Clinical Protocol

207791

A Single Dose Bioequivalence Study of a 2 mg Prototype Mini Nicotine Lozenge vs 2 mg Nicotine Mini Lozenge (Nicorette Minis) in Healthy Smokers Under Fasting Conditions

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Protocol Amendment 2

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Compound Name:	Nicotine Polacrilex
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Sponsor information

Sponsor Legal Registered Address	**GlaxoSmithKline Research & Development Limited** 980 Great West Road Brentford Middlesex, TW8 9GS UK
Sponsor Contact Address	GlaxoSmithKline Consumer Healthcare (GSK CH) 184 Liberty Corner Rd, Warren NJ 07059 The contact information for the sponsor for the study is documented in the study contact list located in the supporting study documentation.

Document History

Document	Version Date	Summary of Changes
Protocol amendment 2	13-Dec-2018	- Changing Inclusion Criteria • increased upper range of BMI from 27 to 28 (criteria #5) • removed criteria of subjects smoking more than 30 minutes of waking (criteria #7)
Protocol amendment 1	26-Nov-2018	– Change in Principal Investigator – Incorporate protocol administrative change letters (PACL) into protocol: • Use of samples for future research (PACL #1) • Clarification on the schedule of activities and study procedures (PACL #2)
Original protocol	16-May-2018	Not applicable (N/A)

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current ICH GCP guidelines.

- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.

- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	Robert Schwab
Investigator Qualifications:	M.D.
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY

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PROTOCOL SUMMARY

Background and Rationale:

Nicotine replacement therapy (NRT) has proven to be an effective aid to smoking cessation by reducing nicotine withdrawal symptoms associated with smoking cessation. There are several oral NRT options available, in a range of formats and flavors to address customer preferences.

GlaxoSmithKline Consumer Healthcare (GSKCH) markets a nicotine mini lozenge (Nicorette Minis), which is a therapeutic equivalent to the larger lozenge (Nicorette), with the added benefit of quicker dissolution. The current mini lozenge has a mint flavor. In order to offer the consumer with a mini lozenge with better tasting aesthetics, a new nicotine prototype mini lozenge has been developed. To confirm that the new prototype mini lozenge delivers the same nicotine blood profile, a bioequivalence study will need to be performed comparing this new prototype mini lozenge to the currently marketed mini mint lozenge (Nicorette Minis), which have been identified as the appropriate Reference Standard (RLD). This investigation will be conducted to confirm the bioequivalence of the 2 mg nicotine prototype mini lozenge to the 2 mg mini mint lozenge (Nicorette Minis).

Objectives and Endpoints

Primary objectives:

- To assess the bioequivalence of the nicotine 2 mg prototype mini lozenge with the 2 mg nicotine polacrilex mini lozenge (Nicorette), in terms of nicotine AUC_{0-t}, AUC_{0-inf} and C_{max}

Primary endpoints

- AUC_{0-t} --Area under the plasma concentration versus time curve from time zero to time t, where t is the time of the last measurable plasma concentration of nicotine, estimated.
- AUC_{0-inf} --Area under the plasma concentration versus time curve from time zero extrapolated to infinity.
- C_{max} --The highest observed plasma nicotine concentration.

Secondary objectives

- To compare the nicotine 2 mg prototype mini lozenge to the 2 mg nicotine polacrilex mini mint lozenge (Nicorette Minis) in terms of t_{max}, $t_{½}$, and K_{el}
- To evaluate the safety of the nicotine 2 mg prototype mini lozenge

Secondary endpoints

- t_{max}, the time of the maximum plasma concentration

- $t_{1/2}$, the plasma half life
- K_{el}, the elimination rate constant
- Safety assessments consists of monitoring and recording adverse events (AEs) and clinical safety laboratory test

Study Design

- This study will be a single center, randomized, open label, single dose, two-way crossover in healthy smokers.
- Each subject will be treated with a single dose of the two study treatments in a randomized sequence.
- Subjects will be confined in the study facility for approximately 60 hours during each study session (for 36 hours pre dosing and for 24 hours post dosing) during which pharmacokinetic (PK) blood samples will be obtained.
- Subjects are to abstain from smoking during the confinement periods and be subject to random measurements of expired carbon monoxide (CO) to confirm abstinence. The CO levels must be ≤ 10 ppm throughout the study session.
- There will be at least 5-day and not more than 7-day clinical furlough period between treatment periods. For each treatment period, the clinical confinement period with restriction of smoking is at least 36 hours prior to dosing. The reported plasma $t_{1/2}$ for nicotine is approximately 1 to 4 hours from previous pharmacokinetics studies CCI [redacted]. The 36 hour smoking restriction period prior to dosing will therefore minimize the residual nicotine amount from smoking during previous furlough.

Type and Planned Number of Subjects

Enough healthy adult smokers will be screened to randomize forty (40) healthy adult smokers, to ensure that thirty-two (32) complete the entire study assuming a 20% dropout and non-evaluable rate. The highest intra-subject CV observed in previous studies was 23%. The protocols that were used to select the highest CV for the sample size calculation are: CCI [redacted] and S6491365 (2mg nicotine polacrilex mini cherry lozenge v.s 2mg nicotine polacrilex mini mint lozenge: C_{max} =13.7%; AUC_{0-t} =10%). A total of thirty-two (32) evaluable subjects will achieve a 90% power at 5% significance level. The true ratio that was used in the sample size calculation was 1.05.

Product Information

	Test Product	Reference Product
Product Name	Nicotine Prototype Mini lozenge 2 mg	Nicorette Mini Lozenge 2 mg
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available CCI [redacted]
Dose	2 mg	2 mg
Route of Administration	Oral/Buccal	Oral/Buccal
Dosing Instructions	Place one lozenge in mouth, occasionally moving it side to side. Allow it to slowly dissolve and try to minimize swallowing. Do not chew lozenge. The lozenge should be completely dissolved.	Place one lozenge in mouth, occasionally moving it side to side. Allow it to slowly dissolve and try to minimize swallowing. Do not chew lozenge. The lozenge should be completely dissolved

Statistical Methods

The PK analysis set, PKAS1 will be used for the PK evaluations. PKAS1 is defined as all randomized subjects who completed both periods, and who had no major protocol deviations concerning pharmacokinetics. Subjects with baseline nicotine concentration >5% of the individual C_{max} for either period will be excluded from the PK population.

The PK parameters that will be used in the primary analyses are AUC_{0-t}, AUC_{0-inf} and C_{max}.

The null and alternative hypotheses to be tested in the primary analyses are:

H0: The (geometric) mean AUC_{0-t} (likewise AUC_{0-inf} and C_{max}) of nicotine prototype mini lozenge 2mg (Test) is less than 80% or greater than 125% of that of Nicorette Mini Lozenge 2mg (Reference).

H1: The (geometric) mean AUC_{0-t} (likewise AUC_{0-inf} and C_{max}) of nicotine prototype mini lozenge 2mg (Test) is between 80% and 125% of that of Nicorette Mini Lozenge 2mg (Reference).

A linear mixed effects model will be fit to the log-transformed PK variables (AUC_{0-t}, AUC_{0-inf} ,and C_{max}), as the dependent variable, and treatment, and period as fixed effects. Subject nested within sequence will be a random effect. Least squares estimates of treatment effects

will be calculated and a 90% confidence interval (CI) for the treatment difference will be computed. The treatment difference and its CI will be exponentiated to obtain the ratio of the geometric means between the test and reference products and its CI.

Bioequivalence between the test and reference treatments will be concluded if the 90% confidence interval for the ratio of the means for each of the PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} of the nicotine profiles lie entirely within the interval 0.8 to 1.25.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure/ Assessment	Screening		Study Period 1			Washout		Study Period 2		
	Visit 1 Days -21 to -2	Visit 2 Checkin (Day -2)	Visit 2 Baseline (Day -1)	Visit 2 Treatment Phase (Day 0)	Visit 2 Treatment Phase (Day 1)	Washout Period[b]	Visit 3 Checkin (Day 3 to 5)	Visit 3 Baseline (Day 4 to 6)	Visit 3 Treatment Phase (Day 5 to 7)	Visit 3 Treatment Phase (Day 6 to 8)
Informed consent	X									
Inclusion/Exclusion criteria[c]	X	X					X			
Medical history	X	X					X			
Demographics	X									
Physical examination – full	X									X[d]
Physical examination - brief		X		X[j]	X[j]		X		X[j]	X[j]

Procedure/ Assessment	Screening		Study Period 1			Washout		Study Period 2		
	Visit 1 Days -21 to -2	Visit 2 Checkin (Day -2)	Visit 2 Baseline (Day -1)	Visit 2 Treatment Phase (Day 0)	Visit 2 Treatment Phase (Day 1)	Washout Period[b]	Visit 3 Checkin (Day 3 to 5)	Visit 3 Baseline (Day 4 to 6)	Visit 3 Treatment Phase (Day 5 to 7)	Visit 3 Treatment Phase (Day 6 to 8)
Fagerstrom Test for nicotine dependence	X									
Smoking history	X									
Clinical laboratory tests	X									X[d]
Urine drug test[f]	X	X					X			
Urine alcohol test[f]	X	X					X			
Urinalysis[g]	X									X[d]
Serum pregnancy test[e]	X	X					X			
Contraception review[e]	X	X					X			
ECG (12-lead)	X									
Vital signs BP, respiratory rate, PR, oral body temperature	X			X	X				X	X
Subject check-in for baseline & treatment		X					X			
Expired CO measurements			X[h]	X[h]	X[h]			X[h]	X[h]	X[h]
Random expired CO measurements				4x randomly					4x randomly	
Meals		X	X	X	X		X	X	X	X

Procedure/ Assessment	Screening		Study Period 1			Washout		Study Period 2		
	Visit 1 Days -21 to -2	Visit 2 Checkin (Day -2)	Visit 2 Baseline (Day -1)	Visit 2 Treatment Phase (Day 0)	Visit 2 Treatment Phase (Day 1)	Washout Period[b]	Visit 3 Checkin (Day 3 to 5)	Visit 3 Baseline (Day 4 to 6)	Visit 3 Treatment Phase (Day 5 to 7)	Visit 3 Treatment Phase (Day 6 to 8)
Randomization				X						
PK blood draw[i]				X	X				X	X
Study treatment administration				X					X	
Concomitant Treatments	X	→	→	→	→		→	→	→	→
Adverse Events[a]	X	→	→	→	→		→	→	→	→
Study conclusion										X

Abbreviations: → = ongoing/continuous event; ECG = electrocardiogram; BP = blood pressure; PR = pulse rate.

[a] Any serious and non serious adverse event assessed as related to study participation that occurs subsequent to the signing of informed consent will be recorded.

[b]Washout period must be at least 5 days to a maximum of 7 days, after first dose. Subjects will be allowed to smoke *ad libitum* during this period.

[c]Confirm subject meets inclusion/exclusion criteria at screening and at baseline visits.

[d]After final blood sample is taken

[e]Serum pregnancy test and contraception review at each visit.

[f]Urine drug and alcohol screens at baseline: results will be available prior to dosing.

[g]Urinalysis Dipstick measurements for pH, specific gravity, protein, glucose, blood, ketones, nitrates, leukocyte esterases, urobilinogen, urine bilirubin.

[h]Breath CO measurement taken at Baseline, immediately prior to randomization in Period 1 and immediately prior to dosing in Period 2 and immediately after the last PK sample in each period.
[i]PK blood samples will be collected at -45, -30, -15 (pre-dose), and at 5, 10, 20, 30, 40, 50, 60, 75 and 90 minutes and 2, 3, 4, 6, 8 10, 14, 16, 20 and 24 hours (post-dose).
[j]Brief physical examination will focused on subject reported symptoms of adverse events, if reported

1 INTRODUCTION

1.1 Mechanism of Action/Indication

Nicotine lozenges are indicated as an aid to smoking cessation, of tobacco dependence through the relief of nicotine withdrawal symptoms, including nicotine cravings in smokers.

1.2 Background and Rationale

Nicotine replacement therapy (NRT) has proven to be an effective aid to smoking cessation by reducing nicotine withdrawal symptoms associated with smoking cessation. Various dosage forms of NRT are available, including nicotine gum, nicotine transdermal system, nicotine inhaler, nicotine nasal spray, nicotine sublingual tablet and nicotine lozenge. Variable patterns, quantities and rates of nicotine are delivered by these formulations. One of the most widely used presentations is the oral administration of nicotine polacrilex, either in the form of a chewing gum or lozenge.

Although effective and well tolerated the standard nicotine lozenge (Nicorette Lozenge) is considered by some users to be rather large and to have some unpleasant organoleptic properties.

The prototype mini lozenge has been developed which is smaller in size and thus more discrete to use as well as having improved organoleptic properties. Nicotine is released upon dissolution of the lozenge in the oral cavity.

The purpose of this study is to assess the bioequivalence of the prototype mini lozenge to the reference product nicotine polacrilex mini lozenge (Nicorette Minis).

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the IB.

The SRSD for the comparative agent is the Drug Facts Label.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the bioequivalence of the nicotine 2 mg prototype mini lozenge with the 2 mg nicotine polacrilex mini lozenge (Nicorette Minis), in terms of nicotine AUC_{0-t}, AUC_{0-inf} , and C_{max}.	• AUC_{0-t} – Area under the plasma concentration versus time curve from time zero to time t, where t is the time of the last measurable plasma concentration of nicotine, estimated. • AUC_{0-inf} – Area under the plasma concentration versus time curve from time zero extrapolated to infinity • C_{max} – The highest observed plasma nicotine concentration
Secondary	
PK	
• To compare the nicotine 2 mg prototype mini lozenge to the 2 mg nicotine polacrilex mini lozenge (Nicorette Minis) in terms of t_{max}, $t_{½}$, and K_{el}	• t_{max} – time to maximum plasma concentration (C_{max}) • $t_{1/2}$ – plasma half-life • K_{el} – apparent elimination rate constant for plasma nicotine
Safety	
• To evaluate the safety of the nicotine 2 mg prototype mini lozenge.	• Safety assessments consists of monitoring and recording adverse events (AEs) and clinical safety laboratory test

This study will be considered successful if bioequivalence between the test and reference treatments conclude that the 90% confidence intervals for the ratio of the means of the primary pharmacokinetic parameters AUC_{0-t} and AUC_{0-inf} and C_{max} of the nicotine profiles lie completely within the range 0.8-1.25.

3 STUDY DESIGN AND SUBJECT POPULATION

- This study will be a single center, randomized, open label, single dose, two-way crossover in healthy smokers.

- Enough healthy adult smokers will be screened to randomize at least 40 subjects to ensure 32 evaluable subjects complete the entire study. This will ensure approximately 32 evaluable subjects per treatment arm.

- Each subject will be treated with a single dose of the two study treatments in a randomized sequence, under fasting conditions.

- Subjects will be confined in the study facility for approximately 60 hours during each study session (for 36 hours pre dosing and for 24 hours post dosing) during which pharmacokinetic (PK) blood samples will be obtained.

- Subjects are to abstain from smoking during the confinement periods and be subject to random measurements of expired carbon monoxide (CO) to confirm abstinence. The CO levels must be ≤ 10 ppm throughout the study session.

- There will be at least 5-day and not more than 7-day clinical furlough period between treatment periods. For each treatment period, the clinical confinement period with restriction of smoking is at least 36 hours prior to dosing. The reported plasma $t_{1/2}$ for nicotine is approximately 1 to 4 hours in a heterogeneous population such as the US. The 36 hour smoking restriction period prior to dosing will therefore minimize the residual nicotine amount from smoking during previous furlough.

- Rationale for study design: This will be an open label study. Blinding is not considered essential as study measurements (blood nicotine concentrations) are biological. A crossover design, using the same subjects to test each product, will be used to reduce variability.

- The blood sampling times have been chosen based on the information available particularly on nicotine absorption, as well as its elimination.

- Smokers have been chosen as the population for this study as they are the population that the investigational product would target, if marketed.

- Dose justification: This is a study to assess the bioequivalence of the test product to a commercial reference product.

4 SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subject must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Male and female subjects who, at the time of screening, are between the ages of 19 and 55 years, inclusive.
3. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
4. Healthy subjects which is defined as in general good physical health, as judged by the investigator and no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure, respiratory rate, oral body temperature and pulse rate measurement, 12-lead ECG or clinical laboratory tests.
5. Body Mass Index (BMI) of 19 to 28 kg/m^2, inclusive; and a total body weight >50 kg (110 lbs).
6. Female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 5 days after the last dose of assigned treatment. Female subjects who are not of childbearing potential must meet requirements in Section 4.4.4.
7. Subject admits to having smoked commercially-available cigarettes daily for the preceding 12 months. Brief periods of non-smoking (e.g., due to illness, trying to quit, participation in a study where smoking was prohibited) during that time will be permitted at the discretion of the PI.

4.2 Exclusion Criteria

Subject with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are GSK employees directly involved in the conduct of the study.
2. Participation in other studies involving investigational drug(s) within 30 days prior to first dose and during study participation.
3. Acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the

judgment of the investigator, would make the subject inappropriate for entry into this study.

4. Pregnant female subjects.
5. Breastfeeding female subjects.
6. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. Unwilling or unable to comply with the Lifestyle guidelines described in this protocol.
8. Subject has used any nicotine replacement therapy within 21 days prior to the first study session.
9. Subject has used chewing tobacco, tobacco products or electronic cigarettes other than cigarettes within 21 days of Visit 1.
10. Use of prescription or non-prescription drugs and dietary supplements within two weeks or 5 half-lives, whichever is longer, prior to the first dose of investigational product until the end of the study.

    Allowed treatments are:

    - systemic contraceptives and hormone replacement therapy, as long as female subject is on stable treatment for at least 3 months and continues treatment throughout the study.
11. Evidence or history of clinically significant laboratory abnormality, hematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease within the last 5 years that may increase the risk associated with study participation.
12. History of regular alcohol consumption exceeding 14 drinks/week (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.
13. A positive urine drug screen for THC, amphetamine, cocaine, 3,4-methylenedioxy-N-methylamphetamine (MDMA)/ecstasy, methamphetamine, or opiates; and urine alcohol testing during screening or baseline testing.
14. Subject is unwilling to abstain from tobacco or nicotine-containing product use during each study session (from start of baseline to the completion of the last PK blood sampling). CO measurement immediately prior to randomization (first treatment session) and dosing (second treatment session) should be ≤ 10 parts per million (ppm) for the subject to be dosed.
15. Subject ingests more than 5 cups of coffee or tea a day (or equivalent xanthine consumption using other products).
16. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product (whichever is longer).
17. A medical history that, in the opinion of the investigator, might jeopardize the safety of the subject, e.g., recent myocardial infarction or cerebrovascular accident (i.e., within

12 weeks prior to the first study session), severe cardiac arrhythmia, history of seizures, orthostatic hypotension, cardiovascular disease, stroke, or TIA.

18. A medical history, which, in the opinion of the investigator, might impact the validity of the study results, may require treatment, or make the subject unlikely to finish the study.
19. Oral surgery within 4 weeks of dosing, dental work or extractions within 2 weeks of dosing, or presence of any clinically significant (as determined by the principal investigator or designee) oral pathology including lesions, sores or inflammation.
20. Diagnosis of long QT syndrome or QTc > 460 msec for males and > 470 msec for females at screening.
21. Any surgical or medical condition which may significantly alter the absorption, distribution, metabolism or excretion of any drug substance including, but not limited to, any of the following:

    i) Presence of active oesophagitis, oral or pharyngeal ulceration, inflammation, gastritis, gastric ulcer or peptic ulcer or other diseases;

    ii) Presence of gum disease, xerostomia, dentures or any dental work that could affect the conduct of the study as determined by the investigator or designee;

    iii) Renal disease or impaired renal function at screening as indicated by abnormal levels of serum creatinine or urea or the presence of clinically significant abnormal urinary constituents (e.g. albuminuria). Minor deviations of laboratory values from the normal range are permitted, if judged by the investigator to have no clinical relevance;

    iv) Ongoing hepatic disease or impaired hepatic function at screening. A candidate will be excluded if more than one of the following lab value deviations are found and are clinically relevant: AST/SGOT, ALT/SGPT, γGGT, alkaline phosphatase, bilirubin or CK. Minor deviations of laboratory values from the normal range are permitted, if judged by the investigator to have no clinical relevance;

    v) History or clinical evidence at screening of pancreatic injury or pancreatitis;

    vi) Evidence of urinary obstruction or difficulty in voiding at screening;

    vii) History of malignancy or neoplastic disease of any organ system (except for localized basal cell skin carcinoma), treated or untreated, within the past 5 years prior to screening, regardless of whether there is evidence of local recurrence or metastases.

    viii) Clinically relevant chronic or acute infectious illnesses or febrile infections within 2 weeks prior to start of the study (enrollment).

    ix) Other clinically significant laboratory findings in the opinion of the Investigator at screening.

22. A positive serum Hepatitis B surface antigen, Hepatitis C antibodies, or human immunodeficiency virus (HIV) test result.

23. Blood

    i) Has donated or experienced significant blood loss (470 mL) within 56 days of Visit 1.

    ii) Hemoglobin value < 12.0 g/dL.

24. Subjects who have previously been enrolled in this study.

4.3 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

4.4 Lifestyle Guidelines

4.4.1 Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the pre-dose pharmacokinetic sample. Water is permitted until 1 hour prior to investigational product administration.
- Non-carbonated water may be consumed without restriction beginning 1 hour after dosing. Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices – see below) may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 12 hours after dosing.
- An evening snack may be permitted approximately 2 hours after evening meal.
- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (e.g., Seville oranges, pomelos, papaw, dragon fruit, kiwi fruit, mango, passion fruit, pomegranate, rambutan, star fruit or products that contain these fruits) from 14 days prior to the first dose of investigational product until collection of the final pharmacokinetic blood sample.
- Boiled sweets will be allowed during the study as needed up to 4 hours prior to investigational product administration. This will not be included in the total daily caloric intake for the subjects.
- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

4.4.2 Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the clinical site and continue abstaining from alcohol until collection of the final pharmacokinetic sample of each study period. Subjects may undergo a urine alcohol test or blood alcohol test at the discretion of the investigator.
- Subjects will abstain from caffeine-containing products for 36 hours prior to the start of dosing until collection of the final pharmacokinetic sample of each study period.
- Subjects will abstain from the use of tobacco- or nicotine-containing products for 36 hours prior to dosing and during confinement at the clinical site.

4.4.3 Activity

- Subjects will abstain from strenuous exercise (e.g., heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests and throughout the entire study. Walking at a normal pace will be permitted.

4.4.4 Contraception

All female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for at least 5 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for the correct use of at least 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the following:

1. Established use of oral, inserted, injected, transdermal, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness as deemed appropriate by the investigator.
2. Copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (i.e., foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
6. Female who meets the criteria for non-childbearing potential as described below.

   Female subjects of non-childbearing potential must meet at least one of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

4.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g., withdrawal of consent), eligibility criteria, and any serious adverse events.

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

4.6 Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the study contact list located in the supporting study documentation.

The contact number can be used by investigational staff if they are seeking advice on medical/dental questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical/dental questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol identifiers, subject study numbers, contact information for the investigational site, and contact details in the event that the investigational site staff

cannot be reached to provide advice on a medical question or problem identified from the subject's healthcare professional other than the investigator.

5 STUDY TREATMENTS

This is a study to assess the bioequivalence of the test product to a commercially available reference product. The details are as follows:

	Test Product 1	**Reference Product 1**
Product Name	Nicotine Prototype Mini lozenge 2 mg	Nicorette Mini Lozenge 2 mg
Dose	2 mg (1 lozenge)	2 mg (1 lozenge)
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available CCI [redacted]
Route of Administration	Oral/Buccal	Oral/Buccal
Dosing Instructions	Place one lozenge in mouth, occasionally moving it side to side. Allow it to slowly dissolve and try to minimize swallowing. Do not chew lozenge. The lozenge should be completely dissolved	Place one lozenge in mouth, occasionally moving it side to side. Allow it to slowly dissolve and try to minimize swallowing. Do not chew lozenge. The lozenge should be completely dissolved

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1 Blinding and Allocation to Treatment/Randomization

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

Celerion will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

Treatments will be provided in an open-label manner. However, the analytical laboratory will remain blinded to treatment during the analysis of the plasma samples.

5.2 Breaking the Blind

Not applicable given the open label study design.

5.3 Subject Compliance

Subject will not smoke or use any tobacco or nicotine containing products 36 hours prior to dosing and for the duration of the confinement period. Compliance will be monitored with expired carbon monoxide (CO) measurements.

Using a calibrated Bedfont Smokerlyzer®, the investigator or designee will perform three (3) scheduled CO measurements, one upon check-in at Baseline, one immediately before randomization (first treatment session) or dose administration (second treatment session), and another immediately after the last PK sample has been collected at each study session. Additionally, the investigator or designee will conduct at least four (4) random CO measurements during each treatment session to verify smoking abstinence. The timing of the random CO measurements will be decided by the investigator or designee. See Section 7.5 Expired Carbon Monoxide (CO) measurement for assessment of subject's CO values. All values, including time of measurement will be recorded in the CRF.

Study treatment will be administered under the supervision of investigator site personnel.

5.4 Investigational Product Supplies

5.4.1 Dosage Form and Packaging

Study lozenges described as test and reference study product will be provided to the study site in specific quantity primary packed vials placed into secondary packaging. The secondary packaging will be tamper proof sealed. Each secondary package will contain a common count of primary packaged units. The site will randomly select the required secondary packages to run the study with and retain the remaining secondary units as retains per FDA guidelines.

Each primary and secondary package of study medication tablets will contain a study label. The study label will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSKCH Clinical Supplies Department.

The primary package study labels will include, but not limited to the following information: the protocol number, product name, contents and batch number.

® Smokerlyzer is a registered trademark of Bedfont Scientific Ltd..

The Secondary package labels will include, but not limited to the following information: the protocol number, product name, contents, storage/handling conditions and the appropriate regulatory precautionary information, study site name and phone # and the sponsor name.

Packaging and labeling of all study products will be carried out according to cGMP guidelines and will be the responsibility of the Clinical Supply Department, GSKCH, Lincoln, NE, USA.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. The study labels are not to be removed or defaced.

5.4.2 Preparation and Dispensing

The study products will be prepared and/or dispensed by qualified unblinded site personnel according to the dosage and administration instruction.

5.5 Administration

Following an overnight fast of least 10 hours, subjects will receive investigational product at approximately 0800 hours (plus or minus 2 hours).

Subjects will keep the lozenge in their mouth, occasionally moving it side to side, allowing it to slowly dissolve completely, and try to minimize swallowing.

Subject will not chew the lozenge.

In order to standardize the conditions on pharmacokinetic sampling days, all subjects will be required to refrain from lying down (except when required for blood pressure, pulse rate, and ECG measurements), eating, and drinking beverages, with the exception of water, for the first 4 hours after dosing. Water may be given after one hour post-dosing.

5.5.1 Medication Errors

Medication errors may result, in this study, from the administration or consumption of:

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage strength (other examples of concern may be added based on the investigational product administration, such as inadvertent exposure).

Such medication errors occurring to a study participant are to be captured in the CRF. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not a medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page.

5.6 Investigational Product Storage

The investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational products, including the comparator are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7 Investigational Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

Study treatments must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access.

Upon receipt, all study treatments should be stored according to the instructions specified on the treatment labels. The provided environmental data logger graph and signed instruction sheet must be returned to the GSKCH Clinical Supplies Department as listed on the data logger instructions. Clinical supplies are to be dispensed only in accordance with the protocol.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All study drugs will be accounted for using a drug accountability form/record.

The inventory must be available for inspection by the study monitor during the study. Monitoring of treatments accountability will be performed by the field monitor during site visits and at the completion of the study.

5.7.1 Destruction of Investigational Product Supplies

All investigational study treatments shipped for this clinical trial will be returned to the Sponsor or designated vendor at the termination of the study. At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of Celerion will inventory all used and unused investigational study treatment. The study treatment inventory record for returned study treatment will then be completed. All investigational product for this clinical study (empty containers), as well as all unused study products, except retentions will be returned to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided.

5.8 Concomitant Treatment(s)

Subjects will abstain from all concomitant treatments, except for contraceptives, and those treatments that needs to be used for the treatment of adverse events unless they jeopardize the integrity of the study. The study Sponsor should be immediately informed.

All concomitant treatments taken during the study must be recorded with indication, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 90 days before the first dose of study investigational product will be documented as a prior treatment. Treatments taken after the first dose of study investigational product will be documented as concomitant treatments.

5.9 Rescue Medication

No rescue therapy is appropriate for this study.

6 STUDY PROCEDURES

6.1 Screening

Subjects will be screened within 21 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study.

The following procedures will be completed:

- Obtain written informed consent and record in the CRF.
- Review Inclusion and Exclusion criteria and record in the CRF.
- Collect demography, including year of birth, gender, ethnicity and race and record in the CRF.
- Collect height and weight. The results for each measurement will be recorded in the CRF.
- Obtain medical history as related to the inclusion/exclusion criteria, including any relevant medical or surgical history, allergies or drug sensitivity, history of illegal drug and alcohol use. Significant findings that are present before consent must be included in the CRF.
- Collect smoking habits, including number of cigarettes smoked per day, time to first cigarettes and Fagerstrom score (from Fagerstrom test for nicotine dependence) and record in the CRF.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 90 days prior to consent, and record in the CRF.
- Obtain supine blood pressure (BP), pulse rate (PR) and oral body temperature. The results for each measurement will be recorded in the CRF.
- Conduct full physical examination. Any clinically relevant findings will be noted in the AE CRF page and enrollment will be based upon investigator judgement.
- Contraceptive review
- Collect single 12-lead electrocardiogram (ECG). Results or any clinically significant abnormalities found will be recorded on the CRF.
- Following at least a 4-hour fast, collect blood and urine specimens for the following, and recorded on the CRF:
  - Safety laboratory tests;
  - Urine drug screening;
  - Alcohol screening; Serum FSH concentration for any female who has been amenorrheic for at least 12 consecutive months;
  - Serum β-hCG for all females
- Adverse events

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines and Concomitant Treatment(s) sections of the protocol.

6.2 Study Period

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- Blood pressure/pulse rate: obtain as close as possible to scheduled time, but prior to blood specimen collection;
- Pharmacokinetic blood specimens: obtain at scheduled time;
- Other procedures, including expired CO measurements: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

6.2.1 Visit 2 (Day -2)

Subjects will be admitted to the clinical site at least 36 hours prior to Day 0 dosing.

The following procedures will be completed following admission to the clinical site:

- Review Inclusion and Exclusion criteria and record in the CRF.
- Brief physical examination including evaluation of general appearance, heart, lung and physical measures (weight only). The results will be recorded in the CRF.
- Collect urine for drug screening. The results will be recorded in the CRF.
- Collect serum pregnancy test for all females. The results will be recorded in the CRF.
- Confirm proper contraception is being used and the results will be recorded on the CRF.
- Collect urine for urine alcohol test. Result will be recorded on the CRF.
- Review changes in the subject's medical history. Any changes will be recorded on the CRF.
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Adverse events
- Review concomitant treatment.

6.2.2 Visit 2 (Day -1)

The following procedures will be completed:

- Collect expired CO measurement. Result will be recorded on the CRF.
- Review concomitant treatment.
- Adverse events
- Meals as required. Time and consumption of meals will be recorded on CRF.

- Subjects will begin fasting at least 10 hours prior to dosing on Day 0.

6.2.3 Visit 2 (Day 0)

Prior to dosing, the following procedures will be completed and recorded on the CRF:

- Expired CO measurements to be collected prior to I/C final check.
- Collect supine blood pressure and pulse rate.
- Collect respiratory rate, oral body temperature and record in the CRF.
- Randomization
- Collect a blood sample for pharmacokinetic analysis at the following time points prior to dosing -45, -30, -15 minutes. A deviation of ±3 minutes will be accepted for the blood samples. Time of blood sampling will be recorded in the CRF.
- After all pre-dose procedures have been completed, administer the investigational product (see Study Treatments and Administration Sections).

After dosing, the following procedures will be completed and recorded in the CRF:

- Collect blood samples for pharmacokinetic analysis at the following time points following dosing on Day 0: 5, 10, 20, 30, 40, 50, 60, 75 and 90 minutes and at 2, 3, 4, 6, 8, 10, 14, 16, 20 hours. A deviation of ±3 minutes will be accepted for the blood samples. Time of blood sampling will be recorded in the CRF.
- Collect 4x random CO measurements (see section 7.5 Expired Carbon Monoxide (CO) measurement), and record in the CRF.
- Record changes in concomitant medication or non-drug treatments/procedures.
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Assess symptoms of spontaneous reporting of adverse events by brief physical examination and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.2.4 Visit 2 (Day 1)

The following procedures will be completed and recorded in the CRF:

- Collect blood samples for pharmacokinetic analysis at 24 (±3 minutes) hours. Time of blood sampling will be recorded in the CRF.
- Assess supine blood pressure and pulse rate 24 hours after dosing on Day 0.
- Collect respiratory rate, oral body temperature and record in the CRF.
- Record changes in concomitant medication or non-drug treatments/procedures.
- Assess symptoms of spontaneous reporting of adverse events by brief physical examination and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Meals as required. Time and consumption of meals will be recorded on CRF.

6.2.5 Washout period

Washout period of at least 5 days to a maximum of 7 days after first dose, where subjects will be allowed to smoke *ad libitum*.

6.2.6 Visit 3 (Day 3 to 5)

Subjects will be admitted to the clinical site at least 36 hours prior to Day 5 to 7 dosing.

The following procedures will be completed following admission to the clinical site:

- Review Inclusion and Exclusion criteria and record in the CRF.
- Brief physical examination including evaluation of general appearance, heart, lung and physical measures (weight only). The results will be recorded in the CRF.
- Collect urine for drug screening. The results will be recorded in the CRF.
- Collect serum pregnancy test for all females. The results will be recorded in the CRF.
- Confirm proper contraception is being used.
- Collect urine for urine alcohol test, Result will be recorded on the CRF.
- Review changes in the subject's medical history. Any changes will be recorded on the CRF.
- Review any concomitant treatments and record in the CRF.
- Adverse events
- Meals as required. Time and consumption of meals will be recorded on CRF.

6.2.7 Visit 3 (Day 4 to 6)

The following procedures will be completed:

- Collect expired CO measurement. Result will be recorded on the CRF.
- Review any concomitant treatments and record in the CRF.
- Adverse events
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Subjects will begin fasting at least 10 hours prior to dosing on Day 5 to 7.

6.2.8 Visit 3 (Day 5 to 7)

Prior to dosing, the following procedures will be completed and recorded in the CRF:

- Collect supine blood pressure and pulse rate.

- Collect respiratory rate, oral body temperature and record in the CRF.
- Expired CO measurements to be immediately collected prior to dosing.
- Collect a blood sample for pharmacokinetic analysis at the following time points prior to dosing -45, -30, -15 minutes. A deviation of ±3 minutes will be accepted for the blood samples. Time of blood sampling will be recorded in the CRF.
- After all pre-dose procedures have been completed, administer the investigational product (see Study Treatments and Administration Sections).

After dosing, the following procedures will be completed:

- Collect blood samples for pharmacokinetic analysis at the following time points following dosing on Day 6-8: 5, 10, 20, 30, 40, 50, 60, 75 and 90 minutes and at 2, 3, 4, 6, 8, 10, 14, 16, 20 hours. A deviation of ±3 minutes will be accepted for the blood samples. Time of blood sampling will be recorded in the CRF.
- Collect 4x random CO measurements (see section 7.5 Expired Carbon Monoxide (CO) measurement), and record in the CRF.
- Record changes in concomitant medication or non-drug treatments/procedures.
- Assess symptoms of spontaneous reporting of adverse events by brief physical examination and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Meals as required. Time and consumption of meals will be recorded on CRF.

6.2.9 Visit 3 (Day 6 to 8)

The following procedures will be completed and recorded in the CRF:

- Collect blood samples for pharmacokinetic analysis at 24 (±3 minutes) hours. Time of blood sampling will be recorded in the CRF.
- Obtain blood and urine samples for safety laboratory tests.
- Assess supine blood pressure, respiratory rate, oral body temperature and pulse rate 24 hours after dosing on Day 5-7.
- Conduct full physical examination.
- Record changes in concomitant medication or non-drug treatments/procedures.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Discharge from clinical site.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the GSK CH medical monitor (or designated

representative) should be notified and depending on the abnormality, the subject may be asked to remain at the clinical site until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain at the clinical site and/or when outpatient follow-up is deemed appropriate, the GSK CH medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

The following circumstances require discontinuation of study treatment and/or premature subject withdrawal:

- Protocol violation that may impact the outcome of the subject's safety
- Protocol violation that may interfere with the drug's PK, including:
    - Vomiting shortly (within 30 minutes) after study drug administration
    - Swallowing the lozenge during the administration period
    - Any reported or suspected noncompliance of the smoking restriction during post dose PK observation period, e.g. CO > 10 ppm at any time during the 24 post dose period (see Section 7.5 Expired Carbon Monoxide (CO) measurement for subject assessment)
    -
- Withdrawal of informed consent
- Subject lost to follow-up
- Pregnancy
- Death

If a subject is discontinued or prematurely withdraws from the study, reasons for discontinuation or withdrawal and associated date must be documented in the relevant section(s) of the CRF.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or site staff should attempt to contact the subject twice. After two attempts, clinical site staff must send a registered letter. If no response is received from the

subject, the subject will be considered lost to follow up. All attempts to contact the subject and information received during contact attempts must be documented in the CRF. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

It may be appropriate for the subject to return to the clinical site for final safety assessments. Subjects should be questioned regarding their reason for withdrawal. Assessments, at the investigator's discretion, will include the following:

- Brief physical examination;
- Supine blood pressure respiratory rate, oral body temperature and pulse rate measurements.

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7 ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to, as soon as possible. The study team must be informed of these incidents in a timely manner.

7.1 Efficacy

Not applicable as there are no efficacy assessments.

7.2 Safety

The following safety assessments will be performed at times defined in the Study Procedures section of this protocol.

7.2.1 Laboratory Tests

Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 7-1 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and Creatinine	pH	Urine drug screen[b]
Hematocrit RBC count	Glucose (fasting)	Glucose (qual)	Serology[c]
MCV	Calcium	Protein (qual)	Serum pregnancy test (WCBP)[d]
MCH	Magnesium	Blood (qual)	Alcohol urine test
MCHC	Sodium	Ketones	GGT
Platelet count	Potassium	Nitrites	CK
MPV	Chloride	Leukocyte esterase	FSH
WBC count	Total CO_2(Bicarbonate)	Urobilinogen	
Total neutrophils (Abs)	AST, ALT	Urine Bilirubin	
Eosinophils (Abs)	Direct Bilirubin	Specific gravity	
Monocytes (Abs)	Indirect Bilirubin	Microscopy[a]	
Basophils (Abs)	Total Bilirubin		
Lymphocytes (Abs)	Alkaline phosphatase		
	Uric acid		
	Albumin		
	Total protein		

Definitions: RBC= Red blood cell; MCV= Mean corpuscular volume; MCH= Mean corpusuclar hemoglobin; MCHC= Mean copusuclar hemoglobin concentration; MPV= Mean platelet volume; WBC= White blood cells; BUN=Blood urea nitrogen; AST= aspartate aminotransferase; ALT= alanine aminotransferase; GGT= Gamma-glutamyl transpeptidase; CK=creatine kinase; FSH= follicle stimulating hormone.

[a] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

[b] Minimum requirement for drug testing includes: cocaine, THC, opiates/opioids, 3,4-methylenedioxy-N-methylamphetamine (MDMA)/ecstasy, methamphetamine and amphetamines; to be done Visit 1, Visit 2 (Day -1) and Visit 3 (Days 5-7)

[c] HIV (human immunodeficiency virus); Hepatitis B surface antigen, Hepatitis C antibodies

[d] Female subjects will be tested for serum human chorionic gonadotropin (hCG) at the Screening and start of each period (Days -1 and 5-7).

Any remaining serum/plasma from samples collected for clinical safety labs at baseline and at all times post-dosing must be retained and stored for the duration of the study.

7.2.2 Pregnancy Testing

For all female subjects, a serum pregnancy test, will be performed by the investigator or designee at Screening and Days -1 and 5-7. Results will be obtained prior to dosing during each period.

A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active study period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of IRBs/ECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.2.3 Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, throat skin and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, cardiovascular and neurological systems.

The brief physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms of adverse events if reported.

Any untoward findings identified on physical exams conducted after informed consent will be captured as an adverse event, if those findings meet the definition of an adverse event.

7.2.4 Height and Weight

Height in centimeters (cm) and body weight in kilograms (kg) to the nearest 0.1 kilogram will be measured.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.2.5 Blood Pressure and Pulse Rate

Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary at the discretion of the investigator, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.2.6 Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes rest in supine position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. When blood pressure is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before blood pressure measurement.

7.2.7 Temperature

Temperature will be measured orally, and results recorded in the CRF.

No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.2.8 Electrocardiogram

A standard 12 lead ECG will be performed at Visit 1. Interpretation of the tracing must be made by a qualified physician or designee and documented on the ECG section of the CRF. Each ECG tracing should be labeled with the study number, subject initials, subject number, date, and kept in the source documents at the study site. Results or any clinically significant abnormalities should be reported in the CRF. Clinically significant abnormalities should also be recorded on the Adverse Event CRF. Clinically significant findings must be discussed with the GSK Clinical Project Lead (CPL) prior to enrolling the subject in the study.

Subjects should be in a quiet environment and not speak during the resting period or measurement. Generally, ECGs should not be collected within 3 hours after food or beverage consumption.

7.3 Pharmacokinetics (PK)

Twenty-two (22) blood samples will be collected for pharmacokinetic analysis: at baseline (-45 minutes, -30 minutes and -15 minutes prior to dosing), and at 5, 10, 20, 30, 40, 50, 60, 75 and 90 minutes and at 2, 3, 4, 6, 8 10, 14, 16, 20 and 24 hours following study drug administration. A blood volume of 6 mL per time point, will be collected via direct venipuncture. If the blood volume is unable to be collected by venipuncture, due to failure or inability draw blood, then catheter will be used for collection. Study drug administration is defined as the placement of the nicotine lozenge in the mouth of the subject.

A total of approximately 296 mL blood will be taken during the trial, including 264 mL for PK samples and 32 mL for safety laboratory tests.

7.3.1 PK samples and safety laboratory tests

During all study periods, blood volumes (6 mL) to provide a minimum of 1.5 mL plasma for pharmacokinetic analysis will be collected into appropriately labeled lavender top tubes containing K2EDTA at times specified in the Study Procedures section of the protocol. The plasma will be split into 2 transfer tubes.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 3 minutes will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (e.g., CRF).

Samples will be analyzed using a validated analytical method in compliance with applicable Celerion standard operating procedures.

The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

Samples will be stored for a period of up to 5 years, until regulatory submissions are completed, or upon the request of GSK, at which all samples will be destroyed. The individual subject samples may also be destroyed upon request of the subject. The samples will be stored according to Celerion's standard operating procedures. There will be no use of these samples for further research.

7.3.2 Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.4 Blood Volume

The total blood sampling volume for each subject in this study is approximately 296 mL. The table below reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at the discretion of the investigator or GSK CH.

Table 7-2 Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Safety Labs	16	1	1		32
Retained Sample (optional)					
PK	6		22 x 2		264
TOTAL					296

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable.

7.5 Expired Carbon Monoxide (CO) measurement

Using a calibrated Bedfont Smokerlyzer®, the investigator or designee will perform six (6) scheduled CO measurements, one upon check-in at Baseline, one immediately before randomization in Period 1, one immediately prior to dose administration in Period 2, and another immediately after the last PK sample has been collected at each study session. Additionally, the investigator or designee will conduct at least four (4) random CO measurements during each study period to verify smoking abstinence. The timing of the random CO measurements will be decided by the investigator or designee. For each CO measurement, subjects will be instructed to inhale deeply, hold their breath for 15 seconds and produce a non-forced, steady 15 second exhalation through the disposable mouthpiece of the inflow valve of the CO monitor.

Prior to randomization: If the CO value is not within limits just prior to randomization, an additional CO measurement can be repeated after 2 hours if the value is ≤15ppm. If CO value remains out of limit, then subject will not be randomized.

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During study: If a CO value is not within limits during the study, an additional CO measurement may be taken to confirm the results.

- If second value is still not within the limits, subject will be discontinued from study
- If second value is within limits, state reason for repeated measure (e.g. incorrect use of CO monitor). Repeat measurement again in 30 minutes to confirm. If the third measurement is within limits, subject may continue with study. If third measurement is not within limits, then subject will be discontinued from study.

All values, including time of measurement and reason for re-measurement will be recorded in the CRF.

8 ADVERSE EVENT

8.1 Definitions of Adverse Events and Serious Adverse Events

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of an investigational or washout product or medical device, whether or not considered related to the investigational or washout product or medical device.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 treatment 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 treatment 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 (if applicable) 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 subject'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 subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g., appendicitis).
- Situations where 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.

8.1.2 Serious Adverse Event

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 serious adverse event is any untoward medical occurrence at any dose that:

- **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 fulfills 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 or significant 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, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption

- **Results in 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.

8.2 Reporting Period

8.2.1 Adverse Event

AEs (serious and nonserious) will be collected from the signing of the ICF and until 5 days following last administration of the investigational product. For studies that have a run-in period or washout period, adverse events will be collected from the time the run-in or washout period begins.

Medical occurrences that begin before obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF).

8.2.2 Serious Adverse Event

SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product and until 5 days following last administration of the investigational product.

SAEs assessed as **not related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or not related to a GSK concomitant medication will be recorded from the time the subject has taken at least 1 dose of investigational product and until 5 days following last administration of the investigational product.

8.3 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study.

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE/SAE 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 instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.1 Adverse Event

All AEs will be reported on the AE page(s) of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE

CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AE should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

8.3.2 Serious Adverse Event

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSK CH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken on study product
- Outcome if known

Celerion will email the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance at GSK (PPD), with copy to the appropriate GSK CH Study Manager as soon as possible, **but not later than 1 business day** after study site personnel learn of the event. The GSK CH Study Manager will be responsible for forwarding the SAE form to other GSK CH personnel as appropriate.

8.3.3 Sponsor's Reporting Requirements to Regulatory Authorities and Ethics Committees

GSK has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC 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 eg, summary or listing of SAE, from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4 Evaluating Adverse Events and Serious Adverse Events

8.4.1 Severity Assessment

The investigator or designee will make an assessment of severity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

Note: An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4.2 Causality Assessment

The causality assessment is one of the criteria used when determining regulatory reporting requirements. 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. The

investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

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. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

There may be situations when 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 prior to 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.

8.5 Withdrawal Due to an Adverse Event and Serious Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.6 Pregnancy

8.6.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported following administration of any investigational product or washout product and until 48 hours after the last dose.

8.6.2 Action to be Taken if Pregnancy Occurs

The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product. The investigator will record pregnancy information on the appropriate form and submit it to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK within 24 hours of learning of the subject becoming pregnant. The subject will be

followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at 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.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be and should be recorded as an SAE.

Any female participant who becomes pregnant while participating will discontinue study treatment or be withdrawn from the study.

Like with SAE and Incident Forms, Celerion will email the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD) with copy to the appropriate GSK CH Study Manager.

8.7 Follow-up of Adverse Events and Serious Adverse Events

After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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.

Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSK by emailing the information to the GSK CH Clinical Operations Safety Reporting email box (PPD). The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD).

The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

9 DATA MANAGEMENT

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

For this study subject data will be entered into a Contract Research Organization (CRO) electronic CRF, using a validated data system.

9.1 Source Documents/ Data

The source documents (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in Section 6 . The CRF can be used as a source document at the discretion of data management.

Each subject will be assigned and identified by a unique Number. Any reference made to an individual subject within the study must be done using the unique Screening Number.

9.2 Case Report Form

A CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSK CH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

GSK CH will obtain and retain all CRFs and associated study data at the completion of the study.

9.3 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

Adverse events will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and concomitant medications terms using an internal validated medication dictionary, GSKDrug.

9.3.1 Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (Adverse Events and Drugs) appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

9.4 Processing Patient Reported Outcomes

There will be no Patient reported outcome (PRO) data for this study.

9.5 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

10 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1 Sample Size Determination

Enough healthy adult smokers will be screened to randomize forty (40) healthy adult smokers, to ensure that thirty-two (32) complete the entire study assuming a 20% dropout and non-evaluable rate. The highest intra-subject CV observed in previous studies was 23%. The protocols that were used to select the highest CV for the sample size calculation are: CCI [redacted] and S6491365 (2mg nicotine polacrilex mini cherry lozenge v.s 2mg nicotine polacrilex mini mint lozenge: C_{max} =13.7%; AUC0-t =10%). A total of thirty-two (32) evaluable subjects will achieve a 90% power at 5% significance level. The true ratio that was used in the sample size calculation was 1.05.

10.2 Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to the database lock and analysis. SAP creation and statistical analysis will be performed by Celerion.

Pharmacokinetic variables will be calculated by Celerion.

All concentration and PK data will be listed. This includes any data for subjects who are not included in the analysis.

10.2.1 Demographic and Baseline Characteristics

Baseline data, relevant screening data, and demographic characteristics will be summarized for all randomized subjects.

10.2.2 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

The number of subjects exposed to each treatment will be tabulated for the safety population. Treatment deviations for individual subjects will be listed and summarized. Cases of partial exposure, including swallowing or premature expulsion of the treatment and subjects with baseline > 5% of the C_{max} will also be summarized. For predose-adjusted data, baseline nicotine concentration is defined as the time zero concentration estimated by the log-linear regression according to a mono-compartmental deconvolution of the three pre-dose time points, i.e. – 45 minutes, - 30 minutes and -15 minutes prior to dosing. Other medications and other concomitant non-drug therapies will be listed for the safety population.

10.2.3 Primary Analysis

10.2.3.1 Criteria for assessing bioequivalency

The bioequivalence between the test and reference treatments will be concluded if the 90% confidence intervals for the ratio of the means of the primary pharmacokinetic parameters AUC_{0-t} and AUC_{0-inf} and C_{max} of the nicotine profiles lie completely within the range 0.8-1.25.

10.2.3.2 Pharmacokinetics Analysis

Variables:

For each study product, the following pharmacokinetic parameters will be estimated:

AUC_{0-t}: Area under the plasma concentration versus time curve from time zero to time t, where t is the time of the last measurable plasma concentration of nicotine, estimated.

AUC_{0-inf}: Area under the plasma concentration versus time curve calculated from time zero to infinity.

C_{max}: The highest observed plasma nicotine concentration.

PK evaluation:

The primary objective will be evaluated based on the following comparison:

The nicotine 2 mg prototype mini lozenge (Test) versus the 2 mg nicotine polacrilex mini lozenge (Nicorette Mini, Reference), in terms of nicotine AUC_{0-t}, AUC_{0-inf} and C_{max}.

The primary statistical analyses will be done based on PK analysis set, PKAS1 (see section 10.2.7 for definition). An additional analysis (for pre-dose adjusted data only) will be performed on PK analysis set, PKAS2. Safety population will be used for individual plasma concentration listings and figures.
Individual plasma concentrations will be listed and summarized descriptively at each time point; the concentration vs. time profile will be graphed by formulation for individual subjects and for the mean on both original and logarithmic scales with Safety population.

All PK parameters (except K_{el}, $t_{½}$ and t_{max}) will be summarized for each treatment by descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum, and maximum). A listing containing individual and summary statistics for each PK parameter will be provided. A similar listing will be provided for log and linear blood concentrations over time containing individual values and summary statistics for each time point.

BE of the test product with reference will be assessed by pairwise comparison of the PK parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) for the nicotine concentration profiles based on the PK analysis set, PKAS1.

A linear mixed effects model will be fit to the log-transformed PK variables (AUC_{0-t}, AUC_{0-inf} and C_{max}), as the dependent variable, and treatment, and period as fixed effects. Subject nested within sequence will be a random effect. For each pairwise comparison, only the data from the two, corresponding treatments will be included in the model. The presence of a statistically significant sequence effect will be noted and its implications will be discussed.

Least squares estimates of treatment effects will be calculated and a 90% confidence interval (CI) for the treatment difference will be computed. The treatment difference and its CI will be exponentiated to obtain the ratio of the geometric means between the test and reference products and its CI. Bioequivalence will be determined if the 90% confidence interval for the treatment geometric mean ratio lies completely within the range 0.80 – 1.25.

10.2.3.3 Correction for non-zero baseline for an additional analysis.

The pre-dose nicotine concentration will be estimated based on a log-linear regression according to a mono-compartmental deconvolution of the three pre-dose time points, i.e. -45 minutes, -30 minutes and -15 minutes prior to dosing. Subsequent plasma concentrations will be corrected by subtracting an estimate of the residual baseline plasma nicotine concentration computed with log-linear regression according to a mono-compartmental deconvolution as follows:

RCt,ij = Cpre-dose,ij *exp (-Kelij*t)

where

RCt = estimated residual concentration (nicotine in plasma) at time t,

Cpre-dose = plasma nicotine concentration before dosing,

Kel = slope calculated by log-linear regression using the elimination portion of the PK profile for the associated treatment.

t = time (h) between the considered blood sampling and the time of pre-dose sampling.

i = treatment (Test or Reference)

j = patient

The plasma concentration at time t, observed after dosing and corrected for baseline, will be equivalent to the following:

Ct,ij(R)=Ct(O)-RCt

Where:

Ct(R) = baseline corrected nicotine concentration Ct(O) = observed nicotine concentration detected in patient plasma

This adjustment will only be applied in cases where the pre-dose value is greater than zero.

10.2.4 Secondary Analysis

The PK analysis set, PKAS1 will be used for the secondary analysis.

For each study product, the following pharmacokinetic parameters will be estimated:

t_{max} time to maximum plasma nicotine concentration;

$t_{1/2}$ apparent elimination half-life;

K_{el} apparent elimination rate constant for plasma nicotine.

The parameters K_{el} and $t_{½}$ and t_{max} be summarized (mean, median, Q1, Q3, minimum, maximum, standard deviation, and coefficient of variation) for each study treatment. A nonparametric analysis will be performed to compare study treatments using the Wilcoxon Signed Rank Test. Median difference, 95% confidence interval and p-value will also be presented.

Additional PK parameters or statistical analyses may be performed as appropriate.

10.2.5 Safety Analysis

Safety variables will be summarized for the safety population.

Adverse Event:

Treatment Emergent adverse events, i.e. AEs that are emergent or that worsen after the first mini lozenge administration, will be summarized by presenting, for each treatment, the number and percentage of subjects having any AE, any AE in each MedDRA System Organ Class (SOC) and having each individual AE. The subset of AEs suspected of a relationship to study drug will be presented similarly. All treatment-emergent AEs will also be tabulated by severity. Any other information collected (e.g. action taken, duration, outcome) will be listed. Each AE will be attributed to the treatment taken most recently before the onset of the AE.

Vital signs:

Vital signs including temperature will be summarized by time-point and treatment. Summary statistics will include mean, standard deviation, minimum, median, and maximum. No inferential statistics will be presented. Data will be listed with abnormal values flagged.

Physical examination

Physical Examination data will be listed with abnormal values flagged.

Safety Laboratory:

Safety Laboratory data will be listed with abnormal values flagged.

10.2.5.1 Criteria for assessing safety

Vital signs, clinical safety laboratory tests and monitoring of adverse events will be used to assess the safety and tolerability of the study products

10.2.6 Other Analysis

Data for the following variables will be listed for the safety population:

- CO monitoring

10.2.7 Definition of Analysis Populations

The safety population is defined as all randomized subjects who receive at least one dose of study medication.

The PK population is defined as all randomized subjects who completed both periods, and who had no major protocol deviations concerning pharmacokinetics.

The following 2 PK analysis sets are defined to address the PK objectives and further PK considerations within this study:

- PKAS1 includes all subjects of the PK population. Subjects with baseline nicotine concentration > 5% of the individual C_{max} for either period will be excluded. This analysis set will be used in PK summaries, the primary analysis, and the secondary analysis..
- PKAS2 includes all subjects of the PK population, for which the relevant predose-adjusted PK parameters (at least one AUC or Cmax) can be derived. This analysis set will be used in PK summaries and an additional analysis.

10.2.8 Exclusion of Data from Analysis

Subjects who deviate from the protocol will be identified and excluded from the pharmacokinetic analyses as agreed by the biostatistician and medical director or designee.

For the primary analysis of PK parameters, subjects with baseline concentrations > 5% of C_{max} will be excluded (from PKAS1).

Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

10.2.9 Handling of Dropouts and Missing Data

All existing data for subjects who are dropouts from the study will be included in the pharmacokinetic statistical analysis.

If any concentration data is missing or deviates from the planned time of collection, then the pharmacokineticist may calculate the PK parameters using the available data.

Missing values of K_{el} can be estimated from the subject's mean K_{el} value from the other treatments. If a K_{el} value cannot be calculated from the other treatments, then the K_{el} will be obtained from the treatment mean value for subjects with non-missing values of K_{el} in the period in which it is not available. This estimated K_{el} can be used to calculate other K_{el} dependent variables. This K_{el} value derivation is only applied for pre-dose concentration adjustments.

For nicotine concentration:

- BLOQ values obtained before C_{max} will be imputed as zero.
- BLOQ values obtained after C_{max} will be imputed as "Not detectable" (ND), which will be shown as missing (explanations will be specified in the footnote of TFLs).

10.2.10 Interim Analysis

No interim analysis is planned for this study

11 STUDY GOVERNANCE CONSIDERATIONS

11.1 Quality Control

In accordance with applicable regulations including GCP, and GSK procedures, GSK or designee (i.e. third party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSK CH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The investigator(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the regulatory authority, the investigator will provide GSK CH or its agents with an opportunity to review and comment on responses to any such findings.

The sponsor will be available to help investigators prepare for an inspection.

11.3 Regulatory and Ethical Considerations

11.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, investigator brochure/safety statement (including any updates) and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and GSK CH in writing immediately after the implementation.

11.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

11.3.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects. The use of initials should be avoided.

The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

11.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

GSK CH will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

11.3.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Within a GSK CH a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in GSK CH- sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

In addition, the investigator will inform GSK CH immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

11.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable GSK processes.

11.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. 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 results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11.6 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

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 Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

11.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of nicotine prototype mini lozenge at any time.

If a study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory

authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension.

Upon completion or premature discontinuation of the study, the GSK CH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures.

11.8 Definition of Study End/ End of Study

Study End (SE) date is defined as the date of the last subject visit of the last subject to complete the study (LSLV).

The End of Study (EOS) is the date of the last event/testing/reading related to the primary and secondary endpoints, to be achieve no later than 8 months after SE.

12 REFERENCES

1. CCI [redacted]
2. CCI [redacted]
3. CCI [redacted]
4. S6491365 (2011) A Single Dose Bioequivalence Study of 2 mg and 4 mg Mini Cherry Nicotine Lozenges. GSK Study

13 APPENDIX

13.1 ABBREVIATION

The following is a list of abbreviations that may be used in the protocol.

Table 13-1 Abbreviation

Abbreviation	Term
AE	adverse event
Abs	absolute

Abbreviation	Term
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	area under the concentration-time curve from time 0 to 24 hours
AUC_{0-inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BA	bioavailability
BE	bioequivalence
BLOQ	below level of quatification
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
C_{av}	average concentration
CDS	core data sheet
C_{eff}	efficacious concentration
CI	confidence interval
CL/F	apparent oral clearance
CL_r	renal clearance
C_{max}	peak or maximum observed concentration
CK	Creatine kinase
CO_2	carbon dioxide (bicarbonate)
CPL	clinical project lead
CRF	case report form
CRO	contract research organization
CSA	clinical study agreement
CSF	cerebrospinal fluid
CTA	clinical trial application
CV	coefficient of variation
DCT	data collection tool
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EOS	end of study

Abbreviation	Term
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
hCG	human chorionic gonadotropin
HDL-C	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICF	informed consent form
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
IUS	Intrauterine system
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LDL-C	low density lipoprotein-cholesterol
LFT	liver function test
LSLV	last subject last visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
N/A	not applicable
ND	not done
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PD	pharmacodynamics
PG	pharmacogenomics
PI	principal investigator
PII	personally identifiable information
PK	pharmacokinetics
PKAS1	PK analysis set 1

Abbreviation	Term
PKAS2	PK analysis set 2
PR	pulse rate
PT	prothrombin time
QC	quality control
QTc	corrected QT
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SE	study end
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
SOP	standard operating procedure
SmPC	summary of product characteristics
SRSD	single reference study document
SS	safety statement
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal half-life
T_{max}	time to reach maximum concentration
TFL	tables, figures and listings
THC	tetrahydrocannabinol
ULN	upper limit of normal
US	United States
USPI	United States package insert
V_z/F	apparent oral volume of distribution
WBC	white blood cell