half the number of subjects in the initial study. The add-on subject study was to be performed using 12 (6 subjects in each group) or more subjects in each part.

In Part 2, using 24 subjects the ratio of the geometric means for the AUC(0-t) of levocetirizine ODT 5 mg to levocetirizine IRT 5 mg was 0.964 and the 90%CI was 0.942 to 0.987, which met the BE criteria. However, the ratio for Cmax was 0.828 and the 90% CI was 0.762 to 0.900, which did not meet the BE criteria. Therefore, BE was not demonstrated in Part 2 of the study. For Cmax, the f %CVw (16.6%) was smaller than the 22% value expected at study planning. However, the ratio 0f 0.828 was different from unity, the assumption at the time of study planning. This may be the reason why BE was not shown in Part 2 of this study. Considering the possibility of meeting the BE criteria by adding further subjects an add-on study with the same design as Part 2 will be performed. An additional 24 subjects (12 subjects in each group) will be studied to increase the number of subjects to be included in the BE assessment.

When an add-on subject study is conducted, the data of the two studies would be combined for analysis.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	Consisting of all participants screened in the study.
Screening Failure	Participants who sign the ICF in the study but are never subsequently randomized. All participants who sign the ICF have the screening test in the study.
Safety	All randomized participants who take at least one dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	This population is defined as all participants administered at least one dose of study treatment and who have blood for plasma drug concentration sample taken and analyzed. Participants will be analyzed according to the treatment they actually received.

9.4. Statistical Analyses

This study will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Final analysis will be performed for each part after completing the following procedures.

1. All participants completed the study.
2. All required database cleaning is completed and data management declares the final database release (DBR) and database freeze (DBF).

For an add-on subject study, the procedures same as above will be performed.

Statistical analysis will be performed for each part separately.

Complete details of the planned statistical analyses will be provided in the Reporting and Analysis Plan (RAP).

9.4.1. PK Analyses

All PK analyses will be performed on the PK Population for each part (Part 1 and Part 2). Further details will be provided in the RAP.

Statistical Analysis Methods
Plasma Drug Concentrations: Plasma levocetirizine concentration-time data will be analysed by non-compartmental methods with WinNonlin (version 6.3 or higher). Calculations will be based on the actual sampling times recorded during the study.

PK Parameters:

From the plasma concentration-time data, the following PK parameters will be determined, as data permit: AUC(0-t), Cmax, AUC(0-inf), Cmax, tmax, t1/2, %AUCex, CL/F, Vz/F, kel, and MRT.

PK parameters will be presented in graphical and/or tabular form and will be summarised descriptively.

Listings will be generated and summary statistics (n, arithmetic mean with associated 95% CI, standard deviation (SD), minimum, median, maximum, geometric mean with associated 95% CI, SD on log-scale and %CVb) will be calculated for each derived plasma PK parameter for each dose.

Bioequivalence between Levocetirizine IRT 5 mg and Levocetirizine ODT 5 mg with and without water (Part 1 and Part 2):

The bioequivalence in both parts (Part 1 and Part 2) will be evaluated according to the criteria described in the Japanese BE Guideline. For both Part 1 and Part 2, after loge-transformation, AUC(0-t) and Cmax of levocetirizine 5 mg when given as ODT or IRT will be analyzed separately using mixed effects model fitting for intervention and period as fixed effects and subject as random effect. The Kenward & Roger (KR) degrees of freedom approach will be used. Point estimates and associated 90% CIs for the difference in means of two interventions [$\log\mu_{test}$ - $\log\mu_{ref}$] will be constructed using the residual variance. These estimate values will then be exponentially back-transformed to provide point estimates and associated 90% CIs for the geometric mean ratio [μ_{test}//μ_{ref}].

In both parts (Part 1 and Part 2), the two interventions are considered to be bioequivalent, if the 90% CIs of the geometric mean ratio of AUC(0-t) and Cmax are within the acceptable range “0.80 - 1.25”.

However, even though the confidence interval is not in the above range, test products are accepted as bioequivalent, if the geometric means (μtest/μref) falls within a range of 0.90 to 1.11., which is in line with the Japanese BE GL.

The same analysis for AUC (0-t) and Cmax will be performed to evaluate bioequivalence of other reference PK parameters (AUC (0-inf), kel, MRT, tmax). For tmax, however, the point estimate value of the median difference and the 90% CI will be calculated using the nonparametric Wilcoxon matched pair method (signed rank order method) (the difference is levocetirizine ODT 5 mg - levocetirizine IRT 5 mg).

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Statistical Analysis Methods
AEs, clinical laboratory values, vital signs, ECG will be summarized by dose in each part. No formal statistical comparisons will be made for the safety data.

9.4.3. Exploratory analyses

Exploratory analysis will be performed on the Safety Population.

Statistical Analysis Methods
Palatability questionnaire items will be summarized descriptively. Further details will be provided in the RAP.

9.4.4. Interim Analyses

No interim analysis is planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
    - The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and the Pharmaceuticals and Medical Devices Act.
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
    - Notifying the IRB of SAE or other significant safety findings as required by IRB procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the Clinical Study Report (CSR). The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic (e)CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies

require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the list of the source documents.

10.1.8. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not

as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet count Red blood cells (RBC) count White blood cells (WBC) count Haemoglobin Haematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) Mean corpuscular haemoglobin concentration (MCHC) Reticulocytes (‰)	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate transaminase (AST) / Serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT / Serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
	Uric acid	Triglyceride	Total cholesterol	Low density lipoprotein (LDL) cholesterol
	High density lipoprotein (HDL) cholesterol	Lactate dehydrogenase (LDH)	Gamma-glutamyltransferase (GT) / Gamma glutamyl transpeptidase (GGT)	Creatine kinase (CK) / Creatine phosphokinase (CPK)
	Amylase	Chloride	Inorganic phosphrus	
Routine Urinalysis	• Specific gravity			

Laboratory Assessments	Parameters
	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Urine drug screen (to include at minimum: Phencyclidines [PCP], Benzodiazepines [BZO], Cocaine [COC], Amphetamines [AMP], Tetrahydrocannabinol [THC], Opiates [OPI], Barbiturates [BAR], Trycyclic antidepressants [TCA]) • Serology (Syphilis [RPR & TP], HIV antigen/antibody, HTLV-1 antibody, HBsAg, and HCV antibody)

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5. All events of ALT ≥3 ×ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**

- **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually

be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention

and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found in Appendix 7.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Contraception Guidance:

Male participants

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral
Highly Effective Methods That Are User Independent
• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and until the completion of the follow-ups.

10.4.2. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.

- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria and required follow-up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥3xULN
If ALT ≥3xULN AND bilirubin[1,2] ≥2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow-Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow-up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow-up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within 24 hours
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for PK analysis within 24 hours of last dose[4]
• Serum CPK and LDH
• Fractionate bilirubin, if total bilirubin ≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative</td></tr>
</table>

Liver Chemistry Stopping Criteria	
perform liver event follow-up assessments within **24-72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that subject if ALT ≥3xULN and bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the threshold value stated will not apply to subjects receiving anticoagulants.
3. Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and Hepatitis B core antibody (HBcAb); Hepatitis C ribonucleic acid (RNA); Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody.
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.6. Appendix 6: Palatability Questionnaire

The following questionnaire will be administered to each subject within 10 minutes following 5 mg dose of the Levocetirizine where it is given as an ODT.
Subjects will be given the questionnaire to read prior to receiving this dose.

Subject #: _____ Date: _____ Treatment: _____

1. Please briefly describe the taste of the product in your own words (one word, short phrase descriptions are acceptable).

2. Please rate the palatability (acceptability of taste) of the product by checking a rating below.

____ 1 = unacceptable (would not use product under any circumstances)
____ 2 = neutral/acceptable
____ 3 = very good

3. Please check **all** the descriptors that apply to the product.

_____ Sweet

_____ Sour/tart

_____ Bitter

_____ Fruity

_____ Nutty

_____ Chalky

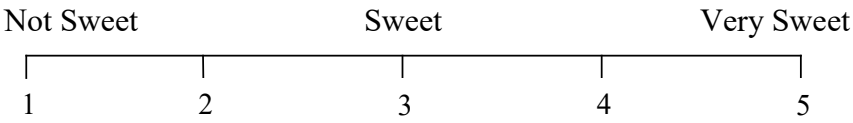
_____ Medicinal

4. Please rate the mouth feel of the product by checking a rating below.

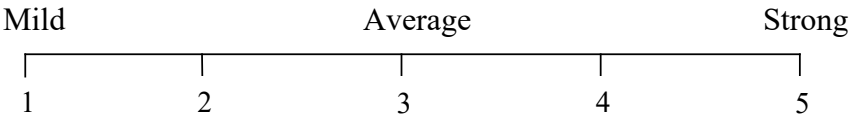
_____ 1 = unacceptable (would not use product under any circumstances)
_____ 2 = neutral/acceptable
_____ 3 = very good

5. For each of the following attributes please circle the number that best describes your perception of each attribute.

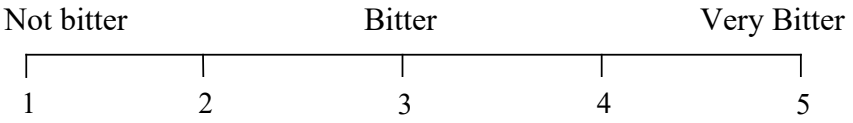
a. Sweetness



b. Sour/tartness



c. Bitterness



10.7. Appendix 7: Country-specific requirements

Sponsor Legal Registered Address

GlaxoSmithKline K.K.
8-1, Akasaka 1-chome Minato-ku, Tokyo 107-0052 Japan
Study Director: Ryutaro Shimamura, Head, Medicines Development, Clinical Pharmacology Office

Sponsor Contact Address

Leading Author:
PPD
GlaxoSmithKline K.K.
Manager, Medicines Development, Clinical Pharmacology Office

Sponsor's Emergency Contact Information (10:00-18:00, Monday to Friday, except national holidays and year-end and new-year holidays);
Medicines Development (Clinical Pharmacology Office), GlaxoSmithKline K.K.
TEL: PPD (direct dialling)
FAX: PPD

Contact Information at Night and on Holidays (Monday to Friday: 18:00-10:00, Saturday, Sunday, national holidays, year-end and new-year holidays)
PPD (mobile: PPD)

Sponsor Medical Monitor/ Sponsor's Medical Expert

PPD
GlaxoSmithKline K.K.
8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 Japan
TEL: PPD (mobile)/PPD (direct dialling)
FAX: PPD

Medical Institution and Investigator:

Masanari Shiramoto
SOUSEIKAI Hakata Clinic
6-18 Tenyamatchi, Hakata-ku, Fukuoka 812-0025 Japan
TEL: PPD
FAX: PPD

Laboratories

Clinical Laboratory: except HTLV-1 serology
SOUSEIKAI Hakata Clinic
Person in charge: PPD
6-18 Tenyamachi, Hakata-ku, Fukuoka 812-0025 Japan

TEL: PPD
FAX: PPD

Clinical Laboratory: HTLV-1 serology (If subject meet Liver chemistry stopping criteria, include anti-nuclear antibody, anti-smooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins, and viral hepatitis serology described in Appendix 5, but except HBsAg)
LSI Medience Inc.
Person in charge: PPD
30-1 Shimura 3-chome, Itabashi-ku, Tokyo 174-8555 Japan
TEL: PPD
FAX: PPD

Pharmacokinetic Measurement Facilities
Shin Nippon Biomedical Laboratories, Ltd
Pharmacokinetics and Bioanalysis Center
Person in charge: PPD
Minamiakasaka 16-1, Kainan City, Wakayama prefecture, 642-0017 Japan
TEL : PPD
FAX : PPD

Pharmacokinetic Analyses

Person in charge: PPD
GlaxoSmithKline K.K., Medicines Development, Clinical Pharmacology Office
8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 Japan
TEL: PPD (direct dialling)
FAX: PPD

Contract Research Organization

Role: Study Monitoring
Person in charge (Monitor Leader): PPD
Mediscience Planning Inc.
8-10 Toranomon 2-chome, Minato-ku, Tokyo 105-0001 Japan
TEL: PPD
FAX: PPD

Role: Medical Writing (Protocol & ICF)
Person in charge: PPD
Mediscience Planning Inc.
6-1 Hirano-machi 3-chome, Chuo-ku, Osaka 541-0046 Japan
TEL: PPD
FAX: PPD

Role: Medical Writing (CSR)
Person in charge: PPD
Mediscience Planning Inc.
8-10 Toranomon 2-chome, Minato-ku, Tokyo 105-0001 Japan

TEL: PPD
FAX: PPD

Role: Data Loading
Person in charge: PPD
Mediscience Planning Inc.
2-1, Nihonbashi-hamacho 1-chome, Chuo-ku, Tokyo 103-0007 Japan
TEL: PPD
FAX: PPD

Study Period

MAY-2018 - SEP-2018

10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

AE(s)	Adverse event(s)
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC(0-48)	Area under the concentration-time curve from time 0 to 48 hours
AUC(0-inf)	Area under the concentration-time curve from time 0 to infinity
AUC(0-t)	Area under the concentration-time curve from time 0 to the last measurable concentration
%AUCex	Percentage of AUC for time t to infinity by extrapolation to AUC(0-inf)
BMI	Body mass index
CCSI	Company Core Safety Information
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
CPK	Creatine phosphokinase
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
%CVb	Coefficient of variation between subjects
CVw%	Within-subject estimates of variability
ECG	Electrocardiogram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline K.K.
h	Hour(s)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTLV-1	Human T-cell lymphotropic virus type 1
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Immediate release tablet
Japanese BE guideline	Japanese Guideline for Bioequivalence Studies of Generic Products
kel	Elimination rate constant
kg	Kilogram
LDH	Lactate dehydrogenase
Levocetirizine	Levocetirizine hydrochloride
mg	Milligram

mL	Millilitre
MRT	Mean residence time
msec	Millisecond
m^2	Square metre
ODT	Oral disintegrating tablet
pH	Pondus Hydrogenii
PK	Pharmacokinetic(s)
QTc	QT interval correction
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RPR	Rapid Plasma Reagin
SAE(s)	Serious adverse event(s)
SD	Standard deviation
SoA	Schedule of Activities
SRM	Study Reference Manual
t1/2	Terminal half-life
tmax	Time to maximum observed concentration
TOST	Two one-sided t-test
TP	Treponema pallidum
ULN	Upper limit of normal
Vz/F	Apparent volume of distribution after oral administration
WBC	White blood cells
μ_{ref}	The geometric mean of the reference product
μ_{test}	The geometric mean of the test product

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Xyzal

Trademarks not owned by the GlaxoSmithKline group of companies
WinNonlin

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