Statistical Analysis Plan

Sponsor Name: GSK Consumer Healthcare

Protocol Number: 217756
Protocol Title: 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 Version and Date: 1.0, 24- Jun-2021

PPD

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This document contains confidentiality statements that are not relevant for this publicly available version

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	08-Sep-2021	PPD	Initial Version
0.2	21-Sep-2021	PPD	Incorporate Sponsor Comments

Signature Approvals

I confirm that I have reviewed this document and agree with the content.

PPD Approval		
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1. Glossary of Abbreviations

Abbreviation	Description
λz	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	blind data review
BE	bioequivalence
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
Cmax	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

Abbreviation	Description
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
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

Abbreviation	Description
SGPT	serum glutamic pyruvic transaminase
SOP	standard operating procedure
SRSD	single reference study document
$t_{½}$	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

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figure which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusion regarding the study objectives. Safety, tolerability, and pharmacokinetic (PK) analyses will all be described.

This SAP is based on the following documents:

- Protocol No. 217756, Version 1.0 dated 24-Jun-2021 (PPD
- Electronic Case Report Form (eCRF) Final 1.0, dated 09-Sep-2021
- Protocol Administrative Change Letter dated 07-Jul-2021

The plan may change due to unforeseen circumstances and any changes made after the plan has been finalized will be documented. If additional analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the clinical study report (CSR). No change will be made without prior approval of the study sponsor. No revision to the SAP is required for changes which do not affect the statistical analysis methods, definitions, or rules defined in this document.

When applicable, all methodologies and related processes will be conducted according to PPD Standard Operating Procedures (SOPs) as appropriate. Shells for all statistical tables, listings, and figures referred to in this SAP will be displayed in a separate document.

2.1 Responsibilities

PPD will perform the statistical analyses and are responsible for the production and quality control of all tables, listings, figures (TLFs) and PK analysis.

2.2 Timings of Analyses

No Interim analysis is planned for this study.

Final Analysis:

The analysis of safety and PK is planned after all subjects complete the final study visit or terminate early from the study.

3. Study Objectives

3.1 Primary objectives

- 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).

3.2 Secondary objective

- Assess the pharmacokinetic profile of the patches
- To monitor adhesion of the patches to the skin

3.3 Safety objective

- Assess the safety profile (local and systemic) of both products

4. Endpoints

4.1 Pharmacokinetic Endpoints

- Primary
  - 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
  - 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 $t_{1/2} = \ln(2)/ \lambda_z$)

All PK parameters, calculated using plasma concentration data, are referred to in Sections 9.1, 9.2, and 9.5.

4.2 Safety Endpoints

Safety will be assessed by:

- Monitoring and recording of adverse events
- Physical examination
- Vital signs
- Laboratory tests

4.3 Adhesion Endpoints

- Adhesion score

5. Study Design

This is a 2-arm, single center, single dose, open-label, randomized, two-sequence, two-period crossover, bioequivalence study.

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

Each subject will be dosed once in each treatment period, 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.

5.1 Subject Selection

Healthy adult smokers (age 21 to 55 years of age, inclusive, at the signing of informed consent) that have smoked more than 10 cigarettes per day for 1 year prior to inclusion in study. Subjects will also be required to have a Body Mass Index (BMI) of 19 to 27 kg/m^2 and a total body weight > 50 kg. Detail all of the inclusion and exclusion criteria may be found in study protocol, Sections 5.2 and 5.3.

5.2 Determination of Sample Size

Twenty (20) healthy adult smokers will be enrolled in the study, 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]

5.3 Randomization and Blinding

Randomization:

Computer generated randomization schedules will be prepared prior to the start of the study. The schedules will be generated through the statistical analysis system (SAS) software, version 9.4. Block randomization will be used. Subjects will be randomly assigned a 3-digit subject number beginning with 0 with the last two numbers being 01-20.

Blinding:

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

5.4 Subject Withdrawal and Replacement

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
    - 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

6. Analysis Sets

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.

The analysis of safety and tolerability parameters will be based on the Safety Population detailed in Section 6.1. The analysis of PK parameters will be based on the PK Population detailed in Section 6.2.

6.1 Safety Population

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

6.2 Pharmacokinetic Population

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 objective and further PK considerations within this study:

- PK analysis set includes all subject 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.

7. General Aspects for Statistical Analysis

7.1 General Methods

SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA) software will be used to perform all data analyses.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by subject number and assessment date/time, when applicable.

The following labels for treatment will be used on all tabulations where the results are displayed by treatment, in the following order:

- NicoDerm CQ Dungarvan (Test)
- NicoDerm CQ Alza (Reference)

7.2 Summary Statistics

Unless otherwise stated, continuous variables will be summarized using the number of observations (n), and the statistics arithmetic mean, standard deviation (SD), geometric mean,

coefficient of variation (CV%), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, arithmetic mean and median will be presented to one more decimal place than the raw data and the SD will be presented to two more decimal places than the raw data. Categorical variables will be summarized with frequency counts and percentages. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population, unless otherwise stated.

For the plasma PK data, the data will be rounded to two decimal places in the listings, except for the following situations:

- λ_z data: rounded off to four decimal digits.
- Pharmacokinetic parameters related to time such as T_{max}, $K_{el\ Lower}$, and $K_{el\ Upper}$ must be reported with the same precision as the actual sampling time: rounded off to 3 decimal digits.
- Concentration versus time data, as well as C_{max}: reported to 4 decimals.

Summary statistics including the geometric mean (three decimal places) and coefficient of variation (CV) (%) (one decimal place).

Only data from nominal protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the listings and figures.

All assessments will be presented in the listings.

7.3 Key Definitions

Study Day:
Study day will be calculated using first patch administration (either Test or Reference) date as the reference date. If the date of interest occurs on or after the first patch administration date, study day will be calculated as (date of interest – first patch administration date) + 1. If the date of interest occurs prior to the first patch administration date, study day will be calculated as (date of interest – first patch administration date). There will be no study day 0.

Prior medication:

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

Concomitant medication:

Medications/treatments taken after the first patch administration will be documented as concomitant medication/treatments.

Treatment: Treatment is assigned as the last received treatment, except in the case of pre-dose measurements. Any non-adverse event assessment occurring on the same calendar date as a given patch application before dosing would be attributed to the same treatment given on that

calendar day. If no patch was applied on the same calendar day then any measurements predose will not be summarized by treatment. Adverse events will be summarized only by the last received treatment.

Age:
Defend as age at Study day 1 = (Study day 1) visit date - date of birth + 1) / 365.25 and truncated to complete years.

Height:
Height (in cm) = height (in inches) * 2.54

Weight:
Weight (in kg) = weight (in lbs) * 0.4536

BMI:
BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

7.4 Handling of Dropouts and Missing Data

All data from subjects who withdraw from the study will be included in the summaries up to the time of withdrawal.

For safety,

- If an AE is recorded with an onset date corresponding to a patch application day, but the time is missing, then the AE will be assigned to the actual treatment with patch application that day and considered treatment-emergent.
- If an AE is recorded with an onset date that does not correspond to a patch application day, but the time is missing, then the AE will be assigned to actual treatment that covers the AE onset day and considered treatment-emergent if appropriate.
- If an AE is recorded with an onset date where day and time are both missing, then the AE allocation to a treatment will be done on a case by case basis considering available information (e.g. AE onset date, AE end date, AE comments, subject disposition) in raw data. It will be considered treatment-emergent if appropriate.
- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate
- Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

For PK analysis, only observed concentration data will be used in the data analysis except for concentration values BLQ as described in Section 9.1 and Section 9.2. No attempt will be made to extrapolate or interpolate estimates for missing data.

8. Demographic, Other Baseline Characteristics and Medication

8.1 Inclusion and Exclusion Criteria

All recorded inclusion/exclusion criteria status will be presented in a data listing for the Safety Population. Each subject's inclusion or exclusion from each population will also be presented in a data listing.

8.2 Demographics and Body Measurements

The demographic characteristics will consist of age (years), sex (female or male), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Chinese, Multiple, Australian Aborigine/Torres Strait Islander, and Other). The body measurements consist of height (cm), weight (kg), and body mass index (BMI) (kg/m^2).

Descriptive statistics (n, mean, SD, Min, median, and Max) will be calculated for body measurements using the last results obtained prior to first patch administration. Frequency counts and percentages will be tabulated for categorical variables. All demographic characteristics will be summarized by treatment group and listed by subject for the Safety Population and PK Population. If the Safety Population and PK Population are the same, the table for the PK Population will not be generated.

8.3 Medical History

Medical history will be listed by subject. Any abnormal findings from the physical exam occurring before the first patch administration will be included in the Medical History. The Medical Dictionary for Regulatory Activities (MedDRA®) Version 24.0 will be used to classify all medical history findings by System Organ Class (SOC) and Preferred Term (PT).

8.4 Urine Illicit Drug Screen and /Alcohol breath test

A urine illicit drug screen will be performed at screening and Day -2 test for testing includes: cocaine, THC, opiates/opioid's, benzodiazepines, 3,4-methylenedioxy-N-methylamphetamine (MDMA)/ecstasy, methamphetamine and amphetamines.

An alcohol breath test will be performed at screening and Day -2.

The urine illicit drug screen and alcohol breath test and restriction assessments will be presented in a separate listing for the Safety Population.

8.5 Virology

Virus serology will be performed at screening for HBs Ag, anti-HBc (IgG + IgM), anti-HCV Ab, HIV 1 and HIV 2 antibodies. Findings from Virology results will be included in listings for the Safety Population.

8.6 Pregnancy Testing and Follicle Stimulating Hormone (FSH) Levels

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. 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

FSH will be performed at the screening visit for females who have been amenorrhoeic for 1 year.

Results from the pregnancy testing and FSH Levels will be listed, separately, for the safety population.

8.7 COVID-19 Testing

Nasopharyngeal swab will be collected to test for COVID-19 using RT PCR or antigen test, at screening, Day -2, early discontinuation or end of study, and at any time during residential period in the study when subjects report symptoms suggestive of COVID-19. A listing including all results from COVID-19 testing will be created.

8.8 Electrocardiogram

A standard 12-lead ECG will be performed at screening. Results of any clinically significant abnormalities should be reported in the CRF. Clinically significant abnormalities should also be recorded on the Adverse Event CRF. All findings will be listed.

8.9 Prior and Concomitant Medications

Concomitant medication use will be recorded from the time the subject signs the ICF until the EOS visit. Concomitant medication use is permitted if indicated by the investigator for premedication or treatment of an AE.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD), Version B3, Mar 2021 or later. For the purpose of inclusion in Prior and concomitant medication tables, incomplete medication start and stop dates on CRF will be imputed as follows:

- If the stop date is incomplete, the following rules will be applied:
  - Missing day: Assume the last day of the month;
  - Missing day, month, and year: Assume that the medication is continuing;
  - In the case of the death of a subject, and if the imputed end date is after the date of death, the end date will be imputed as the date of death.
- If the stop date is incomplete, imputed end date will be used instead of reported end date
- If the start date is incomplete, the following rules will be applied:

- Missing day: Assume the first day of the month;

- However, if the partial date and the date of Patch administration lie within the same month and year and the date of Patch administration is not after the stop date of the medication, set to the date of Patch administration. Otherwise, set to stop date of the medication.
  - Missing day and month: Assume January 1st.

- However, if the partial date and the date of Patch administration lie within the same year and the date of Patch administration is not after the stop date of the medication, set to the date of Patch administration. Otherwise, set to stop date of the medication.
  - Missing day, month, and year: Assume date of Patch administration if it's not after the stop date for the medication. Otherwise, set to stop date for the medication.

For the missing day imputation, the following examples should be used for reference:

- Example 1:

  Medication start: UNJUN2019

  Medication end: 20OCT2019

  Date of administration: 16OCT2019

  Medication start imputed: 01JUN2019

- Example 2:

  Medication start: UNOCT2019

  Medication end: 20OCT2019

  Date of administration: 16OCT2019

  Medication start imputed: 16OCT2019

- Example 3:

  Medication start: UNOCT2019

  Medication end: 20OCT2019

  Date of administration: 24OCT2019

  Medication start imputed: 20OCT2019

Relative start day or end day with respect to the dose date of the patch will not be calculated if the medication start date or end date is incomplete.

All prior and concomitant medications will be presented in data listings for the Safety Population.

8.10 Study Drug Administration

The study drug administration details including date and time of administration, Treatment

Description, and the question "Patch Application applied" (and reason if no) will be listed by Subject. An additional listing for Patch Removal time will also be included.

All patch adhesion summaries and analysis will be conducted on the Safety Population.

Adhesion will be assessed five times during each administration of the patches: within 5 minutes from patch application, at approximately 6, 12, and 18 hours after patch application, and immediately prior to patch removal.

Summary statistics will be derived for all subjects whose patch fell off (adhesion score of 4) and the patch wear time of all subjects, separately (arithmetic mean, SD, minimum, median and maximum).

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

8.11 Study Drug 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.

9. Pharmacokinetic Analyses

All plasma concentration and PK parameter summaries and analysis will be conducted on the PK Population. All concentration and PK data will be listed (Safety Population). This includes any data for subjects who are not included in the analysis (i.e. subjects withdrawn from the study due to adverse events). The listing for plasma concentration will include planned timepoint, sample collection (yes or no), date and times of collection, and the calculated time deviations from the planned timepoint.

9.1 Correction for Non-Zero Baseline of Nicotine

For the primary analysis the following corrections will be performed:

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}).

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

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

9.2 Handling of Concentrations Below the Lower Limit of Quantification (BLOQ), No Reportable Concentration Values, and Missing Data

For the analysis of all individual plasma concentrations and all secondary PK parameter, all concentration BLOQ values that occur before C_{max} will be treated as zero (0). BLOQ values after C_{max} will be treated as "Not Detectable" (ND), which will be shown as missing for plasma PK concentrations and PK parameter estimation.

Samples with invalid concentration (due to bioanalytical or clinical issue) will be replaced by "0.00" when it occurs prior to patch application. Otherwise they will be set to missing for tabulation, graphical representation and calculation purposes if it occurs after patch application.

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 λ_z value from the other treatment. If a λ_z value cannot be calculated from the other treatment, 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.

9.3 Handling of the Difference between the Scheduled and the Actual Sampling Times

The actual clock time for patch application and each collection time for the PK samples will be

recorded. For all sampling times, the actual sampling times relative to patch application will be calculated as the difference between the actual clock time of sampling and the actual clock time of patch application. The actual post-dose sampling times relative to patch application expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to patch application, which will always be reported as zero (0.000), regardless of the time difference. Scheduled sampling times will be presented in concentration tables and mean graphs, while actual sampling times will be presented in the individual graphs.

9.4 PK Sampling Schedule

Blood samples will be collected from each subject during this study for the determination of the PK of nicotine.

PK blood samples of nicotine will be drawn according to the following schedule (acceptable tolerance window):

Predose (within 1 hour before patch application) 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.

Timepoints defined as minor protocol deviations due to sampling window times, only, will not be considered protocol deviations for the analysis of the PK Population.

9.5 Plasma Pharmacokinetic Parameters

Plasma concentrations from nicotine will be used to calculate the following parameters by standard non-compartmental methods for Part A, B, and C (Day 1):

PK Parameter	Definition
Primary PK Parameters	
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
Secondary PK Parameters	
t_{max}	Time to maximum plasma nicotine concentration
$t_{½}$	Apparent elimination half-life, calculated as ln(2)/λz
λ_z	Apparent elimination rate constant for plasma nicotine computed as the slope

PK Parameter	Definition
	of the regression line of ln (C(t)) on time.

-The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.

- λz will be estimated at terminal phase by linear regression after log-transformation of the concentrations.

-Only those data points that are judged to describe the terminal log-linear decline will be used in the period after regression.

-A minimum number of 3 data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} will not be part of the regression slope). The adjusted coefficient of determination (R^2 adjusted) in general should be greater than 0.80. All the derived parameters (e.g., λ_z, $t_{½}$, $AUC_{0\text{-inf}}$) will be flagged accordingly. The time point where ln-linear λ_z calculation begins ($\lambda_{z\ lower}$), the actual sampling time of the last quantifiable concentration used to estimate the λ_z ($\lambda_{z\ upper}$) as well as the R^2 adjusted for the ln-linear regression for the calculation of the elimination rate constant calculation will be reported.

-An appropriate number of decimal places will be used for λ_z to enable the reported value of $t_{½}$ to be calculated.

9.6 Statistical Analyses

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 arithmetic mean (±SD) on both original and logarithmic scales with Safety population. For ease of presentation, actual and scheduled sampling times will be used to present results for individual and mean figures respectively.

The PK parameters ($AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$, and C_{max}) will be summarized for each treatment by descriptive statistics for each study treatment.

The parameters λ_z, $t_{½}$ and t_{max} will be summarized by descriptive statistics (mean, median, Q1, Q3, minimum, maximum, standard deviation, and coefficient of variation) for each study treatment.

9.7 Assessment of Bioequivalence

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 $AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$ and C_{max}.

A linear mixed effects model will be fit to the log-transformed PK variables ($AUC_{0\text{-t}}$, $AUC_{0\ inf}$ 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 (test/reference) 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 SAS code for the analysis model will follow the format given below (The input variables (or datasets) are depicted in slanted red text and have been given generic names).

CCI [redacted]

If the study is dosed in groups due to enrollment issues, the following terms will be included in the model: group, period within group, treatment, and treatment by group. If the term of treatment by group was found to be not statistically significant (i.e. $p>0.05$), then the treatment by group term specified in the previous model would be removed from the model to calculate the ratio and 90% CI for AUC_{0-t}, AUC_{0-inf} and C_{max} as applicable.

9.8 Non-parametric Assessment of PK Parameters

A nonparametric analysis will be performed to compare study treatments using the Wilcoxon Signed Rank Test for the PK parameters t_{max}, $t_{½}$, and λ_z. Median difference, 95% confidence interval of Hodges- Lehmann's median estimate, and p-value will be presented.

If the P-value is significant at the 5% level, then PK parameter values are considered unequal across all dose levels. If the P-value is not significant, then PK similarity may be suggested across the investigated products.

The SAS code to perform the test will follow the format given below (using the univariate Procedure). The input variables, datasets and labels are depicted in slanted red text and have been given generic names.

CCI [redacted]

10. Safety

All safety analyses will be based on the Safety Population and they will be presented separately for each study part unless otherwise specified. Safety will be assessed on the basis of adverse event (AE), clinical laboratory data, vital signs, and physical examination.

10.1 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.
Treatment-emergent AEs (TEAEs) and non-TEAEs will be listed by subject and treatment. TEAEs will be defined as any AEs that first occurs on or after the date and time of patch administration. Any AE that first occurs pre-dose but worsens in severity after the first patch administration will also be considered a TEAE. Non-TEAEs are those that occur prior to the first administration of the study medication and resolved prior to patch application or that first occur prior to the first patch administration but do not worsen in severity after patch application. AEs will be captured during the study until study exit. Adverse events will be followed-up until complete resolution, or until the Principal Investigator or Medical Sub-Investigator judges safe to discontinue follow-up.

The incidence of TEAEs will be summarized using the Safety Population. Adverse events will be coded using the MedDRA® dictionary Version 24.0. 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.

The relationship of TEAEs will be classified according to the study protocol as not related or related (unlikely related, possibly related, or definitely related) to nicotine. The severity of TEAEs will be classified according to the study protocol as mild, moderate or severe.

Incidence of subjects who experienced TEAEs (frequency and the percentage of subjects) will be presented for each treatment and overall by:

- Overall summary of AEs;
- AEs by SOC
- AEs by SOC and PT;
- TEAE by SOC, PT, and maximum severity;
- AEs by SOC, PT, and relationship to the application site;

All AEs will be listed. AE's that are serious, leading to death, leading to study discontinuation, or Treatment Emergent will be flagged.

For the purpose of inclusion in TEAE tables, the CRF question "Onset Date and Time" on "Adverse Events" page will be compared to the date and time of study drug administration, if the answer is not available, the imputed AE onset date will be used. Incomplete AE onset and end dates will be imputed similar to those rules as presented in Section 8.9. Additional rules are as follows:

If an AE is recorded with an onset date corresponding to a patch application day, but the time is missing, then the AE will be assigned to the treatment as a TEAE.

If an AE is recorded with an onset date that does not correspond to the patch application day, but the time is missing, then the AE will be assigned to the treatment as a TEAE if AE onset date is after patch application date.

If an AE is recorded with an onset date where day and time are both missing, then the AE allocation to the treatment will be done on a case by case basis considering available information (e.g., AE end date, AE comments, subject disposition).

10.2 Expired Carbon Monoxide (CO) Measurements

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.

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 listed.

10.3 Clinical Laboratory Parameters

Laboratory analyses of blood and urine samples will be performed by the local laboratory.

The following clinical laboratory assessments will be performed:

Biochemistry:	Standard serum biochemistry will be collected. These include: Albumin, Alkaline Phosphatase, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Gamma Glutamyl Transferase, Calcium, Creatine Kinase, Chloride, Total CO_2 (Bicarbonate), Creatinine, Glucose, Magnesium, Sodium, Potassium, Total Protein, Uric Acid, and Urea Nitrogen/BUN.
Hematology:	Standard blood Hematology will be collected. These include: Basophils (Abs), Eosinophils (Abs), Hemoglobin, Hematocrit, Lymphocytes (Abs), Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Volume, Monocytes (Abs), Total Neutrophils (Abs), Platelet Count, Erythrocytes, Leukocytes, and Mean Platelet Volume will be measured
Coagulation:	Standard plasma coagulation will be collected. These include: prothrombin time and Prothrombin international normalized ratio will be measured.
Urinalysis:	Standard Urinalysis will be collected. This includes: Bilirubin, Glucose (qual), Ketones, Leukocyte Esterase, Nitrite, Occult Blood, pH, Protein (qual), Specific Gravity, and Urobilinogen will be measured.
Local Urinalysis (Microscopic)	Urine samples for Microscopic inspection will be performed only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase. This will include: Leukocytes, Erythrocytes, Epithelial cells, and the results, interpretation, and clinical significance of (Bacteria, Mucous Threads, Crystals, and Casts)

Clinical laboratory testing (hematology, coagulation, biochemistry, and urinalysis) will be performed at screening and at the End of Study visit.

Clinical laboratory values will be flagged as either high or low based on the reference ranges provided by the local laboratories for each laboratory parameter.

Individual clinical laboratory results and reference ranges will be presented in data listings.

10.4 Vital Sign Measurements

Vital signs measurements will include systolic and diastolic blood pressures (BPs), pulse rate, respiratory rate (RR), and oral temperature (OT).

Vital sign measurements will be performed at screening, on Day -2 and Day -1, prior to patch administration (1-30 minutes prior) on Day 1 and Day 5, and at Day 2, 3, 4, 6, and at the end of Study Visit.

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

10.5 Physical Examination

A full physical examination will be performed at screening and Day 6 at the End of Study visit. A brief physical examination will be performed on Day -1 and Day 5 and will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

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, heart (Cardiovascular), and lung (Respiratory) findings.

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

11. Changes from the Protocol

No changes in planned analyses were made compared to the protocol.

12. Reference List

- Han, L. *Calculating the point estimate and confidence interval of Hodges-Lehmann's median using SAS® software*. Paper ST-154.

13. Programming Considerations

All TLFs, and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

For all PK analyses, Phoenix® WinNonlin® version 8.0 (Certara USA, Inc., Princeton, NJ) will be used.

13.1 General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rich text format (RTF) that can be manipulated in MS Word.
- Numbering of TLFs will follow ICH E3 guidance.

13.2 Table, Listing, and Figure Format

13.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Times New Roman font, size 10. The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also the orientation may be changed to portrait if appropriate.
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Times New Roman font, size 10.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters and Unicode characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Unicode characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2 Headers

- All output should have the following header at the top left of each page:
- GSK Consumer Healthcare PPD)

- All output should have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The SAS system date and time output was generated should appear along with the program name as a footer on each page.

13.2.3 Display Titles

- Each TLF are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title is left aligned. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed

13.2.4 Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5 Body of the Data Display

13.2.5.1 General Conventions

Listing 16.2.2.1 Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and

- Numbers containing fractional portions are decimal aligned.

13.2.5.2 Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Listing 16.2.2.2 Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to one more decimal places than the original values, and standard deviations are printed out to two more decimal places than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Every p-value less than 0.0001 will be presented as <0.001. If the p-value is returned as >0.9999, then present as >0.9999.
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 [12.8%], 13 [5.4%]). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the

analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

13.2.5.4 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display and date the program was run (i.e., 'Program : PPD ').

14. Quality Control

SAS programs are developed to produce outputs such as analysis data sets, summary tables, data listings, figures or statistical analyses. These will be developed and undergo quality control as per SOPs 2800 and 2801.

15. Appendices

None