CLINICAL PROTOCOL 217756

A randomized, open label, single center, single dose, two period, two sequence crossover bioequivalence study of 21 mg nicotine transdermal patches (NicoDerm CQ, GSK Dungarvan) compared to the current marketed 21 mg nicotine transdermal patches (NicoDerm CQ, Alza) in healthy adult smokers

Protocol Number:	217756
Compound/Product Name:	NicoDerm CQ
United States (US) Investigational New Drug (IND) Number:	Not applicable
European Clinical Trials Database (EudraCT) Number:	Not applicable
Other Regulatory Agency Identified Number:	Not applicable
Phase:	I

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (GSK CH)** GlaxoSmithKline Consumer Healthcare (GSK CH) 184 Liberty Corner Rd., Warren, NJ 07059 United States

Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1		
Amendment 2		

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Council for Harmonisation Good Clinical Practice (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:	PPD
Investigator Qualifications:	D.O.
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD

Table of Contents

List of in text tables

1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

A bioequivalence study of 21 mg nicotine transdermal patches (NicoDerm CQ, GSK Dungarvan) compared to the current marketed 21 mg nicotine transdermal patches (NicoDerm CQ, Alza) in healthy adult smokers.

Background and Rationale:

NicoDerm CQ patch is manufactured by Alza. GSK will submit an application to support the change of manufacturing site from Alza to Dungarvan.

The purpose of this study is to assess the bioequivalence of the 21mg nicotine transdermal patch from GSK Dungarvan (Test) compared to the 21mg nicotine transdermal patch currently manufactured by Alza (Reference).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Demonstrate the bioequivalence of the 21-mg nicotine transdermal patch from GSK Dungarvan (Test) compared to the 21 mg nicotine transdermal patch manufactured by Alza (Reference)	• C_{max} (The maximum observed post-dose concentration; obtained without interpolation) • AUC_{0-t} (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t,) • AUC_{0-inf} (The area under the plasma concentration versus time curve calculated from time 0 to infinity)
Secondary	
Pharmacokinetics	
Assess the pharmacokinetic profile of the patches	• λ_z (The terminal elimination rate constant) • t_{max} (The time of the maximum observed post-dose concentration) • $t_{1/2}$ (The elimination half-life computed as $t_{1/2} = \ln(2)/ \lambda_z$)
Adhesion	
To monitor adhesion of the patches to the skin	Adhesion score
Safety	

Assess the safety profile (local and systemic) of both products	• Monitoring and recording of adverse events • Physical examination • Vital signs • Laboratory tests

Study Design:

This is a 2-arm, single center, single dose, open-label, randomized, two-sequence, two-period crossover, bioequivalence study in healthy adult smokers that have smoked more than 10 cigarettes per day for 1 year prior to inclusion.

Subjects will be randomly assigned to receive a single-dose of one of the following treatments which will follow a cross-over design:

Treatment A: 21 mg/24h NicoDerm CQ (GSK Dungarvan)-Test

Treatment B: 21 mg/24h NicoDerm CQ (Alza)- Reference

In each treatment period, each subject will be dosed once, i.e., a single NicoDerm patch will be placed under fasted conditions to the upper part of the back for a total duration of 24 hours, and then removed. Blood will be sampled regularly at scheduled times for 36 hours following patch application. The pharmacokinetic profile may be altered when a patch loses its adherence to the skin. Therefore, the adhesion of the patch should be monitored. Adhesion will be assessed five times: within 5 minutes from patch application and approximately 6, 12 and 18 hours after patch application and immediately prior to patch removal.

Carry-over effects will be avoided by a wash-out interval of at least 2 days (but no more than 4 days) from patch removal in the first treatment period to subsequent patch application.

The study will consist of an ambulant screening day within 21 days prior first patch application. Subjects will be confined in the study facility from 48 hours pre dosing until 36 hours post last dosing; pharmacokinetic (PK) blood samples will be obtained at predose (within 1 hour before dosing), 30 minutes and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 25, 26, 27, 28, 30, 32, and 36 hours after administration of the patch.

For each subject the duration of study participation is 27 days of which up to 8 days confined.

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

Study Products:

	Test Product	**Reference Product**
Product Name	NicoDermCQ	

	21 mg /system of 22 cm^2 surface area	NicoDermCQ (USA commercial product) 21 mg /system of 22 cm^2 surface area
Dose/Application	One application	One application
Route of Administration	Topical	Topical

Type and Planned Number of Subjects:

A sufficient number of subjects will be screened to randomize approximately 20 to ensure a minimum of 12 evaluable subjects complete the entire study.

Statistical Methods:

The PK analysis set will be used for the PK evaluations. It includes all randomized subjects of the PK population, for which the relevant predose-adjusted PK parameters (at least one AUC or C_{max}) can be derived.

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 (Test) is less than 80% or greater than 125% of that of (Reference).

H1: The (geometric) mean AUC_{0-t} (likewise AUC_{0-inf} and C_{max}) of (Test) is between 80% and 125% of that of (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.

1.2 Schedule of Activities

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

The investigator may conduct unplanned visits and procedures in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being of the subject and maintain study integrity.

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening	Period 1					Wash Out	Period 2				End of study visit*
Visit	1	2						3				
Study Day	-21 to -2	-2	-1	1	2		3	4	5	6		6
Confinement [c]		x	x	x	x		x	x	x	x		
Informed consent	x											
Demography	x											
Medical History[i]	x		x									
Physical Exam[a]	x		x						x			x
Height and Weight	x											
Vital signs[b]	x	x	x	x	x		x	x	x	x		x
12-lead ECG	x											
Laboratory tests	x											x
COVID-19 test[h]	x	x										x
Virology	x											
Pregnancy test[l]	x	x						x				x
Urine illicit drug screen	x	x										
Alcohol breath test	x	x										
Inclusion/Exclusion Assessment	x	x										
Continued eligibility								x[e]				
Randomization				x								
Patch application				x					x			
Patch removal					x					x		
PK blood sampling[c]				x	x				x	x		
Patch adhesion assessment[d]				x	x				x	x		
Expired CO[g]		x	x	x	x		x	x	x	x		
Concomitant treatments	x	x	x	x	x		x	x	x	x		x
Adverse events[f]	x	x	x	x	x		x	x	x	x		x
Study conclusion												x

Abbreviations: EGC, CO, PK

Footnotes:

* These assessments are also to be conducted for subjects who discontinue study drug. End of Study visit will occur before discharge, on study Day 6

[a] Including site application examination; full physical examination at screening and final visit and examination of the areas on the back only before each patch application

[b] Including body temperature; body temperature will be measured every day; all vital signs will be assessed at screening, pre-treatment in each treatment period (1 – 30 minutes before drug administration) and final visit.

[c] PK blood samples will be collected at predose (within 1 hour before dosing) and at 30 minutes and at 1, 2, 3, 4,5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 25, 26, 27, 28, 30, 32, and 36 hours after administration of the patch. See section 8.2

[d] Within 5 minutes from patch application and approximately 6, 12, 18 hours post application and before patch removal (24 hours after patch application)

[e] At the discretion of the Investigator, the subjects could continue the study if any deviation to the inclusion/exclusion criteria does not anticipate to alter study integrity.

[f] Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

[g] Breath CO measurement taken upon check-in, on day -2 and immediately prior to randomization in Period 1, immediately prior to dosing in Period 2, one during the wash-out, 3 times randomly in each period and immediately after the last PK sample in each period.

[h] Before dosing two consecutive approved (Locally approved tests (PCR or Antigen) will be performed: one test at screening and one test at check-in (Day-2). If the second test is > 72 hours prior to unit admission, subjects should be advised to self -quarantine until entrance to the unit while awaiting final testing clearance. Subjects who report symptoms suggestive of COVID-19 while in the research unit should be isolated in the unit or at home and tested for COVID-19 infection using an approved molecular test. One test (Locally approved tests (PCR or Antigen) should be performed before releasing the subject from the unit i.e. at early discontinuation or end of study.

[i] Includes Smoking history

[l] Serum pregnancy test at screening and end of study and CLIA-waived urine pregnancy test at check-in Day -2 and Day 4

2 INTRODUCTION

Nicotine replacement therapy (NRT) is the most widely used pharmacological therapy for smoking cessation. One of the widely used NRTs is nicotine transdermal system, which is also known as nicotine transdermal patch. The impacts of the change of the manufacturing site will be tested in this bioequivalence study.

2.1 Study Rationale

NicoDerm CQ patch is manufactured by Alza. GSK will submit an application to support the change of manufacturing site from Alza to Dungarvan.

The purpose of this study is to assess the bioequivalence of the 21 mg nicotine transdermal patch from GSK Dungarvan (Test) compared to the 21 mg nicotine transdermal patch currently manufactured by Alza (Reference).

2.2 Background

Nicoderm CQ patch is a marketed formulation for which the pharmacokinetics, efficacy and safety has been demonstrated in clinical studies and post marketing data.

2.3 Benefit/Risk Assessment

Complete information for this product may be found in the single reference safety document (SRSD), which for this study is the US prescribing information (OTC Drug Facts label & Package Insert).

2.4 Mechanism of Action/Indication

Nicotine replacement therapy (NRT) has proven to be an effective aid to smoking cessation by reducing nicotine withdrawal symptoms associated with smoking cessation.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Demonstrate the bioequivalence of the 21 mg nicotine transdermal patch from GSK Dungarvan (Test) compared to the 21 mg nicotine transdermal patch manufactured by Alza (Reference)	• C_{max} (The maximum observed post-dose concentration; obtained without interpolation) • AUC_{0-t} (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule)

	• $AUC_{0\text{-}inf}$ (The area under the plasma concentration versus time curve calculated from time 0 to infinity)
Secondary	
Pharmacokinetics	
Assess the pharmacokinetic profile of the patches	• λ_z (The terminal elimination rate constant) • t_{max} (The time of the maximum observed post-dose concentration) • $t_{1/2}$ (The elimination half-life computed as $t_{1/2} = \ln(2)/ \lambda_z$)
Adhesion	
To monitor adhesion of the patches to the skin	Adhesion score
Safety	
Assess the safety profile (local and systemic) of both products	• Monitoring and recording of adverse events • Physical examination • Vital signs • Laboratory tests

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 $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ and C_{max} of the nicotine profiles lie completely within the range 0.8-1.25.

4 STUDY DESIGN

4.1 Overall Design

This is a 2-arm, single center, single dose, open-label, randomized, two-sequence, two-period crossover, bioequivalence study in healthy adult smokers that have smoked more than 10 cigarettes per day for 1 year prior to inclusion.

Subjects will be randomly assigned to receive a single-dose of one of the following treatments which will follow a cross-over design:

Treatment A: 21 mg/24h NicoDerm CQ (GSK Dungarvan)-Test

Treatment B: 21 mg/24h NicoDerm CQ (Alza)- Reference

In each treatment period, each subject will be dosed once, i.e., a single NicoDerm patch will be placed under fasted conditions to the upper part of the back for a total duration of 24 hours, and then removed. Blood will be sampled regularly at scheduled times for 36 hours following patch application. The pharmacokinetic profile may be altered when a patch loses its adherence to the skin. Therefore, the adhesion of the patch should be monitored. Adhesion will be assessed five times: immediately after patch application, approximately 6, 12 and 18 hours after application and immediately prior to patch removal.

Carry-over effects will be avoided by a wash-out interval of at least 2 days (but no more than 4 days) from patch removal in the first treatment period to subsequent patch application.

The study will consist of an ambulant screening day within 21 days prior first patch application. Subjects will be confined in the study facility from 48 hours pre dosing and for 36 hours post last dosing; pharmacokinetic (PK) blood samples will be obtained at predose (within 1 hour before dosing), 30 minutes and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 25, 26, 27, 28, 30, 32, and 36 hours after administration of the patch.

For each subject the duration of study participation is 27 days of which up to 8 days confined.

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

Procedures must be in place to avoid nicotine cross-contamination i.e. all staff members at the clinical site and the bioanalytical laboratory who are involved in this study must not use any tobacco or nicotine containing products to avoid nicotine cross-contamination.

4.2 Scientific Rationale for Study Design

The reported plasma $t_{1/2}$ for nicotine is approximately 1 to 4 hours in a heterogeneous population such as the US. The 48-hour smoking restriction period prior to dosing will therefore minimize the residual nicotine amount from smoking during previous furlough.

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.

The following guidance have been followed for designing the study:

- US-FDA's recommendations for BE/PK studies with transdermal nicotine products (FDA Guidance on Nicotine 2019)
- Draft guidance Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (FDA 2013)
- US-FDA's recommendations for assessing adhesion with transdermal delivery systems and topical patches for Abbreviated New Drug Applications products (FDA 2018)

4.3 Justification for Dose

This is a study to assess the bioequivalence of the test product to a commercial reference product. The transdermal system will be applied to the back and worn for 24 hours.

4.4 End of Study Definition

The End of Study is defined as the date of the last visit of the last subject to complete the study.

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

A sufficient number of subjects will be screened to randomize approximately 20 to ensure at least 12 evaluable subjects complete the entire study.

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorized representative and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

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 non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

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

5.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible to be included into the study:

1. Subject provision of a 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. Subject is male or female. An effort will be made to include similar proportions of males and females in the study.
3. Subject is 21 to 55 years of age inclusive, at the signing of the informed consent
4. Subject is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
5. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, as determined by medical evaluation, including a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG or clinical laboratory tests.
6. Body Mass Index (BMI) of 19 to 27 kg/m^2; and a total body weight >50 kg (110 lbs).
7. Any female subject 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 5.4.4 of protocol.
8. Subject admits to having smoked more than 10 cigarettes per day for the preceding one year (prior to initial dose).
9. Subject with two negative tests (one at screening and one at check in Day-2) for active COVID-19, separated by > 24 hours.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving any investigational product(s) within 30 days before first dosing.
3. A subject with, in the opinion of the investigator or medically qualified designee, an 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 or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A subject who is pregnant as confirmed by a positive serum pregnancy test or intending to become pregnant over the duration of the study.
5. A subject who is breastfeeding.
6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients ethylene vinyl acetate-copolymer, polyisobutylene and high density polyethylene
7. Diagnosis of long QT syndrome or QTc > 450 msec for a male subject and > 470 msec for a female subject at screening
8. A subject unwilling or unable to comply with Lifestyle Considerations described in this protocol.
9. Subject is unwilling to abstain from tobacco or nicotine-containing product use during the study (from check-in 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.
10. Subject has used chewing tobacco, tobacco products or electronic cigarettes other than cigarettes within 21 days of Visit 1.
11. Use of any medication (including over-the-counter medications and herbal remedies) within 2 weeks before first scheduled study drug administration or within less than 10 times the elimination half-life of the respective drug (whichever is longer), or is anticipated to require any concomitant medication during that period or at any time throughout 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;
12. 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, as assessed by the Investigator or medically qualified designee
13. A subject with a positive urine drug screen, for THC, amphetamine, cocaine, 3,4-methylenedioxy-N-methylamphetamine (MDMA)/ecstasy, methamphetamine, or opiates

14. Clinically relevant chronic or acute infectious illnesses or febrile infections within two weeks prior to start of the study.
15. Subject with signs and symptoms suggestive of COVID-19 (i.e. fever, cough, etc)* within 14 days of inpatient admission.
16. Subject with known COVID-19 positive contacts in the past 14 days
17. Presence of tattoo, excessive hair (including shaved hair) or scarring on the test site on the back which in the opinion of the investigator would interfere with the study assessments.
18. Subject who currently in the opinion of the investigator, after medical review, has any of the following conditions:
    - Thrombophlebitis, thromboembolic disorders
    - A history of deep vein thrombophlebitis or thromboembolic disorders
    - Cerebrovascular or coronary artery disease (current or history)
    - Valvular heart disease with complications
    - Severe hypertension
    - Diabetes with vascular involvement
    - Headaches with focal neurological symptoms
    - Major surgery with prolonged immobilization
19. Surgical procedures or use of topical pharmacologic treatments directly over the test site(s) within 90 days before enrollment.
20. A subject with any condition possibly affecting drug absorption, distribution, metabolism or excretion of any drug substance but not limited to any of the following:
    - History or current evidence of dermatologic disorders/skin diseases including sunburn and keloids, that may interfere with the transdermal absorption of the study drug(s) at the test site;
    - History or current evidence of renal disease or impaired renal function at screening as indicated by abnormal levels of serum creatinine (≥ 1.4 mg/dL) or BUN (≥ 25 mg/dL) or the presence of clinically significant abnormal urinary constituents (e.g. albuminuria);
    - History or current evidence of 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: 1) AST/SGOT (≥ 1.2 ULN), ALT/SGPT (≥ 1.2 ULN), 2) GGT (≥ 1.2 ULN), ALP (≥ 1.2 ULN), 3) bilirubin (≥ 1.0 mg/dL) or CK (≥ 3 to 5 ULN). A single deviation from the above values is acceptable and will not exclude the candidate, unless specifically advised by the Investigator;
    - Evidence of urinary obstruction or difficulty in voiding at screening.
21. Evidence, as reported by analcohol breath testing during screening, for current alcohol abuse or reports a regular average alcohol consumption exceeding 18 g (women) or 35 g (men) of pure alcohol per day, i.e., 1 drink/day for women or 2 drinks/day for men (1 drink = 5 oz of wine or 12 oz of beer or 1.5 oz of hard liquor) within 6 months of screening.
22. Subject reported regular consumption of > 5 cups of coffee or tea per day (or equivalent consumption of ≥ 500 mg xanthine per day using other products)
23. Subject reports consumption of any drug metabolizing enzyme (e.g., CYP3A4 or other cytochrome P450 enzymes) inducing or inhibiting aliments, beverages or food

supplements (*e.g.,* broccoli, Brussels sprouts, grapefruit, grapefruit juice, star fruit, St. John's Wort *etc*.) within 2 weeks prior to dosing

24. Positive results at screening in any of the virology tests for HIV-Ab, HCV-Ab, HBsAg and HBc-Ab (IgG + IgM)
25. Performance of unaccustomed strenuous physical exercise (body building, high performance sports) from 2 weeks prior todosing.
26. Allergy to skin disinfecting agents, tape, or latex rubber, whenever appropriate substitutions cannot be applied or in the Investigator's opinion may pose a risk to the candidate.
27. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study
28. Participation in a clinical trial with at least 470ml blood drawn, or blood donation within 30 days prior to the start of the study.
29. Hemoglobin value < 11.0 g/dL
30. Subjects who have previously been enrolled in this study.

**as defined by WHO or local guidance*

5.4 Randomization Criteria

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

5.5 Lifestyle Considerations

5.5.1 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.
- Meals intake during the study will also be standardized

5.5.2 Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol for at least 24 hours prior to first dosing 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 at least 36 hours prior to first dosing until collection of the final pharmacokinetic sample of each study period.
- Subjects will abstain from the use of tobacco or nicotine containing products including nicotine patches and other delivery devices such as electronic cigarettes or vaporizers for at least 48 hours prior to dosing and during confinement at the clinical site.

5.5.3 Activity

- Subjects will not be permitted to assume a fully recumbent position for four hours following dosing.
- Subjects will not apply make-up, creams, lotions, powders, or other topical products to the skin area where the system will be placed, within 24 hours prior to first dosing and during the entire study.
- After application, patches must not be touched. Actions with the intent to re-apply a detached area of the patch, to apply pressure to the patch, or to reinforce the patch adhesion with the skin (e.g., overlays) must be avoided throughout the study
- Subjects are not allowed to shower while wearing the study patches
- 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.

5.5.4 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.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. 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, any protocol deviations and any adverse events or incidents as applicable.

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

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the Study Contact List located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical questions or problems if the established communication pathways between the investigational site and the study team are not available.

5.8 Rater/Clinical Assessor Qualifications

No rater/clinical assessor qualifications are required for this study.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

This includes 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.

6.1 Investigational/Study Product Supplies

The selection of the Reference product (the currently marketed and commercially available NicoDerm CQ patch form Alza), will be based on assay content to ensure that this product does not differ by more than 5% from that of the batch used as Test product (NicoDerm CQ patch from Dungarvan).

The following study products will be supplied by the Clinical Supplies Department, GSK CH:

Table 6-1 Investigational/Study Product Supplies

	Test Product	Reference Product
Product Name	NicoDermCQ 21 mg /system of 22 cm^2 surface area	NicoDermCQ (USA commercial product) 21 mg /system of 22 cm^2 surface area
Pack Design	One 21 mg patch in each pouch Patches are packaged in a pouch.	One 21 mg patch in each pouch Patches are packaged in a pouch.
Dispensing Details	Use one patch every 24hours	Use one patch every 24hours
Product Master Formulation Code (MFC)	CCI [redacted]	CCI [redacted]
Dose/Application	One application	One application
Route of Administration	Topical	Topical
Usage Instructions	• Apply patch on skin that is dry, clean and hairless. • Apply on the back • Press hand against the entire patch, hold for 10 seconds approximately, the applied	• Apply patch on skin that is dry, clean and hairless. • Apply on the back • Press hand against the entire patch, hold for 10 seconds approximately, the applied

	pressure will help the patch adhere to the skin securely	pressure will help the patch adhere to the skin securely
Return Requirements	Dispose of used patches by folding sticky ends together. Replace in the pouch. All unused samples, packaging and drug labels to be returned to Sponsor	Dispose of used patches by folding sticky ends together. Replace in the pouch. All unused samples, packaging and drug labels to be returned to Sponsor

Detailed instructions for the return of unused study product/study supplies for the accountability checks will be provided by GSK CH during the study in time for study close out visit. Sundry items will be supplied by the site/vendor, or if necessary, by GSK CH.

6.1.1 Dosage Form and Packaging

NicoDermCQ patch will be supplied to the clinical site as packaged in individual pouches for dispensing by the pharmacy.

The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSK CH Global Clinical Supplies group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

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. Subjects should be instructed to not remove or deface any part of the study label.

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

6.1.2 Preparation and Dispensing

NicoDermCQ patch will be prepared and/or dispensed by qualified unblinded site personnel according to the dosage and administration instruction.

Subjects will be assigned to products in accordance with the randomization schedule generated by an approved GSK CH vendor, prior to the start of the study, using validated software.

Study product will be dispensed by qualified site personnel per the dosage/administration instructions. Procedure should be in place to avoid nicotine cross-contamination. An additional member of site staff should ensure the dispensing procedures are completed accurately.

6.2 Administration

Only subjects enrolled in the study may receive study products and only authorized site staff may supply or administer study products. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized site staff only.

The patches will be applied according to the instruction provided in the US prescribing information (OTC Drug Facts label & Package Insert).

NicoDerm CQ patch (either Test or Reference patch according to randomization list) will be applied after an overnight fasting period of at least 10 hours, with subjects in a sitting position.

Patches will be applied on morning of study Day 1 of each treatment period. The patch will be applied to a clean and dry skin site on the upper back. The site must be relatively free of hair and free of any tattoos, scarring, or redness and free any conditions which in the opinion of the investigator may impact patch adhesion. Hair at the intended patch site could be clipped but cannot be shaved. To ensure adequate adhesion of the patch, the patch should be pressed down firmly on the skin for at least 10 seconds, making sure all the edges are attached. Staff will wash their hands after application. After application, patches may not be touched. No patch reinforcement or over taping is allowed.

Patches will be removed 24 hours after each application. Staff will wash their hands after patch removal.

The patch that will be applied during Period 2 will not to be applied to the same position as the patch that was applied during Period 1 but on the upper back of the contralateral side of the body.

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 measurements), eating, and drinking beverages excepting water which is allowed from 1 hour post dosing, for the first 4 hours after dosing.

6.2.1 Medication/Dosing Errors

Medication/dosing 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.

Such medication/dosing errors occurring to a study subject are to be captured in the CRF. In the event of medication dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

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

- Medication/dosing errors involving subject exposure to any of the study products;
- Potential medication/dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a medication/dosing error is accompanied by an AE, as determined by the investigator, the medication/dosing error and, any associated adverse event(s) are to be captured in the CRF AE form.

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol.

Overdose is not likely to occur in this study.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

6.3 Investigational/Study Product Storage

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study products received and any discrepancies are reported and resolved before use according to the supplied shipping documentation.

The investigator, or designee, will ensure that all study products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the 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 first 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 to appropriate site staff upon discovery and communicated to sponsor as soon as possible. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Excursions from the storage requirements, including any actions taken, must be documented as a protocol deviation and reported to the Sponsor.

Once an excursion is identified, the affected product (or products) must be quarantined and not used until the sponsor provides documentation of permission to use. Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

6.4 Investigational/Study Product Accountability

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

All study products 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 products should be stored according to the instructions specified on the product labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

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

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All unused study product for this clinical study will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided. The used study product will be destroyed by the study site. Detailed instructions for the return of unused study product/study supplies for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit.

6.5 Blinding and Allocation/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.

An approved GSK CH vendor 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.

6.6 Breaking the Blind

Not applicable given the open label study design.

.

6.7 Compliance

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

Subject will not smoke or use any tobacco or nicotine containing products 48 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 (3) 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 9.5 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.

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

6.8 Concomitant Medication/Treatment(s)

Subjects will abstain from all concomitant treatments, except for contraceptives and hormone replacement therapy, and those treatments that need to be used for the treatment of adverse events unless they jeopardize the integrity of the study. The study Sponsor should be immediately informed. Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about medications/treatments at each site visit.

Medication/treatments taken within 90 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after the first dose will be documented as concomitant medication/treatments.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures.

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

- Protocol violation that may impact the subject's safety
- Positive test for COVID-19, conducted during the study, at times deemed necessary by Investigator
- Protocol violation that may interfere with the drug's PK profile, including:
    - 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 36 post dose period (see Section 9.5 Expired Carbon Monoxide (CO) measurement for subject assessment)
    - Patch falls off or patch is inadvertently removed by the subject or those removed due to subject decision to discontinue from the study
- Withdrawal of informed consent
- Subject lost to follow-up
- Pregnancy

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

7.2 Lost to Follow up

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

Final safety assessments may be carried out when the subject returns to the study site, as deemed necessary by the Investigator

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

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 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.

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities section.

Adherence to the study design requirements, including all procedures are essential and required for study conduct.

8.1 Visit 1/Screening

Screening procedures will be conducted by the Investigator, or suitably qualified designee.

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:

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by GSK CH.

The investigator, or designee, should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The time the subject signed the informed consent form will be captured as this is the point at which all Adverse Events will be captured from. The date and time of consent will be captured in the CRF.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender, ethnicity and race.

Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005.

8.1.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information, as specified in Section 5, will be documented in the CRF.

8.1.4 Medical History, Smoker History and Prior Medication/Treatment

Details of relevant medical, smoker and surgical history (in the last 5 years), including allergies or drug sensitivity, will be documented in the eCRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 90 days and prior to signing the informed consent form, will be documented in the eCRF.

8.1.5 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical trial. This will be documented in the CRF.

To prepare for study participation, subjects will be instructed in the Lifestyle Guidelines and any Concomitant Medication/Treatment(s) requirements of the protocol.

8.1.6 Screening Procedures

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 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), respiratory rate and oral body temperature. The results for each measurement will be recorded in the CRF.
- Conduct full physical examination and skin site application evaluation. Any clinically relevant findings will be noted in the AE CRF page and enrollment will be based upon investigator judgement.
- Contraceptive review.
- Collect nasopharyngeal swab sample for COVID19 test. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.
- Collect single 12 lead electrocardiogram (ECG). Results (normal or abnormal) and clinical significance 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 and virology;
  - 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 of childbearing potential.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

8.2 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

8.2.1 Visit 2/Day -2

Subjects will be admitted to the clinical site at least 48 hours prior to Day 1 dosing.

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

- Obtain oral body temperature. The results for each measurement will be recorded in the CRF.
- Collect nasopharyngeal swab sample for COVID19 test. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.
- Collect urine for drug screening. The results will be recorded in the CRF.
- Collect urine pregnancy test for females of childbearing potential. The results will be recorded in the CRF.
- Confirm proper contraception is being used and the results will be recorded on the CRF.
- Collect expired CO measurement. Result will be recorded on the CRF.
- Collect alcohol breath test. Result will be recorded on the CRF.
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

8.2.2 Visit 2/Day -1

- Review Inclusion and Exclusion criteria and record in the CRF.
- Brief physical examination including evaluation of general appearance, heart, lung. The results will be recorded in the CRF.
- Obtain oral body temperature. The results for each measurement will be recorded in 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.
- Subjects will begin fasting at least 10 hours prior to dosing on Day 0.

- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.3 Visit 2 /Day 1

Prior to dosing, within 1 hour of patch application, the following procedures will be completed and recorded on the CRF:

- Expired CO measurements to be collected prior to Inclusion/Exclusion 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. 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) and record in the CRF.

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 1: 30 minutes and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20 hours. A deviation of ±3 minutes will be accepted for the blood samples. Time of blood sampling will be recorded in the CRF.
- As needed for period 1, collect 3x random CO measurements (see section 9.5 Expired Carbon Monoxide (CO) measurement), and record in the CRF.
- Conduct adhesion assessment within 5 minutes from patch application and 6, 12 and 18 hours post application.
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.4 Visit 2/Day 2

- Collect blood samples for pharmacokinetic analysis at 24, 25, 26, 27, 28, 30, 32, and 36 hours post dosing at Day 1 continuing into Day 2. A deviation of ±3 minutes will be accepted for the blood samples. Time of blood sampling will be recorded in the CRF
- Conduct adhesion assessment directly before patch removal (24 hours after patch application)
- Patch removal and record in the CRF

- As needed for period 1, collect 3x random CO measurements and one measurement after the last PK sample (see section 9.5 Expired Carbon Monoxide (CO) measurement), and record in the CRF
- Obtain oral body temperature. The results for each measurement will be recorded in the CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.
- Meals as required. Time and consumption of meals will be recorded on CRF.

8.2.5 Washout period

Washout period of at least 2 days after the first dose.

- Obtain oral body temperature. The results for each measurement will be recorded in the CRF.
- Collect expired CO measurement. Result will be recorded on the CRF.
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.6 Visit 3/Day 4

- Obtain oral body temperature. The results for each measurement will be recorded in the CRF.
- Collect expired CO measurement prior to continued eligibility check. Result will be recorded on the CRF.
- Collect urine pregnancy test for all females of childbearing potential. The results will be recorded in the CRF
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.7 Visit 3/Day 5

Prior to dosing, within 1 hour of patch application, the following procedures will be completed and recorded on the CRF:

- Brief physical examination including evaluation of general appearance, heart, lung. The results will be recorded in the CRF.
- Review Inclusion and Exclusion criteria and record in the CRF
- Collect expired CO measurements. Result will be recorded on the CRF.
- Collect supine blood pressure and pulse rate.
- Collect respiratory rate, oral body temperature and record in the CRF.
- Collect a blood sample for pharmacokinetic analysis. 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) and record in the CRF.

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 5: 30 minutes and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20 hours. A deviation of ±3 minutes will be accepted for the blood samples. Time of blood sampling will be recorded in the CRF.
- As needed for period 2, collect 3x random CO measurements (see section 9.5 Expired Carbon Monoxide (CO) measurement), and record in the CRF.
- Conduct adhesion assessment within 5 minutes from patch application and 6, 12, 18 hours post application.
- Meals as required. Time and consumption of meals will be recorded on CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

8.2.8 Visit 3/Day 6

- Collect blood samples for pharmacokinetic analysis at 24, 25, 26, 27, 28, 30, 32, and 36 hours. A deviation of ±3 minutes will be accepted for the blood samples. Time of blood sampling will be recorded in the CRF
- Conduct adhesion assessment directly before patch removal (24 hours after patch application)
- Patch removal and record in the CRF
- As needed for period 2, collect 3x random CO measurements and one measurement after the last PK sample (see section 9.5 Expired Carbon Monoxide (CO) measurement), and record in the CRF

- Obtain oral body temperature. The results for each measurement will be recorded in the CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.
- Meals as required. Time and consumption of meals will be recorded on CRF.

8.3 End of Study/Day 6

The exit examination procedure will be done before check-out from the clinic.

- 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. The results will be recorded in the CRF.
- Collect nasopharyngeal swab sample for COVID-19 test. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.
- Collect serum pregnancy test for all females of childbearing potential. The results will be recorded in the CRF.
- Obtain blood and urine samples for safety laboratory tests.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

If a subject has any clinically significant, study related abnormalities or AEs at the end of the study, the GSK CH medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

8.4 Follow-up Visit

The study site may contact a subject to follow up an AE post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional examinations may be carried out at such visits.

9 STUDY 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 complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment 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 Sponsor must be informed of any missed assessments in a timely manner.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol

9.2 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

9.2.1 Laboratory Tests

The following laboratory tests/analytical measures will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures of this protocol.

Table 9-1 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and Creatinine	pH	Urine drug screen[b]
Hematocrit	Glucose (fasting)	Glucose (qual)	Urine cotinine screen
RBC count	Calcium	Protein (qual)	Serum FSH[c]
MCV	Magnesium	Blood (qual)	Serum pregnancy test (WCBP)[d]
MCH	Sodium	Ketones	Urine pregnancy test (WCBP)[d]
MCHC	Potassium	Nitrites	breath alcohol test
Platelet count	Chloride	Leukocyte esterase	
MPV	Total CO2 (Bicarbonate)	Urobilinogen	
WBC count	AST, ALT	Urine Bilirubin	
Total neutrophils (Abs)	Direct Bilirubin	Specific gravity	
Eosinophils (Abs)	Indirect Bilirubin	Microscopy[a]	
Monocytes (Abs)	Total Bilirubin		
Basophils (Abs)	Alkaline phosphatase		
Lymphocytes (Abs)	Uric acid		
	Albumin		

Hematology	Chemistry	Urinalysis	Other
	Total protein		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

Definitions: RBC= Red blood cell; MCV= Mean corpuscular volume; MCH= Mean corpuscular hemoglobin; MCHC= Mean corpuscular hemoglobin concentration; MPV= Mean platelet volume; WBC= White blood cells; BUN=Blood urea nitrogen; HIV= Human immunodeficiency virus; AST= transaminase; ALT= alanine transaminase; PT/INR= prothrombin time/ international normalized ratio; GGT= Gamma-glutamyl transpeptidase.

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

[b] Minimum requirement for drug testing includes: cocaine, THC, opiates/opioid's, benzodiazepines, 3,4-methylenedioxy-N-methylamphetamine (MDMA)/ecstasy, methamphetamine and amphetamines; to be done as described in Study Procedures

[c] FSH done at Screening only in females who have been amenorrhoeic for 1 year.

[d] WCBP= Female subjects of childbearing potential will be tested for serum human chorionic gonadotropin (hCG) as applicable -see section 9.2.5

Additional laboratory results may be reported on these samples because 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.

Subjects may undergo random urine drug screening at the discretion of the investigator. Drug screening conducted prior to dosing must be negative for subjects to receive investigational product.

Any remaining serum/plasma from samples collected for clinical safety labs will be destroyed at the end of the study.

9.2.2 Virology

Virus serology will be performed at times specified in the Section 8: Study Procedures for HBs Ag, anti-HBc (IgG + IgM), anti-HCV Ab, HIV 1 and HIV 2 antibodies. Serology will be performed by using the same sample drawn for chemistry; therefore, no additional blood needs to be drawn for serology. In case of a positive finding in virus serology screen, the subject must be excluded from trial participation.

9.2.3 Urine illicit drug screen

Urine will be collected at times specified in the Section 8: Study Procedures. In case of a positive finding for any substance class, the subject must be discontinued from the trial (or excluded from trial participation in case of positive findings at the screening visit).

9.2.4 Alcohol test

An alcohol breath test will be conducted at times specified in the Section 8: Study Procedures. In case of a positive finding in the alcohol test, the subject must be discontinued from the trial.

9.2.5 Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test, will be performed at screening and end of study (or early termination) . A urine pregnancy test will be performed at day -2 and day 4. Results will be obtained prior to dosing during each period.

The investigator and site personnel will remind subjects at each visit to inform site personnel if their menstrual cycle has changed or if they have any other reason to suspect they may be pregnant (e.g. had unprotected intercourse since the last visit).

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.

9.2.6 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, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, vascular and neurological systems.

A brief physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

Any untoward findings identified on physical exams conducted after the administration of the first dose of investigational product will be captured as an adverse event, if those findings meet the definition of an adverse event.

9.2.7 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.

9.2.8 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 a minimum 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.

9.2.9 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.

9.2.10 Body Temperature

Temperature will be measured orally.

9.2.11 COVID-19 Test

Nasopharyngeal swab will be collected to test for COVID-19 using RT PCR or antigen test, at times specified in the Section 8: Study procedures. Two consecutive negative tests for active COVID-19 separated by > 24 hours are required for inclusion in the study. One test will be done at screening and one test will be done on Day -2.

For detection of COVID-19, test/s are to be performed as follows:

- At screening visit
- At check-in (Day -2) and early discontinuation or end of study
- At any time during residential period in study, when subjects report symptoms suggestive of COVID-19

9.2.12 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 CH 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.

9.3 Pharmacokinetics (PK)

Twenty-three (23) blood samples will be collected for pharmacokinetic analysis predose (within one hour before dosing) with an intravenous catheter , 30 minutes and at 1, 2, 3, 4,5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 25, 26, 27, 28, 30, 32, and 36 hours following study drug administration. Time zero ("0") as reference for post-dose PK samplings is defined as the time of complete patch application. Time zero will be recorded in the eCRF.

9.3.1 Plasma for Analysis of Nicotine

During all study periods, blood samples 3 mL to provide a minimum of 1mL plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing K2EDTA at times specified in the protocol.

The actual sample 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, if 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 Syneos 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.

9.3.2 Shipment of Pharmacokinetic Samples

PK samples will be refrigerated (or kept cold in a cooler with a frozen ice pack) until transported to the laboratory for analysis. The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

Samples will be transported to the assay lab in at least two separate shipments, with each set of aliquots in separate shipments. Once the assay lab confirms receipt of the first shipment, the second set of aliquots may be sent. The samples should be packed on sufficient dry ice to keep them frozen for at least 72 hours.

All PK samples will be stored till it is properly disposed of at the end of its retention period (*i.e.* till study report is issued), or useful life (*i.e.* till expiry of stability), or upon receipt of a request to destroy the PK samples due to withdrawal of consent. No sample will be retained beyond 2 years from last participant last visit.

9.4 Blood Volume

The total blood sampling volume for each subject in this study is approximately 171.4 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 9-2 Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	End of study	
Safety Labs screening	21.7	1			21.7
Safety Labs end of study	11.7			1	11.7
PK	3		46		138
TOTAL					171.4

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

9.5 Expired Carbon Monoxide (CO) measurement

Using a calibrated Bedfont Smokerlyzer®, the investigator or designee will perform twelve (12) scheduled CO measurements, one upon check-in at Baseline, one immediately before randomization in Period 1, one during the wash-out, 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 three (3) 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.

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.

9.6 Patch Adhesion

Patch adhesion will be evaluated and scored five times: within 5 minutes from patch application, approximately, 6, 12 and 18 hours after patch application and immediately prior to patch removal (morning). The deviations from the scheduled time points exceeding 10 min before or

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

after the theoretical time will be recorded and commented as protocol deviations. The assessment will be performed by a trained evaluator based on the FDA recommend scoring system:

Table 9-3 Patch adherence grades

Adherence Grade	Adherence condition
0	≥90% adhered (essentially no lift off the skin)
1	≥ 75% to <90% adhered (some edges only lifting off the skin)
2	≥ 50% to <75% adhered (less than half of the patch lifting off the skin)
3	>0% to <50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
4	0% adhered patch detached (patch completely off from the skin)

No patch reinforcement or over taping is allowed.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

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

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in 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 product including any washout or lead-in product (or medical device).

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product 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 product 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 NOT 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.

10.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a particular category of an adverse event where the adverse outcome is serious. 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 subject 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 subject 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 AEs. 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but it does cause 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 subject 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.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements of an AE versus an SAE.

10.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs will be collected immediately after a subject provides consent to participate in the study by the completion (signature) of the ICF and until 5 days following last administration of the study product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to non-leading such as "How do you feel" will be assessed and any AE's recorded in the CRF and reported appropriately.

The investigator (or medically qualified designee) 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 a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g., 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 in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to GSK CH in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by GSK CH. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to GSK CH.

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE if known and not the individual signs/symptoms. (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page 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 AE CRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available

- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- 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 in relation to the study product
- Outcome if known

QPS will email the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance at GSK CH PPD), with copy to the appropriate Syneos Project Manager and 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.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

The investigator or medically qualified designee will assess the intensity for each AE 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 should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious 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. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

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

For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where 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 US prescribing information (OTC Drug Facts label & Package Insert), 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.

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.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK CH. **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 CH.** The investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.

As the product falls under the combination products rule an assessment must also be made for the medical device.

10.6 Follow-up of AEs and SAEs

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

All AEs (serious and non-serious) 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 CH to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE CRF page and on the SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to GSK CH within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify the Case Management Group, Global Clinical Safety and Pharmacovigilance at GSK PPD with copy to the appropriate GSK CH Study Manager.

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

As the product fall under the combination product rule, a medical device incident form must also be completed.

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an 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.

10.8 Regulatory Reporting Requirements for SAEs

GSK CH 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 CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Both the investigator and the sponsor will comply with all local medical device reporting requirements

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g,. summary or listing of SAE from the sponsor will review and then file it along with the US prescribing information (OTC Drug Facts label & Package Insert) in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 14 days after last administration of study product.

10.9.2 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 at GSK (PPD) 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 at GSK (PPD). 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, QPS 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. Original pregnancy information forms will be retained in the investigator study master file.

10.10 Medical Device Incidents

The definitions and procedures detailed are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

In the USA, NicoDermCQ is classified as Drug/Device - Combination Type 2 (Prefilled Drug Delivery Device).

10.10.1 Definition of an Incident

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.

Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

An **incident** associated with a device happened and

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

10.11 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH **immediately and under no circumstance should this exceed 24 hours** of the investigator or designee becoming aware of the situation.

Any medical device incident occurring during the study will be documented in the subject's medical records, if in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE (serious and non-serious), the appropriate AE CRF page and SAE form will be completed and reported as per the AE and SAE reporting sections.

The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK CH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

The completed Incident Report Form should be scanned and emailed to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (uk.gsk-rd-gcsp-ctsm-admin@gsk.com) with copy to the appropriate GSK CH Study Manager.with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE form should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will be retained in the investigator study master file.

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

The investigator will follow the following directions regarding the reporting of a device failure (malfunction):

- Notify GSK CH immediately (by following the process described above).
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by GSK CH, return the failed device to the sponsor as soon as possible, including documentation of the details of the failure
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by the Investigator site, report the incident to the device manufacturer and follow the manufacturer instructions for the return of the failed device (whilst keeping GSK CH informed).

10.12 Follow-up of Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed Incident Report form with all changes signed and dated by the investigator.

10.13 Regulatory Reporting Requirements for Medical Device Incidents

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during all periods of the study in which the medical device is used.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

11 DATA MANAGEMENT

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

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, 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. 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 Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

11.1 Case Report Form

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

For each subject who has given informed consent/assent the CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Management of clinical data will be performed in accordance with Third Party BDM Vendor applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no Personal Information (PI) (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 as applicable at the completion of the study.

11.2 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 Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal validated medication dictionary, GSK Drug.

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, 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 (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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.

11.3 Processing Patient Reported Outcomes

Not applicable.

11.4 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 quality control process will be 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.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

A sufficient number of healthy adult smokers will be screened to randomize approximately 20 healthy adult smokers, to ensure that 12 complete the entire study assuming a 40% dropout and non-evaluable rate. The highest intra-subject CV calculated from previous studies was 13%.

CCI [redacted]

12.2 Populations for Analysis

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 regardless of patch adhesion score.

The following PK analysis set is defined to address the PK objectives and further PK considerations within this study:

- PK analysis set includes all subjects of the PK population, for which the relevant predose-adjusted PK parameters (at least one AUC or C_{max}) can be derived. This

analysis set will be used in PK summaries, the primary analysis, and the secondary analysis.

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding/analysis (as appropriate). This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

SAP creation and statistical analysis will be performed by CCI

Pharmacokinetic variables will be calculated by CCI

All concentration and PK data will be listed. This includes any data for subjects who are not included in the analysis (i.e. subjects withdrawn from the study due to adverse events).

12.3.1 Primary Analysis(es)

Criteria for assessing bioequivalence (on baseline adjusted data).

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.

Analysis criteria:

When predose concentrations are greater than the lower limit of quantification (LLOQ), baseline-adjusted nicotine plasma concentrations will be used to determine the following pharmacokinetic parameters using standard noncompartmental techniques: maximum plasma concentration observed (C_{max}), area under the plasma concentration versus time curve from time zero to the real time corresponding to the last concentration above LLOQ (AUC_{0-t}) and the area under the plasma concentration versus time curve extrapolated to infinity (AUC_{0-inf}).

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, computed using the linear trapezoidal rule

AUC_{0-inf}: Area under the plasma concentration versus time curve calculated from time zero to infinity. $AUC_{0-inf} = AUC_{0-t} + C(t)/\lambda_z$ where C(t) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant)

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

Analyses

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

The nicotine 21 mg patch manufactured at Alza (Reference) versus the 21 mg patch manufactured at GSKCH Dungarvan (Test), in terms of nicotine AUC_{0-t}, AUC_{0-inf} and C_{max}.

The statistical analyses will be done based on PK analysis set, (see section 12.2 for definition). Safety population will be used for individual plasma concentration listings and figures.

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 (on baseline-adjusted data) 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.

The PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{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 plasma concentrations over time containing individual values and summary statistics for each time point.

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.

Correction for non-zero baseline for the primary analysis.

The pre-dose nicotine concentration will be estimated using the using the λ_z calculated from the subjects own data as follows:

$C(t)\ adjusted = C(t)\ observed - C(0)\ e^{-\lambda_z t}$

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

12.3.2 Secondary Analysis(es)

The PK analysis set 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;

λ_z apparent elimination rate constant for plasma nicotine computed as the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time.

The parameters λ_z and $t_{1/2}$ 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.

Adhesion

A frequency table showing the adhesion score for each patch per assessment timepoint.

Summary statistics (mean, sd, minimum, median and maximum) of duration (days) of patch wear for those that fall off.

12.3.3 Safety Analysis(es)

Criteria for assessing safety:

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

Adverse events:

The assessment of safety will be based on the frequency and severity of AEs that are emergent after subject randomization, including all application site reactions.

The incidence of treatment-emergent AEs will be tabulated after grouping by preferred term within System Organ Class (SOC). AEs will be summarized as the number and percentage of subjects having any AE, an AE by SOC, and an AE by preferred term within SOC. The subset of AEs suspected of a relationship to study patch application will be summarized similarly. All treatment emergent AEs will also be tabulated by severity. Each AE will be attributed to the patch whose application immediately preceded 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.

12.3.4 Other Analysis(es)

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

- CO monitoring

12.3.5 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.

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

12.3.6 Demographic and Baseline Characteristics

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

12.3.7 Study Drug/Product Compliance and Use of Other Therapies

12.3.7.1 Study Drug/Product 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, and subjects with baseline > 5% of the C_{max} will also be summarized.

12.3.7.2 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the safety population.

12.3.8 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 λ_z can be estimated from the subject's mean λ_z value from the other treatments. If a λ_z value cannot be calculated from the other treatments, then the λ_z will be obtained from the treatment mean value for subjects with non-missing values of λ_z in the period in which it is not available. This estimated λ_z can be used to calculate other λ_z dependent variables. This λ_z 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 "Not detectable" (ND), which will be shown as missing (explanations will be specified in the footnote of TFLs).

12.3.9 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and GSK CH procedures, GSK CH 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 CH 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 CH 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 Syneos. 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.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK CH 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.

13.3 Regulatory and Ethical Considerations

13.3.1 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.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and 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), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), 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.

13.3.3 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.

13.3.4 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.

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

Within 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.

13.4 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 CH processes.

GSK intends to make anonymized subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

13.5 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 CH site or other mutually-agreeable location.

GSK CH 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 CH Policy.

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

13.6 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 CH 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 as per the signed contractual agreement, from the issue of the final Clinical Study Report (CSR) or 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 CH 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 CH 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.

13.7 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 study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of nicotine formulation 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 CRF's 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.

14 REFERENCES

1. CCI [redacted]
2. ICH Topic E6 (R2) Guideline for Good Clinical Practice, Nov 2016.
3. World Medical Association Declaration of Helsinki, 64th General Assembly, Fortaleza 2013.
4. [FDA Guidance on Nicotine 2019]
5. [FDA Draft guidance, Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs October 2018]
6. [FDA Draft guidance, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application December 2013]

15 APPENDICIES

15.1 ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
λ_z	The terminal elimination rate constant
Abs	absolute
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the curve
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of the last measurable sampling time point, t
AUC_{0-inf}	area under the concentration time curve from time 0 to infinity
BA	bioavailability
BDR	blinde data review
BE	bioequivalence
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
C_{max}	peak or maximum observed concentration
CO	expired carbon monoxide
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
K_2EDTA	dipotassium ethylene diamine tetra acetic acid
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
N/A	not applicable
NRT	nicotine replacement therapy

Abbreviation	Term
PCR	polymerase chain reaction
PI	principal investigator
PI	Personal information
PK	pharmacokinetics
PR	pulse rate
PT	prothrombin time
QC	quality control
QTc	corrected QT
RBC	red blood cell
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	standard operating procedure
SRSD	single reference study document
$t_{1/2}$	terminal half-life
THC	tetrahydrocannabinol
t_{max}	time to reach maximum concentration
ULN	upper limit of normal
US	United States
USPI	United States package insert
WCBP	Women of childbearing potential
WBC	white blood cell

Signature Page for 217756 TMF-208654 v1.0

Reason for signing: Approved	Name: PPD Role: A Date of signature: PPD GMT+0000

Reason for signing: Approved	Name: PPD Role: A Date of signature: PPD GMT+0000

Signature Page for TMF-208654 v1.0