Statistical Analysis Plan for Protocol

207791

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

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STATISTICAL REPORTING AND ANALYSIS PLAN

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

Protocol Number: 207791

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Protocol: 207791

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The purpose of this Statistical Reporting and Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report (CSR) for Protocol 207791.

This statistical reporting and analysis plan (RAP) is intended to describe the bioequivalence analyses required for the study.

List of Abbreviations

AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC0-inf	Area under the plasma concentration versus time curve calculated from time zero to infinity
AUC0-t	Area under the plasma concentration versus time curve from administration to last observed concentration t
BDRM	Blinded Data Review Meeting
BE	Bioequivalence
BLOQ	Below lower limit of quantitation
BMI	Body mass index
CI	Confidence interval
Cmax	The highest observed plasma nicotine concentration
CO	Carbon monoxide
CSR	Clinical study report
CV%	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
GMR	Geometric mean ratio
GSKDrug	GSK Drug Dictionary
ICH	International Council for Harmonisation
Kel	Apparent elimination rate constant for plasma nicotine
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
Q1	1st quantile
Q3	3rd quantile
RCt	Estimated residual concentration (nicotine in plasma) at time t
SAE	Serious adverse event
SBP	Systolic blood pressure
SEM	Standard error of the mean
SD	Standard deviation
SOC	System organ class
RAP	Statistical reporting and analysis plan
t1/2	Apparent elimination half life
TEAE	Treatment emergent adverse event
TFLs	Tables, figures, and listings
Tmax	Time to maximum plasma nicotine concentration

1 Summary of Key Protocol Information

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

The study will follow a randomized, open label, single dose, single center crossover design with 2 treatments. However, the analytical laboratory, pharmacokinetic scientist, programmer responsible for programming PK TFLs, and sponsor personnel, with the exception of the sponsor's biostatistician, will remain blinded to treatment during the analysis of the plasma samples. After a 21-day screening period, subjects will check into the clinic on Day -2 and will be randomized to a sequence prior to dosing. Subjects will be randomized by sequence to receive 2 mg prototype mini lozenges in Period 1 followed by 2 mg nicotine mini lozenges (Nicorette Minis) in Period 2 or 2 mg nicotine mini lozenges (Nicorette Minis) in Period 1 followed by 2 mg prototype mini lozenges in Period 2 according to a randomization scheme.

1.1 Study Design

This study will be a single center, randomized, open label, single dose, two-way crossover in healthy smokers that smoke their first cigarette within 30 minutes of waking. Each subject will be treated with a single dose of the two study treatments in a randomized sequence. Subjects will be confined in the study facility for approximately 60 hours during each study session (for 36 hours pre dosing and for 24 hours post dosing) during which pharmacokinetic (PK) blood samples will be obtained. Subjects are to abstain from smoking during the confinement periods and be subject to random measurements of expired carbon monoxide (CO) to confirm abstinence. The CO levels must be ≤ 10 ppm throughout the study session. There will be at least a 5-day and not more than a 7-day clinical furlough period between treatment periods. For each treatment period, the clinical confinement period with restriction of smoking is at least 36 hours prior to dosing. The reported plasma half-life (t1/2) for nicotine is approximately 1 to 4 hours from previous pharmacokinetics studies (GSK study S3010466). The 36 hour smoking restriction prior to dosing will therefore minimize the residual nicotine amount from smoking during previous furlough.

Treatment sequences are presented in Table 1-1: Treatment Sequences

Table 1-1: Treatment sequences

Sequence	Period 1	Period 2
1	A	B
2	B	A

Treatment A: 2 mg Prototype Mini Nicotine Lozenge
Treatment B: 2 mg Nicorette Mini Lozenge

1.2 Study Objectives

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To assess the bioequivalence of the nicotine 2 mg prototype mini lozenge with the 2 mg nicotine polacrilex mini lozenge (Nicorette Minis), in terms of nicotine AUC0-t, AUC0-inf and Cmax	• AUC0-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. • AUC0-inf – Area under the plasma concentration versus time curve from time zero extrapolated to infinity. • Cmax – The highest observed plasma nicotine concentration.
Secondary Objectives	**Secondary Endpoints**
• To compare the nicotine 2 mg prototype mini lozenge to the 2 mg nicotine polacrilex mini lozenge (Nicorette Minis) in terms of tmax, t1/2, and Kel	• Tmax – The time of the maximum plasma concentration • t1/2 – The plasma half life • Kel – The elimination rate constant
• To evaluate the safety of the nicotine 2 mg prototype mini lozenge	• Safety assessments consists of monitoring and recording adverse events (AEs) and clinical safety laboratory tests

1.3 Treatments

In each treatment period, each subject will receive one single dose of the respective study drug according to the treatment sequence they would be randomized to (See Table 1-1: Treatment Sequences).

Following an overnight fast of least 10 hours, subjects will receive investigational product at approximately 8:00 AM (plus or minus 2 hours). Subjects will keep the lozenge in their mouth, occasionally moving it side to side, allowing it to slowly dissolve completely, and try to minimize swallowing. Subjects will not chew the lozenge. In order to standardize the conditions on pharmacokinetic sampling days, all subjects will be required to refrain from lying down (except when required for blood pressure and pulse rate), eating, and drinking beverages, with the exception of water, for the first 4 hours after dosing. Water may be given after one hour postdose.

The nicotine prototype mini lozenge (test) and the Nicorette Mini lozenges (reference) will be supplied as 2 mg lozenges.

For PK and safety analyses, treatments will be described as follows:

Table 1-2: Treatment Descriptions

Treatment	Short Description (text, tables headers, figures, listings, SAS output)	Long Description
A	Prototype 2 mg Lozenge	2 mg Prototype Mini Nicotine Lozenge
B	Nicorette 2 mg Lozenge	2 mg Nicorette Mini Lozenge

1.4 Sample Size Calculation

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

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned; however, there will be 2 Blinded Data Review Meetings (BDRMs) where blinded data (Safety and PK) will be reviewed.

2.2 Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and database has been locked.
3. All criteria for unblinding the randomization codes have been met and the randomization codes have been distributed.

3 Considerations for data analyses and Data Handling Conventions

3.1 Baseline Definition

For PK endpoint analyses:

The predose nicotine concentration will be estimated based on a log-linear regression according to a mono-compartmental deconvolution of the three predose time points, i.e. -45 minutes, -30 minutes, and -15 minutes prior to dosing. Blood samples for calculation of predose nicotine concentrations will be collected during both study periods. If mono-compartmental deconvolution cannot be computed due to high variability between the -45 minutes, -30 minutes, and -15 minutes time points, then the -15 minutes time point will be used as predose. If the -15 minutes time point is missing, then the -30 minutes time point will be used. Likewise, if the -30 minutes time point is missing, then the -45 minutes time point will be used.

The individual residual baseline nicotine concentration at time t (RCt,ij) will be estimated using log-linear regression according to a mono-compartmental deconvolution as follows:

$Ct,ij(R) = Ct,ij(O) – [Cpredose,ij * \exp(-Kelij*t)]$

Where:

Ct,ij(R) = baselineadjusted nicotine concentration at time t,

Ct,ij(O) = observed nicotine concentration detected in subject plasma at time t,

Cpredose = plasma nicotine concentration before dosing (estimated by mono-compartmental deconvolution of the three predose time points (-45 minutes, -30 minutes, and -15 minutes)),

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

for the associated treatment,

t = time (h) between the considered blood sampling and the time of predose sampling,

i = treatment (Test or Reference), and

j = Subject

For baseline-adjustment, if Kel cannot be calculated for an associated treatment, the Kel for the same subject from the other period will be used. Where Kel is not calculable for both periods, no baseline-adjustment will be performed for that subject.

Unless otherwise stated, if baseline data is missing, no derivation will be performed and the predose value will be set to one-half of the lower limit of quantitation (LLOQ). After correction for baseline adjustment values, some concentrations may be below the lower limit of quantitation and some may be negative values. Negative values will be assigned a value of zero in the analyses and all other values obtained will be reported as is even if these values are BLQ.

For safety endpoint analyses:

- Subject level baseline is defined as the latest assessment with a non-missing value before the first dosing (e.g. clinical laboratory tests and vital signs).
- Treatment level baseline is defined as the latest assessment with a non-missing value before the Treatment dosing (e.g. expired CO measurements).

3.2 Subgroups/Stratifications

Not applicable

3.3 Centers Pools

This will be a single center study.

3.4 Timepoints and Visit Windows

Not Applicable

4 Data Analysis

Data analysis will be performed by Celerion Data Management and Biometrics. The statistical analysis software used will be SAS version 9.3 or higher in a WINDOWS environment using SAS Enterprise Guide.

Prior to database closure, 2 BDRMs will be conducted in which various aspects of the trial will be discussed and study populations will be agreed upon.

Except as described below, all listings will be produced for all randomized subjects.

4.1 Populations for Analysis

Tables described in this section will be produced for all randomized subjects. Subject disposition (Table 14.1-1) will include all screened subjects. All screening failure subject data will be listed.

4.1.1 Subject Disposition and Eligibility for Analysis Populations

Subject disposition for all screened subjects will be summarized as the number of subjects screened, number of subjects enrolled (subjects are considered enrolled when they check in and have at least one assessment on Day -2 of Period 1), number of subjects not randomized with discontinuation reason, number and percentage of subjects who received test product, completed the study, and who discontinued with discontinuation reason within each period by

sequence and overall (Table 14.1-1). All randomized subject disposition data will be presented in Listing 16.2.1-1.

Data from screening failures and any non-randomized subjects (screening number, date of screening, date of informed consent, year of birth, sex, race, ethnicity, occurrence of SAE during the screening period and before randomization, if applicable, primary reason for screening failure and criteria number met/not met) will be presented in Listing 16.2.1-2. The Inclusion/ Exclusion criteria will be presented by number in Listing 16.2.1-3, with subject eligibility for study presented in Listing 16.2.5-1. Subject check-in and return responses will be presented in Listing 16.2.5-2. A complete listing of subjects with screening and randomization numbers is presented in Listing 16.2.1-4.

The number and percentage of subjects eligible for each of the subject analysis populations, and the number of subjects excluded from each population broken down by the reason for exclusion will be presented (Table 14.1-3.1 and Table 14.1-3.2). Subjects will be listed with their inclusion status to each analysis population, and the reason for exclusion if applicable (Listing 16.2.3-1and Listing 16.2.3-2).

4.1.2 Protocol Deviations

Protocol deviations will be collected and stored in the Celerion SharePoint system. All deviations collected in SharePoint will be categorized and subcategorized according to the Protocol Deviation Management Plan by the Celerion clinical study manager and provided as a Microsoft Excel file and read into SDTM to generate the data listing.

Prior to database lock, any protocol deviation reported will be classified as major or minor.

Major protocol deviations are those that may affect the integrity of the study data or may impact the eligibility or validity of subjects or data points for the analysis.

The number and percentage of subjects with any major protocol deviation will be presented by treatment (Table 14.1-2). All major and minor protocol deviations will be listed (Listing 16.2.2-1). Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, subject management or subject assessment) will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to unblinding and closure of the database to ensure all important deviations are captured and categorized.

4.1.3 Analysis Populations

Three analysis populations are defined.

Population	Definition / Criteria	Analyses Evaluated
Randomized	The randomized population is defined as all subjects who were randomized. Any subject who received a randomization number will be considered to have been randomized.	• Safety and PK
Safety	The safety population is defined as all randomized subjects who receive at least one dose of study medication.	• Safety
Pharmacokinetic	The PK population is defined as all randomized subjects who completed both periods, and who had no major protocol deviations concerning pharmacokinetics.	• PK

NOTES :

- Please refer to Attachment 1: List of Data Displays which details the population to be used for each displays being generated.

The number of subjects included in each of the analysis populations, and the number excluded from each population broken down by the reason for exclusion will be presented (Table 14.1.3-1 and Table 14.1.3-2). Subjects eligible for analysis populations will be listed (Listing 16.2.3-1). Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3-2, with the reason for exclusion.

The primary analysis will be to assess bioequivalence of both test products. The secondary analysis will be to assess similarities of Tmax and t1/2 of both test products. Pharmacokinetic analysis set 1 (PKAS1) will be used to draw conclusions for the primary and secondary analyses using baseline-adjusted data.

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

- PKAS1 includes all subjects of the PK population. Subjects with baseline nicotine concentration > 5% of the individual Cmax for either period will be excluded. This analysis set will be used in PK summaries of observed and baseline-adjusted data, the primary analysis, and the secondary analysis. Both observed concentrations and baseline-adjusted concentrations are subsets of PKAS1. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables only and excluded from the PKAS1.
- PKAS2 (for baseline-adjusted data only) includes all subjects of the PK population, for which the relevant baseline-adjusted PK parameters (at least one AUC or Cmax) can be derived, including those with baseline nicotine concentrations > 5% of the

individual Cmax for either period. This analysis set will be used in PK summaries and an additional analysis.

4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the Safety Population, PKAS1, and PKAS2 if different from PKAS1.

4.2.1 Demographic Characteristics

Categorical demographic variables sex, race, and ethnicity will be summarized by frequency tables. Continuous variables age, weight, height, and body mass index (BMI) will be summarized using descriptive statistics (mean, standard deviation, minimum, median, and maximum, Table 14.1-4). All demographic information will be listed in Listing 16.2.4-1. Age, while not included in the CRF, will be extracted from the clinical database and included in the demographic source data.

4.2.2 General Medical History

Medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 according to the primary system organ class (SOC) and preferred term (PT). Medical diagnoses/surgeries, with start date and end date or ongoing at the start of study drug, will be listed in Listing 16.2.4-2.

4.2.3 Substance Use and Fagerstrom Test Of Nicotine Dependence

Subject substance use and Fagerstrom test of nicotine dependence will be listed in Listing 16.2.4-3 and Listing 16.2.4-4 respectively.

4.3 Treatments (Study Products, Other Concomitant Therapies, Compliance)

Exposure to study products and other medications, as well as carbon monoxide (CO) monitoring results will be summarized on the Safety Population.

4.3.1 Study Product Compliance and Exposure

Study product exposure and compliance to the treatment will be summarized as follows by treatment (Table 14.3-1.1):

- number (%) of subjects exposed to study drug;
- number (%) of subjects fully compliant to dosing requirements (without any deviation);
- number (%) of subjects with deviation from dosing requirements:
  - any deviation (total)
  - partial exposure (e.g. swallowing or premature expulsion of the lozenge)
- number (%) of subjects with baseline nicotine concentration > 5% of the C_{max} post-dose.

Study drug administration will be listed in Listing 16.2.5-3.

4.3.2 Non-Smoking Compliance and CO Monitoring Results

CO monitoring results will be listed in Listing 16.2.5-5.

Number (%) of subjects with elevated maximum CO results (elevated CO threshold is > 10 ppm) will be summarized by treatment in Table 14.3-1.2.

4.3.3 Prior and Concomitant Medication

Prior and concomitant medications will be coded using Anatomical Therapeutic Chemical (ATC) classification and GSK Drug Dictionary (GSKDrug 1.4).

The number (%) of subjects with concomitant medication during the study (ongoing or started after randomization) and the number (%) of subjects with concomitant medication during each treatment period (i.e. by treatment) will be summarized in a frequency table (Table 14.3-2). Frequncy counts of the number (%) of subjects in each ATC class will also be summarized by overall and treatment in the same table.

All prior and concomitant medications will be listed (Listing 16.2.5-6); the listing will include the ATC 1st and 2nd levels, ATC code, GSKDrug preferred term , indication, dose, frequency, route, start date/time, and end date/time (or ongoing at final visit, as appropriate).

Listing 16.2.5-6 will include all screened subjects while Table 14.3-2 will summarize only the safety population.

4.4 Analysis of Pharmacokinetics

4.4.1 Primary Pharmacokinetic Endpoint

4.4.1.1 Primary Pharmacokinetic Endpoint Definition

PK blood samples will be collected at predose (-45, -30, and -15 minutes), and 5, 10, 20, 30, 40, 50, 60, 75, and 90 minutes and 2, 3, 4, 6, 8, 10, 14, 16, 20, and 24 hours postdose.

Plasma concentrations of nicotine will be determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods validated with respect to accuracy, precision, linearity, sensitivity, and specificity at Celerion, Lincoln, Nebraska. The LLOQ for nicotine is expected to be 0.2 ng/mL.

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

The nicotine 2 mg prototype mini lozenge (Test) versus the 2 mg nicotine polacrilex mini lozenge (Nicorette Mini) Reference, in terms of nicotine AUC0-t, AUC0-inf and Cmax.

The primary statistical analyses will be done based on baseline-adjusted data from the PK analysis set PKAS1 (see Section 4.1.3 for definition). An additional analysis (for baseline-adjusted data only) will be performed on PK analysis set, PKAS2. Safety population

will be used for individual plasma concentration listings and figures. The PKAS1 and PKAS2 will be used for mean concentration-time figures.

The PK evaluation will be done for the following two nicotine plasma concentration variables (details on correction are given in Section 4.4.1.4):

- Observed concentration for PKAS1
- Baseline-adjusted concentration (adjusted for non-zero baseline, as described in Section 4.4.1.4) for PKAS1 and PKAS2

4.4.1.2 Calculation of Primary Pharmacokinetic Parameters

The appropriate noncompartmental PK parameters will be calculated from the plasma nicotine concentration-time for observed and baseline adjusted data using Phoenix® WinNonlin® Version 7.0 or higher or SAS Version 9.3 or higher, as appropriate. Baseline-adjustment on concentration data will be completed prior to PK parameter generation by the Data Analyst at Celerion. Actual sample times will be used in the calculations of PK parameters. The calculation of the actual time for nicotine will be in respect to the start of dose administration time of prototype mini nicotine lozenges (test) and nicotine mini lozenges (Nicorette Minis) Reference on Day 1. All PK parameters included in the protocol are listed in Table 4-1 below, and are defined as appropriate for study design.

Table 4-1: Noncompartmental PK Parameters to be Calculated

Parameter	Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
AUC_{0-t}	AUC0-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	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC_{0-inf}	AUC0-inf	Area under the plasma concentration versus time curve calculated from time zero to infinity	$AUC0-\infty = AUC0-t + (Clast/kel)$ where Clast is the last observed/measured concentration
C_{max}	Cmax	The highest observed plasma nicotine concentration	Taken directly from bioanalytical data

Pharmacokinetic parameters will not be calculated for subjects with less than 3 consecutive postdose time points with quantifiable concentrations. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables only and excluded from the statistical analysis (summary and inferential statistics). If a subject

is missing AUC0-inf in a given period, they will be included in the ANOVA model for the period in which they have calculable AUC0-inf parameter, as appropriate.

The Kel will be determined using linear regressions composed of least 3 data points. The Kel will not be assigned if 1) the terminal elimination phase is not apparent, 2) if Tmax is one of the 3 last data points, or 3) if the R2 value is less than 0.70. In cases where the Kel interval is not assigned, the values of AUC0-inf are considered not calculable and will not be reported. Wherever the resulting t1/2 is more than half as long as the sampling interval, the Kel values and associated parameters AUC0-inf may not be presented as judged appropriate and in accordance with Celerion SOPs.

4.4.1.3 Statistical Hypothesis, Model, and Method of Analysis

The PK analysis set, PKAS1 will be used for the PK evaluations on observed and baseline-adjusted data. Subjects with baseline nicotine concentration > 5% (as observed at the -15 minute time point) of the individual Cmax for either period, as well as subjects with less than 3 consecutive postdose time points with quantifiable concentrations, will be excluded from the PKAS1 population.

The PK parameters that will be used in the primary analyses are AUC0-t, AUC0-inf, and Cmax on baseline-adjusted concentration data. The AUC0-t, AUC0-inf, and Cmax on observed concentration data will also be presented for information purposes only.

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

H0: The (geometric) mean AUC0-t (likewise AUC0-inf and Cmax) of nicotine prototype mini lozenge 2mg (Test) is less than 80.0% or greater than 125.0% of that of Nicorette Mini Lozenge 2mg (Reference).

H1: The (geometric) mean AUC0-t (likewise AUC0-inf and Cmax) of nicotine prototype mini lozenge 2mg (Test) is between 80.0% and 125.0% of that of Nicorette Mini Lozenge 2mg (Reference).

Individual plasma concentrations will be listed and summarized descriptively by treatment at each time point (n, arithmetic mean, standard deviation [SD], standard error of the mean [SEM], coefficient of variation [CV%], median, minimum, and maximum). The concentration vs. time profile will be graphed by formulation for individual subjects and for the mean on both original and logarithmic scales with PK Population (PKAS1).

Observed and baseline-adjusted PK parameters will be summarized for each treatment by descriptive statistics (n, arithmetic mean, SD, SEM, geometric mean, CV%, geometric CV%, median, minimum, and maximum). A listing containing individual PK parameter values will be provided. A similar listing will be provided for observed and baseline-adjusted linear/raw plasma concentrations over time containing individual values and summary statistics for each time point.

The level of precision for each concentration and PK parameter statistic will be presented as follows:

- Minimum/maximum in same precision as in bioanalytical data or parameter output,
- Geometric mean/arithmetic mean/median in one more level of precision than minimum/maximum,
- SD in one more level of precision than geometric mean/arithmetic mean/median,
- n will be presented as an integer, and
- Geometric CV%/CV% will be presented to the nearest tenth.

BE of the test product with reference will be assessed by pairwise comparison of the PK parameters (Cmax, AUC0-t, and AUC0-inf) for the baseline-adjusted nicotine concentration profiles based on the PK analysis set PKAS1.

A linear mixed effects model will be fit to the natural log-transformed PK variables (AUC0-t, AUC0-inf and Cmax), as the dependent variable, and treatment, period, and sequence as fixed effects. Subject nested within sequence will be a random effect. The presence of a statistically significant sequence effect at 5% significance level will be noted and its implications will be discussed in text, when applicable.

Least squares estimates of treatment effects will be calculated and a 90% confidence interval (CI) for the treatment difference will be computed. The treatment difference and its CI will be exponentiated to obtain the ratio of the geometric means between the test and reference products and its CI. Bioequivalence will be determined if the 90% confidence interval for the treatment geometric mean ratio lies completely within the range 80.0 – 125.0%.

Example SAS code:

```
PROC MIXED DATA=XXX;
     CLASS TREATMENT SUBJECT PERIOD SEQUENCE;
     MODEL LOG_PK = TREATMENT PERIOD SEQUENCE / OUTPRED=RESIDS DDFM=KR;
     RANDOM SUBJECT(SEQUENCE);
     ESTIMATE "TEST A VS REFERENCE B" TREATMENT 1 -1 / CL ALPHA=0.1 E;
     LSMEANS TREATMENT / PDIFF ALPHA=0.1;
     ODS OUTPUT LSMEANS=LSM;
     ODS OUTPUT DIFFS=DIFF;
RUN;
```

4.4.1.4 Correction for non-zero baseline for an additional analysis

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

$C_{t,ij(R)} = C_{t,ij(O)} – [C_{predose,ij} * \exp(-Kel_{ij}*t)]$

Where:

$C_{t,ij(R)}$ = baseline-adjusted nicotine concentration at time t,

$C_{t,ij(O)}$ = observed nicotine concentration detected in subject plasma at time t,

$C_{predose}$ = plasma nicotine concentration before dosing (estimated by mono-compartmental deconvolution of the three predose time points (-45 minutes, -30 minutes, and -15 minutes)),

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

t = time (h) between the considered blood sampling and the time of predose sampling,

i = treatment (Test or Reference), and

j = Subject

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

If mono-compartmental deconvolution cannot be computed due to high variability between the -45 minutes, -30 minutes, and -15 minutes time points, then the -15 minutes time point will be used as predose. For further details, see Section 5 (Changes to the Protocol and Defined Statistical Analysis Plan).

4.4.2 Handling of Missing Values/Censoring/Discontinuations

Subjects who deviate from the protocol will be identified and excluded from the PK analyses as agreed by the biostatistician and medical director or designee. For the primary analysis of PK parameters, subjects with baseline concentrations greater than 5% Cmax will be excluded from PKAS1.

Exclusion of any data from the analyses will be determined during a Blinded Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable. Formal documentation of these exclusion will be provided to Celerion from GSK prior to postlock analysis commencing.

For nicotine concentration:

- Below lower limit of quantitation (BLOQ) values obtained before Cmax will be imputed as zero.
- BLOQ values obtained after Cmax will be imputed as “Not detectable” (ND), which will be treated as missing (explanations will be specified in the footnote of the tables, figures, and listings [TFLs]).

If any concentration data is missing or deviates from the planned time of collection (i.e., if there are overlapping blood draw collection time points with subsequent blood draws), then

the pharmacokineticist may calculate the PK parameters using the available data, except if subjects have less than 3 consecutive postdose time points with quantifiable concentrations.

Missing values of Kel can be estimated from the subject's Kel value from the other treatment. If a Kel value cannot be calculated from the other treatment, then the Kel will be obtained from the treatment mean value for subjects with non-missing values of Kel in the treatment in which it is not available. This estimated Kel may be used to calculate other Kel dependent variables and may also be applied for predose concentration adjustments.

All existing data for subjects who do not complete the 2 periods from the study will be excluded from the PK statistical analysis (PKAS1 and PKAS2).

4.5 Analysis of Secondary Objectives

4.5.1 Pharmacokinetic (Secondary)

4.5.1.1 Secondary Pharmacokinetic Endpoint Definition

The PK analysis sets PKAS1 and PKAS2 will be used for the secondary analysis.

The PK evaluation will be done for the following two nicotine plasma concentration variables (details on correction are given in Section 4.4.1.4):

- Observed concentration
- Baseline-adjusted concentration (observed and adjusted for non-zero baseline, as described in Section 4.4.1.4)

4.5.1.2 Calculation of Secondary Pharmacokinetic Parameters

The appropriate noncompartmental PK parameters will be calculated from the plasma nicotine concentration-time for baseline and baseline adjusted data using Phoenix® WinNonlin® Version 7.0 or higher or SAS Version 9.3 or higher, as appropriate. Actual sample times will be used in the calculations of the PK parameters. The calculation of the actual time for nicotine will be in respect to the start of dose administration time of prototype mini nicotine lozenges (test) and nicotine mini lozenges (Nicorette Minis, reference) on Day 1. All PK parameters included in the protocol are listed in Table 4-2 below, and are defined as appropriate for study design.

Table 4-2: Noncompartmental PK Parameters to be Calculated

Parameter	Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
t_{max}	Tmax	Time to maximum plasma nicotine concentration. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.	Taken from clinical database as the difference in the time of administration and the time of the blood draw which is associated with the Cmax.
$t_{1/2}$	t1/2	Apparent elimination half-life.	Calculated as t1/2 = ln(2) / Kel
K_{el}	Kel	Apparent elimination rate constant for plasma nicotine	The negative of the slope of a linear regression of the log(concentration)-time for all concentrations > LLOQ

Pharmacokinetic parameters will not be calculated for subjects with less than 3 consecutive postdose time points with quantifiable concentrations. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables only and excluded from the statistical analysis (summary and inferential statistics).

The Kel will be determined using linear regressions composed of least 3 data points. The Kel will not be assigned if 1) the terminal elimination phase is not apparent, 2) if Tmax is one of the 3 last data points, or 3) if the R2 value is less than 0.7. In cases where the Kel interval is not assigned, the values of t1/2 are considered not calculable and will not be reported. Wherever the resulting t1/2 is more than half as long as the sampling interval, the Kel values and associated parameters (t1/2) may not be presented as judged appropriate and in accordance with Celerion SOPs.

4.5.1.3 Statistical Hypothesis, Model, and Method of Analysis

The parameters Kel, t1/2 and tmax will be summarized (n, mean, median, first quantile [Q1], third quantile [Q3], minimum, maximum, SD, SEM) for each study treatment. A nonparametric analysis for Tmax will be performed to compare treatment differences using the Wilcoxon Signed Rank test. Median difference (Test-Reference), the Hodges-Lehmann estimator, and estimated confidence interval will be used to examing the location shift in Tmax (Hollander and Wolf (1999)). Tmax will not be ln-transformed.

The following methodology will be used for the nonparametric analysis for Tmax;

- The treatment differences (D_i, i=1, …, n) within each subject were calculated.
- The M = [n(n+1)/2] Walsh averages were calculated using the following definition:
  $W_{ij} = (D_i + D_j)/2$, for i<=j, i=1, …, n and j=1, …, n

- The M Walsh averages were ordered in sequential ascending order (denoted as $W^{(1)} <= W^{(2)} <= \ldots <= W^{(M)}$).
- The median of the M Walsh averages was calculated.
- The following was defined (using a normal approximation):

  $C\alpha^* = [n(n+1)/4] - Z\alpha/2\ [(n^*(n+1)^*(2n+1))/24]^{1/2}$,

  where $Z\alpha/2$ is the upper $\alpha/2$ percentile of the standard normal distribution.
- The 1-α CI (ΔL, ΔU) are given by:

  $\Delta L = W^{(C\alpha + 1)}$, $\Delta U = W^{(M - C\alpha)}$,

  where Cα is the largest integer less than or equal to Cα*.

  For the purposes of analysis, α was 0.05 in order to provide a 95% CI.

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

Pharmacokinetic parameters will be reported to 3 significant figures for individual parameters, with the exception of Tmax, which will be presented with 2 decimal places. The level of precision for each PK parameter statistic will be presented as follows:

- Minimum/maximum/Q1/Q3 in same precision as in parameter output,
- Mean/median in one more level of precision than minimum/maximum/Q1/Q3,
- SD and SEM in one more level of precision than mean/median, and
- n will be presented as an integer

4.6 Analysis of Safety

4.6.1 Adverse Events and Serious Adverse Events

All treatment-emergent adverse events (TEAEs) will be summarized by primary system organ class and preferred term. All TEAEs will be coded using MedDRA Version 21.0.

TEAEs will be summarized with an overview (Table 14.3.1-1) and then by the number and percentage of subjects having any adverse event, an adverse event in each System Organ Class, and each individual adverse event (preferred term) (Table 14.3.1-2). TEAEs suspected of a relationship to study medication will be presented in a similar manner (Table 14.3.1-3). All TEAEs will also be tabulated by maximum severity (Table 14.3.1-4).

Additionally, all adverse events and serious adverse events will be listed (Listing 16.2.7-1 and Listing 16.2.7-2). Also, any adverse events that occur in screening failure subjects will be listed (Listing 16.2.7-3).

Deaths occurring during treatment (if any) will be listed by treatment, including the date and study day of death, and the principal cause of death (Listing 14.3.2-1). Non-fatal serious adverse events and adverse events causing study treatment discontinuation will be listed (Listing 14.3.2-2 and Listing 14.3.2-3).

4.6.2 Laboratory Tests

Laboratory normal ranges will be listed in Listing 16.2.8-1.1. Listings of all clinical laboratory evaluations (hematology, clinical chemistry, urinalysis) will be provided with the abnormal values flagged (Listing 16.2.8-1.2, Listing 16.2.8-1.3, and Listing 16.2.8-1.4). Urine illicit drug screen will be listed in Listing 16.2.8-2.

Out-of-normal range flags will be recorded and presented as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a computer clinically significant (CS) range. If the value falls within the computer CS range, it will be noted as “N” for not clinically significant. If the value fails (i.e., fall outside of the CS range) the computer CS range, it will be flagged with a “Y” which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. To distinguish the PI flag from the computer CS range flags, the PI flags of “N” and “Y” will be presented as “-“ and “+”, respectively, in the data listing. Additionally, a derived flag based on a search of the PI comments for a comment of “CS” or “Clinically Significant” will be used. The derived flag will be populated with “+” if the positive clinically significant determination is found in the comments for cases when the PI flag is populated with a “^” or an “R”.

4.6.3 Vital Signs

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiration, and body temperature) will be summarized with descriptive statistics (mean, standard deviation, minimum, median, and maximum) for the observed values by time point and treatment (Table 14.3-3). A listing of vital signs results, including body weight, will be provided with the abnormal values flagged (Listing 16.2.9-1).

Normal vital signs are as follows: oral body temperature between 35.0 and 37.5 ºC; SBP between 90 and 140 mmHg; DBP between 55 and 90 mmHg; pulse rate between 50 and 100 bpm. Low/high (L/H) values based upon normal ranges, the repeated measurement (R), and the scheduled measurement not done (*) will be flagged.

4.6.4 Findings on Physical Examination

Any abnormal findings judged to be clinically significant which occurred before signing the informed consent form were to be documented as medical history and those occurring after signing the informed consent form were to be recorded as an AE. Any physical examination findings documented as AEs will be included in the summary of AEs.

Findings from physical examination will be listed in Listing 16.2.9-4. Any abnormal findings judged to be clinically significant which occurred before signing the informed consent form will be documented as medical history and those occurring after signing the informed consent form will be recorded as an AE.

4.6.5 Other Safety Variables

Data for the following variables will be listed only:

- ECG (Listing 16.2.9-2)
- Confirm Contraception (Listing 16.2.9-3)

4.6.6 Handling of missing values/censoring/discontinuations

- No imputation of missing values is foreseen for any safety data. Incomplete dates recorded on the CRF will not be imputed.

4.7 Analysis of Other Variables

Meal records will be listed in Listing 16.2.9-5. Phone call records will be listed in Listing 16.2.9-6. Comments from all domains will be listed in Listing 16.2.9-7.

5 Changes to the Protocol Defined Statistical Analysis Plan

As per the Amended protocol (Amendment 2 dated 13 December 2018), the concentrations and PK parameters were to be presented on linear and log scales. However, after further discussion with GSK Consumer Healthcare, it was decided to present both the concentrations and PK parameters on linear scale only.

As per the Amended protocol (Amendment 2 Dated 13 December 2018), the predose nicotine concentrations would be estimated bsed on a log-linear regression according to a mono-compartmental deconvolution of the three predose time points (-45 minutes, -30 minutes, and -15 minutes). However, due to the high degree of variability of nicotine concentrations at the three predose time points, the log-linear regression according to a mono-compartmental deconvolution to zero time was not possible in a large proportion of subjects. Therefore, the baseline (time zero) concentation for all analyses was taken as being equivalent to the closest time prior to product administration (15 minutes).

6 Reference List

Hollander and Wolf. (1999). *Nonparametric Statistical Methods*, 2nd Edition, Wiley.

Attachment 1: List of Data Displays

Study 207791 List of Outputs.xlsx