A Randomised, Cross-Over, Single-Blind, Relative Bioavailability Study of Nicotine Delivery From Selected Oral Nicotine Products

NCT05452278

Statistical Analysis Plan Final Version 1.0 – 23 Nov 2021

CLINICAL TRIAL CONSULTANTS AB

CONFIDENTIAL

Statistical analysis plan (SAP)

Sponsor:	Imperial Tobacco Ltd
Study code:	IB-OND-ZONEX-11
CTC project no:	369-62-2021
Study title:	A RANDOMISED, CROSS-OVER, SINGLE-BLIND, RELATIVE BIOAVAILABILITY STUDY OF NICOTINE DELIVERY FROM SELECTED ORAL NICOTINE PRODUCTS
SAP version and date:	Final version 1.0 23NOV2021
CTC biostatistician:	[redacted]

1 TABLE OF CONTENTS

2 VERSION HISTORY

This statistical analysis plan (SAP) for study IB-OND-ZONEX-11 is based on the protocol dated 21JUN2021.

Table 1 SAP version history summary

SAP version	Approval Date	Changes	Rationale
0.1	08NOV2021	-	Version ready for internal review
0.2	10NOV2021		Version ready for Sponsor review
1	23NOV2021	NA	Original version

3 INTRODUCTION

This SAP gives details regarding the statistical analyses and data presentation outlined in the final clinical study protocol (CSP) for the study IB-OND-ZONEX-11. Any changes from the final CSP are given in Section 9.

4 CLINICAL STUDY DETAILS

4.1 Clinical study objectives and endpoints

Table 2 Clinical study objectives and endpoints

Objectives	Estimands/Endpoints
Primary	
1. To evaluate and compare the maximum plasma concentration (C_{max}) and the area under the curve at the last timepoint measured (AUC_t) of nicotine after the use of each product.	1.1 C_{max} and AUC_t
Secondary	
2.1 To evaluate other PK parameters of nicotine after the use of each product.	2.1.1 AUC timepoint 0 to 90 minutes (AUC_{0-90}), AUC timepoint 0 to infinity (AUC_{inf}), time to C_{max} (T_{max}), plasma concentration at last timepoint measured (C_{last}), and terminal elimination half-life ($T_{1/2}$).
2.2 To evaluate orally extracted dose of nicotine in used products (oral nicotine delivery [OND]).	2.2.1 The orally extracted dose of nicotine from each pouch will be calculated to evaluate the correlation between baseline-

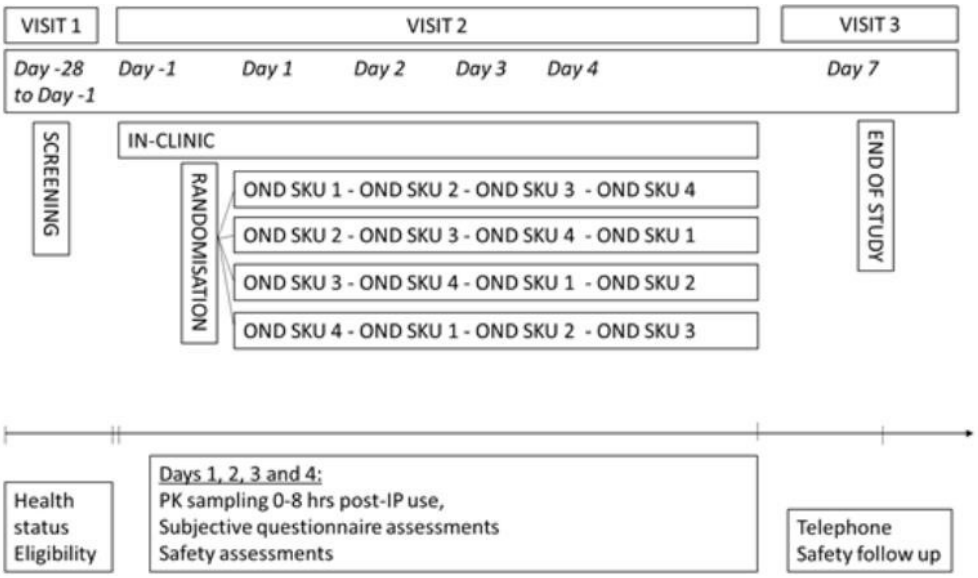
	adjusted AUC_{inf} and orally extracted dose of nicotine.
2.3 To evaluate product perception and preference by use of subjective assessments.	2.3.1 Subjective assessment endpoints including: Product evaluation scale (PES), Product preference scale (PPS) and the Urge to use questionnaire.
2.4 To evaluate the tolerability and safety of each of the products used.	2.4.1 Frequency, intensity and seriousness of adverse events (AEs). 2.4.2 Clinically significant changes in laboratory parameters, vital signs and electrocardiogram (ECG).
Tertiary/Exploratory	
NA	NA

4.2 Clinical study design

This will be a randomised, cross-over, single-blind, confinement study conducted in 27 male or female snus or nicotine pouch users. The study will investigate 4 different nicotine containing products in a cross-over design, incorporating pharmacokinetic (PK) evaluation, nicotine extraction evaluation, subjective questionnaire assessments as well as safety and tolerability evaluation.

During the study participation, subjects will come for 2 visits to the clinic, including a screening visit and a 4-day confinement period. A final follow up end-of-study telephone call will be performed within a week of last product use.

The following figure gives an overview of the study design:



4.3 Statistical hypotheses

4.3.1 Statistical hypotheses related to primary objective

The main statistical hypothesis that will be tested in the study is that AUC_t and C_{max} does not significantly differ for test product A-B [redacted] respectively in comparison to product D ([redacted] I.e., the primary objective will be examined by the following statistical comparisons for AUC_t and C_{max}:

- Product A does not significantly differ from Product D
- Product B does not significantly differ from Product D
- Product C does not significantly differ from Product D

More information about the statistical tests to be performed can be found in Section 8.1.

4.4 Number of subjects

Approximately 54 subjects will be screened to achieve a total of 27 randomised subjects.

4.5 Randomisation

On Day 1, subjects will be randomised to one of 4 treatment sequences. The 4 different products are:

- A: ZoneX[redacted] nicotine/pouch
- B: ZoneX[redacted]nicotine/pouch
- C: ZoneX[redacted]nicotine/pouch
- D: [redacted] nicotine/ pouch (comparator product)

The 4 randomisation sequences are described in the table below:

Sequence	**Order**			
Sequence 1	A	B	C	D
Sequence 2	B	C	D	A
Sequence 3	C	D	A	B
Sequence 4	D	A	B	C

A computer-generated randomisation list will be created by CTC using SAS Proc Plan, SAS Version 9.4 (or later). The randomisation list will contain subject number, sequence and treatment and will be kept by the randomiser until database lock. A copy of the randomization list will be provided to the research clinic.

4.6 Blinding

This is a single-blind study, i.e., the Investigator and study staff, but not the subjects, will know the identity of each IP.

The IP:s differ somewhat in size but are otherwise identical in appearance. The subjects will not know the strength/nicotine content of each IP.

5 STATISTICAL AND ANALYTICAL PLANS

5.1 Sample size determination

No formal sample size calculation has been performed for this study. The proposed sample size is considered sufficient to provide adequate information for the study objectives.

5.2 Definition of analysis sets

5.2.1 Full analysis set

The Full Analysis Set (FAS) will consist of all subjects who have been randomised and used at least one of the IPs and who has at least one post-baseline assessment of data.

5.2.2 Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PKAS) will consist of all subjects who used at last one of the IPs and provided an evaluable plasma concentration profile and who have no AEs or protocol deviations judged to affect the PK analysis. Individual PK values may be excluded from the analysis as specified in the SAP. The PKAS will be used as the per protocol analysis set.

5.2.3 Use of analysis set

The use of the analysis sets/populations is indicated for each table/figure/listing under statistical output layout .

5.3 Definition of baseline

The baseline measurement is defined as the latest measurement prior to first IP exposure of each treatment period of the IP.

5.4 Output rounding principles

Generally, no rounding of data will be done prior to calculating statistics. However, if reported data contains more than 8 significant digits it will be rounded to 8 significant digits in the database.

In statistical output and descriptive summaries, the following principles will be followed:

- 3 significant digits will be used for PK and similar parameters.
- 2 significant digits will be used for percentages (for example relative change from baseline).
- p-values and similar statistical output will be presented using 4 decimal points.
- All descriptive summaries of numerical data (e.g. mean, SD etc.) will be presented with one extra decimal compared to reported input data.

5.5 Significance level

When testing equivalence (as for the primary endpoint), a significance level of 10% will be used (α=0.10). All other hypothesis testing (when not testing equivalence) will use a 5% significance level (α=0.05).

5.6 Multiple comparisons/multiplicity

No adjustment for multiple comparison/multiplicity will be performed. All significant findings will be reviewed for medical relevance.

5.7 Handling of dropouts, missing data and outliers

Outliers will be included in summary tables and listings and will not be handled separately in any analyses. Generally, no imputation of data will be performed. However, clinical safety laboratory parameters that are outside the detection limit, will be replaced with the detection limit when calculating statistics. Also, when calculating statistics for PK plasma concentrations, concentrations under LLOQ will be replaced with LLOQ if more than 50% of the values for a given time point is above LLOQ. Otherwise, no statistics will be calculated for that time point. For imputation of PK plasma concentration under LLOQ with the purpose of calculating PK parameters, see section 6 below.

6 PHARMACOKINETIC ANALYSIS

The PK analysis will be based on the PKAS and performed by CTC. The PK parameters will be calculated by Non-Compartmental Analysis (NCA) using the software Phoenix WinNonlin® version 8.1 or later (Certara, U.S.A).

The following non-compartmental PK parameters will be determined for each IP use:

- C_{max} - The maximum observed plasma concentration
- AUC_t - The area under the plasma concentration versus time curve (AUC) from timepoint 0 to t, where t represents the timepoint of the last detectable plasma concentration
- T_{max} - Time to C_{max}
- C_{last} - The last observed plasma concentration
- $AUC_{0\text{-}90}$ - AUC from timepoint 0 to 90 minutes
- AUC_{inf} - AUC from timepoint 0 extrapolated to infinity using $lambda_z$
- $T_{1/2}$ – The terminal plasma elimination half-life

Also, the PK parameters normalised by dose will be calculated.

Analysis will be based on the actual sampling times recorded during the study. of calculating PK parameters, concentrations below lower limit of quantification (LLOQ) occurring before C_{max} will be treated as zero. Concentrations below LLOQ occurring after C_{max} will be omitted from the analysis.

C_{max}, T_{max} and C_{last} will be derived from the observed plasma concentration data. AUC will be assessed by integration of the plasma concentration vs time curve using linear interpolation for increasing plasma levels and logarithmic interpolation for decreasing plasma levels

(Linear Up-Log Down method). AUC_t will be calculated from time 0 to the time t of the last detectable plasma concentration. AUC_{0-90} is the AUC truncated at 90 min. If there is no actual sampling time point at 90 min, the concentration at 90 min will be determined by interpolation between the surrounding actual sampling points (according to linear up, log down principles). For AUC_{inf} the area will be calculated to the last timepoint showing a measurable plasma concentration and then extrapolated to infinity using the concentration in the last quantifiable sample and $lambda_z$. $T_{½}$ will be calculated by ln 2 / $lambda_z$.

$Lambda_z$, the first order rate constant associated with the terminal portion of the curve will be determined by lin-logarithmic regression of the terminal elimination phase of individual plasma concentration vs time curves. Determination of $lambda_z$ requires identification of a sufficiently linear terminal phase (as determined by visual inspection of the lin-log plasma concentration vs time plot with the regression line) consisting of at least 3 terminal concentration values (not including C_{max}). If this is not achieved, $lambda_z$ and its dependent PK parameters will not be reported for that profile. In the following cases, $lambda_z$ dependent PK parameters will be flagged in listings as potentially unreliable:

- $Lambda_z$ estimation is based on a period of less than 1.0 times the resulting T½.
- The adjusted R2 value of the regression line is < 0.85.
- The estimated % extrapolated AUC is > 20% ((AUC_{inf} -AUC_t / AUC_{inf})*100).

Where plasma nicotine concentrations are above LLOQ immediately prior to product administration (pre-dose sample), PK parameters will also be calculated from baseline adjusted concentrations using a subject's elimination rate constant ($lambda_z$) (from the curve during the specific treatment period) and observed pre-dose concentration (considered to have been collected at time 0). Baseline adjustments will be calculated according to the formula:

$$C(t)_{adjusted} = C(t)_{observed} - C(0)e^{-lambdaz(t)}$$

In cases of a generated negative $C(t)_{adjusted}$, the value will be replaced with zero.

Where plasma nicotine concentrations are below LLOQ immediately prior to product administration (pre-dose sample), baseline adjusted PK parameters will be considered the same as non-baseline adjusted PK parameters.

For subjects where $lambda_z$ cannot be calculated, baseline adjusted PK parameters (C_{max}, AUC_t, T_{max}, C_{last}, AUC_{0-90}, AUC_{inf} and $T_{1/2}$) will not be generated and reported. For subjects where $lambda_z$ can be calculated but where the acceptance criteria for $lambda_z$ determination have not be fulfilled, baseline adjusted PK parameters will be calculated, but reported PK parameters will then be flagged in listings as potentially unreliable.

In addition to PK parameters specified in the protocol , t_{last} (the time of Clast), $AUC_{extr\%}$, $lambda_z$ and details about $lambda_z$ determination (adjusted R_2, span, number of timepoints and lower/ upper timepoints used for $lambda_z$ calculation) will be presented in the listing section.

If there is a confirmed dosing error during the study, the PK data for that period will only be included in the listings but excluded from descriptive and statistical analyses. In case of missed blood samples, potential impact on PK parameters will be assessed for each individual case. PK parameters with a high degree of uncertainty due to missing samples (e.g. multiple

samples missing around C_{max}) will be flagged as unreliable in the report and may in rare cases be excluded from summary tables, descriptive statistics, and statistical analysis.

7 CLINLCAL DATABASE PROCESSING

7.1 General information

The standards set forth by the Clinical Data Interchange Standards Consortium (CDISC) will be followed. CDISC develops and publishes standards in order to normalise the structure of clinical study data and thereby simplify submissions to and reviews by authorities such as the Food and Drug Administration (FDA). These standards include naming conventions, code lists, and data structure formats.

The study data will be structured into a database model reflecting the Study Data Tabulation Model (SDTM) and be compliant to SDTM Implementation Guide (SDTM-IG) version 3.2. The data used for statistical analysis will be structured to reflect the Analysis Data Model (ADaM) and be compliant to ADaM Implementation Guide (ADaM-IG) version 1.1. Both SDTM and ADaM are data-model standards developed by CDISC, and the versions used are mentioned as preferred versions in the FDA data standards catalogue.

Data values are collected according to, or mapped into, Controlled Terminology (CT) codelists defined by CDISC, whenever possible. The codelists are updated annually at CTC and the latest version available at study start will be used. As per default, CT codelists will be used in all tables, listings, and figures. Custom codelists for test or parameter names will be used if applicable upon Sponsor's request, to align with protocol texts, or to adhere to other standard naming conventions (e.g. PK parameter name "Tmax" will be used instead of the CDISC term "Time of CMAX"). These custom codelists will be mapped in the "Parameter Name" field in the ADaM structure, while the CT will be kept in the SDTM predecessor fields to provide traceability back to CDISC codelists.

7.2 Database modeling of study design

The SDTM study design model contains the following structural components:

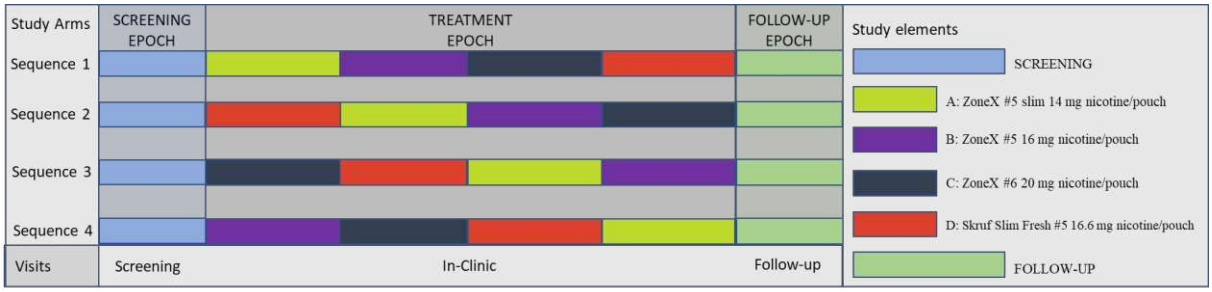
EPOCH: Study epochs follow a controlled terminology to represent the different study parts (e.g. SCREENING, TREATMENT [X], FOLLOW-UP)

ELEMENT: Building blocks used to build up the entire study length for all subjects. Information on ELEMENTs are extracted from the study design and schedule of events in the protocol. ELEMENTs are defined to span the entire study without gaps. One EPOCH may contain one or several ELEMENTs. All ELEMENTs must have transition rules in accordance with the protocol to determine start and end.

ARM: Subjects are allocated to study arms depending on the study design, either by randomisation or other allocation processes defined in the study protocol. ARMs are defined as the total number of planned ways a subject can go through the study (unique combination of study ELEMENTs). All ARMs must contain a unique sequence of ELEMENTs.

VISIT: Study visits are defined as planned timepoints during the study where study data is collected. A visit can be performed in clinic, by off-site contact with study personnel (phone call, video conference or similar), or by subject initiated recordings of data. The visit schedule is extracted from protocol and eCRF design.

Below is a schematic representation of the SDTM study design:



8 STATISTICAL METHODOLOGY

All relevant collected data will be listed. Additional statistical analyses and descriptive summaries are specified below.

8.1 Primary endpoint(s) analysis

8.1.1 C_{max} and AUC_t

This section refers to the primary objective 1, endpoint 1.1.

C_{max} and AUC_t and baseline adjusted C_{max} and AUC_t will be summarised descriptively. Also, log transformed nicotine C_{max} and AUC_t estimates will be evaluated separately in a linear mixed-effects analysis of variance model with fixed effects for product and a random effect for subject. The above product differences will be back-transformed to present the ratios of geometric least squares (LS) means coupled with the 90% confidence intervals (CIs). If the CI falls within the range of 0.8-1.25, the corresponding two products are considered equivalent with respect to that comparison.

8.1.2 Tables and Figures relating to the primary endpoint(s)

Analysis and output related to the primary endpoint(s) are specified under section statistical output layout. The following tables and figures relate to the primary endpoint(s):

Table 14.4.1 PK parameters (Pharmacokinetic analysis set)

Table 14.4.2 PK parameters – Normalised by dose (Pharmacokinetic analysis set)

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8.2 Secondary endpoint(s) analysis

8.2.1 Definition of endpoint(s)

8.2.1.1 Other Pharmacokinetic parameters T_{max}, C_{last}, AUC_{0-90}, AUC_{inf} and $T_{1/2}$ and and baseline adjusted T_{max}, C_{last}, AUC_{0-90}, AUC_{inf} and $T_{1/2}$

This section refers to the secondary objective 2.1, endpoints 2.1.1.

See Section 6. All PK parameters (and PK parameters normalised by dose) will be summarised descriptively.

8.2.1.2 Extracted dose of nicotine

This section refers to the secondary objective 2.2, endpoint 2.2.1.

Content pre-use is calculated by multiplying the mean content of the weight normalised reference samples with the pouch weight of the study pouches. Content post-use is the measured content left in the study pouches post-use. Extracted amount (mg/unit) of nicotine, for each pouch, is calculated as the difference of content pre-use and content post-use, i.e.:

Equation 1

$$(D \times E_i) - F_i \quad i = 1, \ldots, N$$

where N=number of study pouches used in analysis

D= Mean content of weight normalised reference samples

E_i = Weight of the unused pouch

F_i = Content post-use

D is calculated by:

$$D = \frac{\Sigma_{j=1}^{M} C_j}{M},$$

where $C_j = \frac{A_j}{B_j}$ is weight normalised content for reference samples, and A_j=reference nicotine amount and B_j=reference weight, $j = 1, \ldots, M$. M =Number of reference samples .

Extracted fraction (%) of nicotine, for each pouch $i = 1, \ldots, N$, is calculated as the extracted amount divided by the content pre-use, i.e.:

Equation 2

$$\frac{(D \times E_i) - F_i}{D \times E_i}$$

Extracted dose of nicotine will be summarised descriptively and analysed using a Wilcoxon signed rank test to assess differences between IPs.

Pearson correlation coefficients for baseline adjusted AUC_{inf}, AUC_t, baseline adjusted AUC_{inf} and baseline adjusted $AUC_t$and the derived extracted dose of nicotine (attained via Equation 1 above) will be estimated and presented for each IP, with corresponding p-value.

8.2.1.3 Product evaluation scale (PES)

This section refers to the secondary objective 2.3, endpoint 2.3.1.

Each question of the PES will be answered using a 7-point Likert scale. Responses will be presented as the following factor scores: 1 = not at all, 2 = very little, 3 = a little, 4 = moderately, 5 = a lot, 6 = quite a lot, 7 = extremely.

Four multi-item subscales will be derived from the PES categories:

- "Satisfaction" (items 1, 2, 3, and 12)
- "Psychological Reward" (items 4-8)
- "Aversion" (items 9, 10, 16, and 18)
- "Relief" (items 11, 13, 14, 15, and reversed for item 20)

These four multi-item subscales will be summarized descriptively by IP and overall, at applicable assessment timepoints. Single items 17, 19 and 21 will also be summarized in the same way as the multi-item subscales. Also, PES sub-category and total scores will be presented visually with individual and mean figures.

In addition, PES-differences between products on total and sub-category PES score, at each time point, will be analysed using Wilcoxon Rank Sum tests.

8.2.1.4 Product preference scale (PPS)

This section refers to the secondary objective 2.3, endpoint 2.3.1.

PPS will be summarised descriptively by IP. The PPS data collected in the eCRF will therefore be derived so the results will be presented by IP, instead of presented by day (as collected) i.e., derived according to the following:

Rank the 4 pouch products in relation to each other.

Study product used at:	**Order of preference:**			
Day 1	(1)	2	3	4
Day 2	1	2	3	(4)
Day 3	1	2	(3)	4
Day 4	1	(2)	3	4

Rate the 4 pouch products in order of preference

Study product:	**Preference result:**			
Product A	1	2	(3)	4
Product B	(1)	2	3	4
Product C	1	(2)	3	4
Product D	1	2	3	(4)

Note: this is just an illustrative example with made up subject evaluations, to explain the data derivation. The table layout for PPS can be found in Table 14.2.3 Products preference scale (PPS) (Full analysis set)

8.2.1.5 Urge to use questionnaire

This section refers to the secondary objective 2.3, endpoint 2.3.1.

The answer from the Urge to use questionnaire is graded on a Visual Analogue Scale (VAS) from 0-100 mm, where 0 is “No urge at all” and 100 is “extreme urge”.

The following parameters will be calculated for the urge to use assessments:

- E_{max} - The maximum change from baseline VAS score ($VAS_{pre\text{-}use}$ - $VAS_{post\text{-}use}$).
- T_{Emax} - Time of the E_{max}. If the maximum value occurs at more than one time point, T_{Emax} will be defined as the first time point with this value.

- $AUEC_{0\text{-}120}$ - The area under the change from baseline VAS score versus time curve from time 0 to 120 minutes, calculated using the linear trapezoidal method with linear interpolation using actual sample times.

Responses and the derived parameters mentioned above will be summarized by IP and overall using descriptive statistics, including change from baseline. Also, urge to use questionnaire (VAS score) will be presented visually with individual and mean figures.

8.2.1.6 Adverse events

This section refers to the secondary objective 2.4, endpoint 2.4.1.

An overview of all AEs, including SAEs, intensity, relationship to IP, and deaths will be presented by IP and overall. Incidence of AEs and SAEs will also be summarised by SOC and PT by IP and overall. For both summaries, any AE that occurred during follow-up, will be presented separately (in an own column, in the same tables).

8.2.1.7 Safety laboratory analyses

This section refers to the secondary objective 2.4, endpoint 2.4.2.

Clinical laboratory data will be summarised by IP with absolute and percent change from baseline.

8.2.1.8 Vital signs

This section refers to the secondary objective 2.4, endpoint 2.4.2.

Vital signs (systolic/diastolic blood pressure and pulse) will be summarised by IP. Data will be presented with absolute and percent change from baseline.

8.2.1.9 12-lead ECG

This section refers to the secondary objective 2.4, endpoint 2.4.2.

All ECGs will be categorised as ”normal”, ”abnormal, not clinically significant”, or ”abnormal, clinically significant” (as judged by the Investigator) and summarised by IP using frequency tables.

8.2.2 Tables and Figures relating to the secondary endpoint(s)

Analysis and output related to the secondary endpoint(s) are specified under section statistical output layout. The following tables and figures relate to the secondary endpoint(s):

Table 14.2.1 Products evaluation scale (PES) (Full analysis set)
Table 14.2.2 Products evaluation scale (PES) – Wilcoxon Rank Sum tests comparison of treatments (Full analysis set)

Table 14.2.3 Products preference scale (PPS) (Full analysis set)

Table 14.2.4 Urge to use questionnaire (Full analysis set)

Table 14.2.5 Urge to use questionnaire – Treatment comparisions (Full analysis set)

Table 14.3.1 Overview of adverse events (Full analysis set)

Table 14.3.2 Adverse events by system organ class and preferred term (Full analysis set)

Table 14.3.3 Safety laboratory measurements - clinical chemistry (Full analysis set)

Table 14.3.4 Safety laboratory interpretations - clinical chemistry (Full analysis set)

Table 14.3.5 Safety laboratory measurements - haematology (Full analysis set)

Table 14.3.6 Safety laboratory interpretations - haematology (Full analysis set)

Table 14.3.7 Vital signs measurements (Full analysis set)

Table 14.3.8 Vital signs interpretations (Full analysis set)

Table 14.3.9 ECG measurements (Full analysis set)

Table 14.3.10 ECG interpretations (Full analysis set)

Table 14.3.11 Physical examinations (Full analysis set)

Table 14.3.12 Physical examinations interpretations (Full analysis set)

Table 14.3.13 Plasma concentrations (Pharmacokinetic analysis set)

Table 14.4.1 PK parameters (Pharmacokinetic analysis set)

Table 14.4.2 PK parameters – Normalised by dose (Pharmacokinetic analysis set)

8.2.2.1.1.1 Table 14.4.3 PK parameters – Treatment comparisons (Pharmacokinetic analysis set)

Table 14.4.4 Extracted dose of nicotine - normalised by weight and relative amount (Full analysis set)

Table 14.4.5 Extracted dose of nicotine – Wilcoxon Signed Rank tests comparison of treatments (Pharmacokinetic analysis set)

Table 14.4.6 Extracted dose of nicotine – Pearson correlations to PK parameters (Pharmacokinetic analysis set)

Figure 14.2.1 Products evaluation scale (PES) sub-category and total scores individual graphs (Full analysis set)

Figure 14.2.2 Products evaluation scale (PES) sub-category and total scores mean graphs (Full analysis set)

Figure 14.2.3 Urge to use (VAS score) individual graphs (Full analysis set)

Figure 14.2.4 Urge to use (VAS Score) mean graphs (Full analysis set)

Figure 14.4.1 Individual plasma concentrations over time (lin-log) (Pharmacokinetic analysis set)

Figure 14.4.2 Individual plasma concentrations over time (lin-lin) (Pharmacokinetic analysis set)

Figure 14.4.3 Mean plasma concentrations over time (lin-log) (Pharmacokinetic analysis set)

Figure 14.4.4 Mean plasma concentrations over time (lin-lin) (Pharmacokinetic analysis set)

8.3 Tertiary/exploratory endpoint(s) analysis

NA

8.4 Other data analysis/presentation

8.4.1 Demographics and baseline characteristics

Descriptive statistics for demographics, physical examinations, weight and height will be presented by sequence.

8.4.2 Medical/surgical history and prior/concomitant medication

Medical/surgical history will be presented by system-organ-class (SOC) and preferred term (PT). Prior/concomitant medications will be presented by ATC level 3 and 5.
Medical/surgical history and prior medications will be presented overall by descriptive statistics and listings. Concomitant medications will be presented by sequence.

In addition to the primary and secondary endpoint(s) described above, the following tables and figures will be produced:

Table 14.1.1 Baseline characteristics and demographics (Full analysis set)

Table 14.1.2 Subject disposition (all subjects)

Table 14.1.3 Medical history events by system organ class and preferred term (Full analysis set)

Table 14.1.4 Concomitant medications by ATC levels 3 and 5 (Full analysis set)

Table 14.1.5 Prior medications by ATC levels 3 and 5 (Full analysis set)

8.5 Interim analysis

NA

9 CHANGES FROM THE CSP

9.1 Changes of product comparisons for primary analysis

In the protocol (Synopsis and Section 17.5) it was stated that the primary objective will be examined by the following statistical comparisons for AUC and C_{max}:

- Product A versus Product B, C and D, respectively

- Product B versus Product C and D, respectively
- Product C versus Product D

Instead, the primary objective will be examined by the following statistical comparisons for AUC_t and C_{max}:

- Product A does not significantly differ from Product D
- Product B does not significantly differ from Product D
- Product C does not significantly differ from Product D

The reason for the change is that the test products are Products A-C and the Comparator product is Product D, so there is no need for multiple comparisons.

9.2 Changes of fixed effects for primary analysis

In the protocol (Synopsis and Section 17.5) it was stated that the linear mixed-effects model for the primary analysis should include fixed effects for period, sequence, and product, and a random effect for subject. The fixed effects for period and sequence will be removed for the statistical analysis. The subjects will be allowed to use their own nicotine containing products ad lib after the 8-hour timepoint until 10 pm. Hence, keeping period and sequence in the model adds no extra value to the analysis.

9.3 Change of analysis method for Urge to use questionnaire for secondary analysis

In the protocol it was stated that the same statistical method as described for the PK analysis will be used to compare Urge to use parameters. Instead, change from baseline will be evaluated descriptively for each IP.

10 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
- Statistical analyses, summary tables, listings and figures as described under section 14.
- Clinical study database delivered as a SAS-export file.

11 SOFTWARE

All statistical analyses will be performed using SAS Version 9.4 (SAS institute, Cary, NC).

CLINICAL TRIAL CONSULTANTS AB

12 APPROVAL

Issued by: [redacted]

[redacted]

Responsible Biostatistician Date

CTC Representative

Approved by: [redacted]

[redacted]

13 SUPPORTIVE DOCUMENTATION

13.1 Appendix 1 – list of abbreviations

Abbreviation of term	Explanation
ADaM	Analytical Data Model
AE	Adverse event
ATC	Anatomical-therapeutic-chemical
APTT	Activated partial thromboplastin time
CDISC	Clinical Data Interchange Standards Consortium
CF	Clean file
CI	Confidence interval
CRF	Case report form
CSP	Clinical study protocol
ECG	Electrocardiogram
FAS	Full analysis set
IP	Investigational product
LLOQ	Lower level of quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Affairs
Min	Minimum
NA	Not applicable
OND	Oral nicotine delivery
PES	Product evaluation scale
PPS	Product preference scale
PPS	Per protocol set
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation

14 STATISTICAL OUTPUT LAYOUT

Placeholder descriptions like “GROUP 1”, “Treatment A”, “ELEMENT 1” etc. below should be replaced by
appropriate.

14.1 Template tables

Template tables will be adjusted as needed depending on the collected data. For example, if there is only one
will be dropped and the Result category column will also be dropped, as there is no second time point for whi
baseline to. Optional columns will not be included in specific output unless explicitly stated.

Template table A Descriptive statistic table – continuous variables

				GROUP 1	GR
Assessment (unit)	Result category	Assessment timepoint			
[Parameter 1] (unit)	Measured value	[Assessment timepoint 1]	n	x	x
			Mean (SD)	x.xxx (x.xxx)	x.xxx (x.x
			Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.x
		[Assessment timepoint 2]	n	x	x
			Mean (SD)	x.xxx (x.xxx)	x.xxx (x.x
			Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.x
	Absolute change from baseline	[Assessment timepoint 2]	n	x	x
			Mean (SD)	x.xxx (x.xxx)	x.xxx (x.x
			Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.x
	Relative change from baseline (%)	[Assessment timepoint 2]	n	x	x
			Mean (SD)	x.x (x.x)	x.xxx (x.x
			Median (Min, Max)	x.x (x, x)	x.xxx (x.x

Data based on [ANALYSIS SET]. Baseline at [Assessment timepoint 1]. ND: Not defined - no evaluable observati
missing observations. NC: Not calculated - number of non-missing observations less than 3
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: descriptive_stat_tables.sas. Run by: [USERNAME], [TIM

Template table B Descriptive statistic table – discrete variables

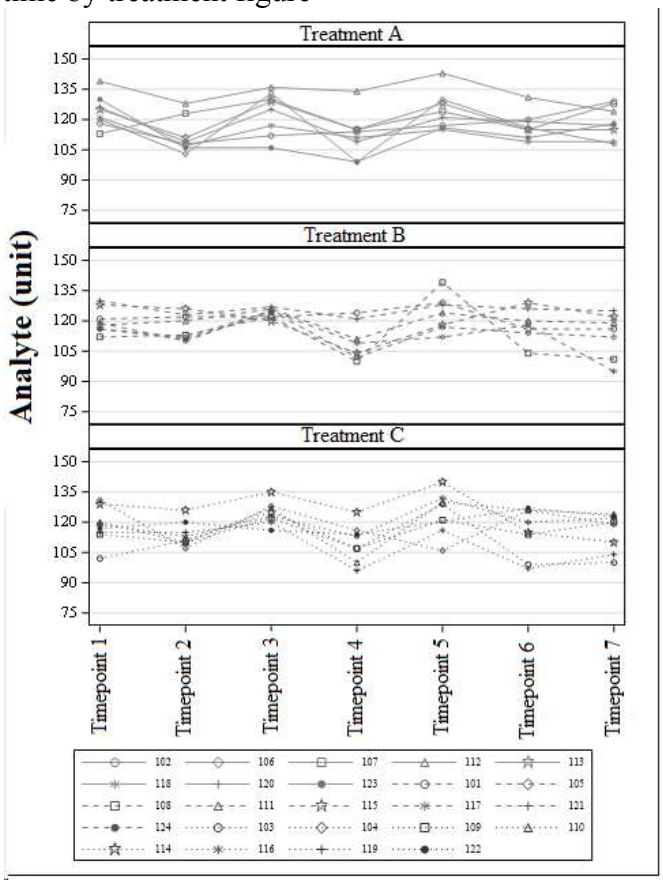
			GROUP 1	GROUP 2	[Tota
Assessment	Assessment timepoint	Result			
[Parameter 1]	[Assessment timepoint 1]	[RESULT 1]	x(x.x%)/X	x(x.x%)/X	x(x.x%)/
		[RESULT 2]	x(x.x%)/X	x(x.x%)/X	x(x.x%)/
	[Assessment timepoint 2]	[RESULT 1]	x(x.x%)/X	x(x.x%)/X	x(x.x%)/
		[RESULT 2]	x(x.x%)/X	x(x.x%)/X	x(x.x%)/

Data based on [ANALYSIS SET].
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: descriptive_stat_tables.sas. Run by: [USERNAME], [TIME

14.2 Template figures

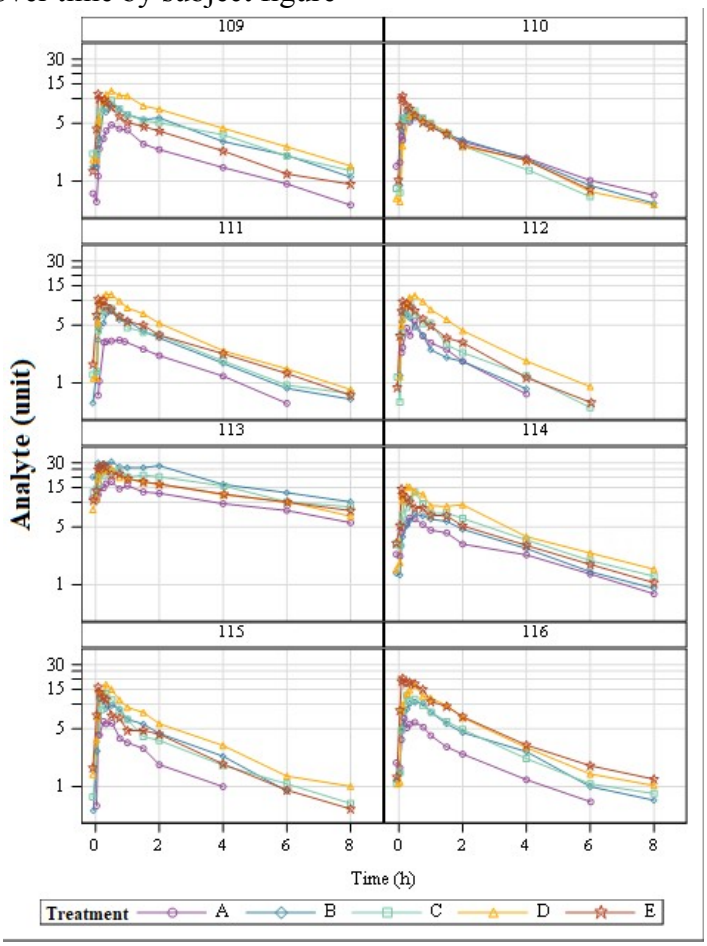
Template figures will be adjusted as needed depending on the collected data.

Template figure A Subject measurements over time by treatment figure



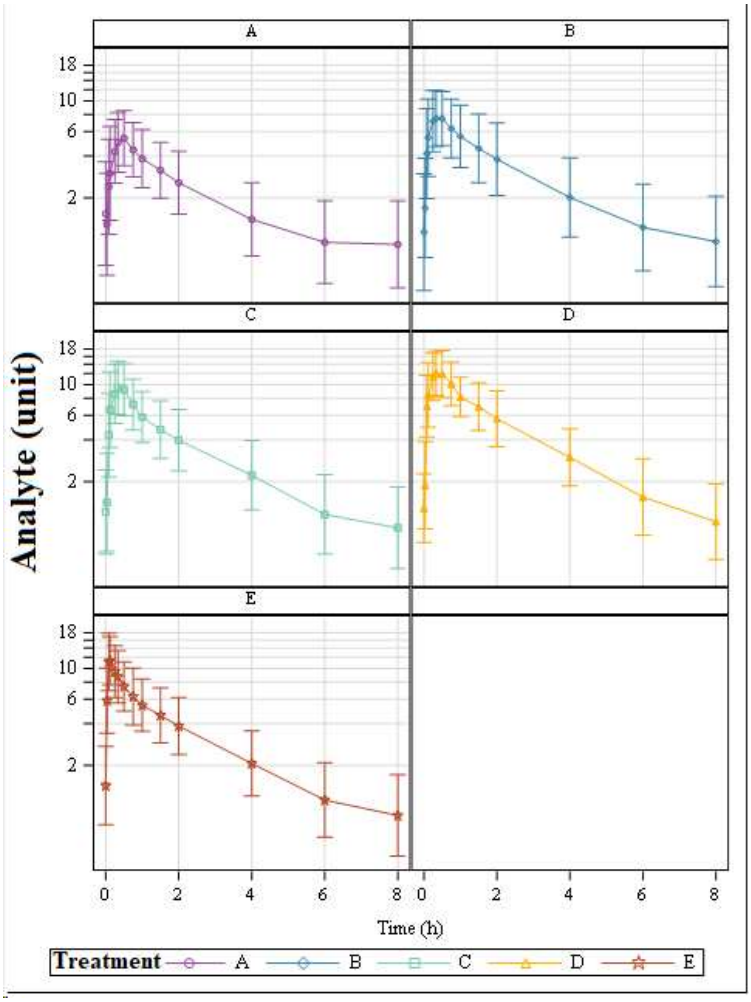
Data based on [ANALYSIS SET].
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [TIMESTAMP]

Template figure B Treatment measurements over time by subject figure



Data based on [ANALYSIS SET].
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [TIMESTAMP]

Template figure C Measurements over time by treatment with confidence interval bars figure



Data based on [ANALYSIS SET]. Confidence intervals calculated from a normal distribution.
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [TIMESTAMP]

14.3 Tables

Table 14.1.1 Baseline characteristics and demographics (Full analysis set)

		A:B:C:D (N=X)	B:C:D:A (N=X)	C:D:A:B (N=X)
Age (years)	n/nmiss	x/x	x/x	x/x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median (Min, Max)	x.x (x, x)	x.x (x, x)	x.x (x, x)
Body Mass Index (kg/m^2)	n/nmiss	x/x	x/x	x/x
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x
Height (cm)	n/nmiss	x/x	x/x	x/x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median (Min, Max)	x.x (x, x)	x.x (x, x)	x.x (x, x)
Weight (kg)	n/nmiss	x/x	x/x	x/x
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x
Sex	Female	x (x.x%)	x (x.x%)	x (x.x%)
	Male	x (x.x%)	x (x.x%)	x (x.x%)
Ethnicity	Hispanic Or Latino	x (x.x%)	x (x.x%)	x (x.x%)
	Not Hispanic Or Latino	x (x.x%)	x (x.x%)	x (x.x%)
	Not Reported	x (x.x%)	x (x.x%)	x (x.x%)
	Unknown	x (x.x%)	x (x.x%)	x (x.x%)
Race	American Indian Or Alaska Native	x (x.x%)	x (x.x%)	x (x.x%)
	Asian	x (x.x%)	x (x.x%)	x (x.x%)
	Black or African American	x (x.x%)	x (x.x%)	x (x.x%)
	Native Hawaiian or other Pacific Islander	x (x.x%)	x (x.x%)	x (x.x%)

	A:B:C:D (N=X)	B:C:D:A (N=X)	C:D:A:B (N=X)
White	x (x.x%)	x (x.x%)	x (x.x%)

```
[STUDYID] Summarised demographics data.
Data based on the [Full analysis set].
SAS program: summary_demographics.sas. Run by: [USERNAME], [TIMESTAMP]
```

Table 14.1.2 Subject disposition (all subjects)

	Total
Screened subjects	x
Withdrawn prior to dose	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
Included subjects	x
--- A:B:C:D	x
--- B:C:D:A	x
--- C:D:A:B	x
--- D:A:B:C	x
Withdrawn subjects	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
Completed subjects	x
Included in full analysis set	x
Included in PK analysis set	x
Subjects at Screening	x
Subjects at In-Clinic	x
Subjects at Phone Call	x

[STUDYID] Disposition, SAS program: disposition.sas. Run by: [USERNAME], [TIMESTAMP]

Table 14.1.3 Medical history events by system organ class and preferred term (Full analysis set)

System organ class Preferred term	Total N=X n(%)	m
Total	**x(x.x%)**	**x**
SOC 1	**x(x.x%)**	**x**
SOC 1 PT 1	x(x.x%)	x
SOC 1 PT 2	x(x.x%)	x
SOC 1 PT 3	x(x.x%)	x
SOC 2	**x(x.x%)**	**x**
SOC 2 PT 1	x(x.x%)	x
SOC 2 PT 2	x(x.x%)	x

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the treatment period included in the [Full analysis set]
[STUDYID] Medical history events by system organ class and preferred term, [analysis set], SAS program: mh_s
[USERNAME], [TIMESTAMP]

Table 14.1.4 Concomitant medications by ATC levels 3 and 5 (Full analysis set)

	A:B:C:D N=X		B:C:D:A N=X		C:D:A:B N=X		D
ATC Name Level 3 ATC Name Level 5	n(%)	m	n(%)	m	n(%)	m	
Total	**x(x%)**	**x**	**x(x%)**	**x**	**x(x%)**	**x**	
…	**x(x%)**	**X**	**x(x%)**	**X**	**x(x%)**	**X**	

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the full analysis set
[STUDYID] Medical history events by system organ class and preferred term, [Full analysis set], SAS program: by: [USERNAME],] [TIMESTAMP]

Table 14.1.5 Prior medications by ATC levels 3 and 5 (Full analysis set)

	Total N=X	
ATC Name Level 3 ATC Name Level 5	n(%)	m
Total	**x(x%)**	**x**
…	**x(x%)**	**X**

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the full analysis set
[STUDYID] Medical history events by system organ class and preferred term, [Full analysis set], SAS program: by: [USERNAME], [TIMESTAMP]

Table 14.2.1 Products evaluation scale (PES) (Full analysis set)

[Note to programmer: multi-items and single-items are defined in Section 8.2.1.3]

			A	B	C
Assessment	Assessment timepoint	Result			
Satisfaction (multi-item 1)	[Assessment timepoint 1]	Not at all (1)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		Very little (2)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		…	…	…	…
	[Assessment timepoint 2]	Not at all (1)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		Very little (2)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
	…	…	…	…	…
Psychological Reward (multi-item 2)	[Assessment timepoint 1]	Not at all (1)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		Very little (2)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		…	…	…	…
	[Assessment timepoint 2]	Not at all (1)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		Very little (2)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
…	…	…	…	…	…
Was it easy to use? (single-item 17)	[Assessment timepoint 1]	Not at all (1)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		Very little (2)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		…	…	…	…
	[Assessment timepoint 2]	Not at all (1)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		Very little (2)	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
…	…	…	…	…	…

Table 14.2.2 Products evaluation scale (PES) – Wilcoxon Rank Sum tests comparison of treatmen

Question multi-item sub-category	Assessment timepoint	Test product	Reference product	95% CI lower bound	Estimated difference	95% CI upper bound	p-value
Satisfaction	[Assessment timepoint 1]	Product A	Product D	x.xx	x.xxxx	x.xxx	x.xxxx
		Product B	Product D	x.xx	x.xxxx	x.xxx	x.xxxx
	…	Product C	Product D	x.xx	x.xxxx	x.xxx	x.xxxx
Psychological Reward	[Assessment timepoint 1]	Product A	Product D	x.xx	x.xxxx	x.xxx	x.xxxx
		Product B	Product D	x.xx	x.xxxx	x.xxx	x.xxxx
…	…	…	…	…	…	…	…

Table 14.2.3 Products preference scale (PPS) (Full analysis set)

[Note to programmer: PPS will be summarised descriptively by IP. The PPS data collected in the eCRF will therefore be derived so of presented by day (as collected), see Section 8.2.1.4]

Product preference order	Result	Total
Product A	1	x(x.x%)/X
	2	x(x.x%)/X
	3	x(x.x%)/X
	4	x(x.x%)/X
Product B	1	x(x.x%)/X
	2	x(x.x%)/X
	3	x(x.x%)/X
	4	x(x.x%)/X
Product C	1	x(x.x%)/X
	2	x(x.x%)/X
	3	x(x.x%)/X
	4	x(x.x%)/X
Product D	1	x(x.x%)/X
	2	x(x.x%)/X
	3	x(x.x%)/X
	4	x(x.x%)/X

Data based on [ANALYSIS SET].
Results are presented as n(%)/N, where N is the total number of observations at that specific timepoint. Orde
products: 1 = most preferred product, 4 = least preferred product.
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: descriptive_stat_tables.sas. Run by: [USERNAME], [TIME

Table 14.2.4 Urge to use questionnaire (Full analysis set)

			A	B	C	
Assessment (unit)	Assessment timepoint					
Urge to use (unit)	[Assessment timepoint 1]	n	x	x	x	x
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx
		Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx
	[Assessment timepoint 2]	n	x	x	x	x
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx
		Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx
	…	…	…	…	…	…
Emax (unit)	[Assessment timepoint 1]	n	x	x	x	x
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx
		Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx
	[Assessment timepoint 2]	n	x	x	x	x
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx
		Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx
	…	…	…	…	…	…
TEmax (unit)	[Assessment timepoint 1]	n	x	x	x	x
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx
		Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx
	[Assessment timepoint 2]	n	x	x	x	x
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx
		Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx
	…	…	…	…	…	…
$AUEC_{0-120}$ (unit)	[Assessment timepoint 1]	n	x	x	x	x
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx
		Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx

			A	B	C	
Assessment (unit)	Assessment timepoint					
	[Assessment timepoint 2]	n	x	x	x	x
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx
		Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx
	…	…	…	…	…	…

Table 14.2.5 Urge to use questionnaire – Treatment comparisions (Full analysis set)

Assessment (unit)	Test formulation	Reference formulation	90% CI lower bound	Ratio of geometric LSMeans	90% CI upper bound	p-value
Emax (unit)	A	D	x.xxx	x.xxxx	x.xxx	x.xxxx
	B	D	x.xxx	x.xxxx	x.xxx	x.xxxx
	C	D	x.xxx	x.xxxx	x.xxx	x.xxxx
TEmax (unit)	A	D	x.xxx	x.xxxx	x.xxx	x.xxxx
	B	D	x.xxx	x.xxxx	x.xxx	x.xxxx
	C	D	x.xxx	x.xxxx	x.xxx	x.xxxx
…	…	…	…	…	…	…

Data based on PK analysis set. Pairwise treatment comparisons are based on a repeated measurement mixed model
model has p-value of x.xxxx. [STUDYID] [Full analysis set], SAS program: [PROGRAM NAME]. Run by: [USERNAME],

Table 14.3.1 Overview of adverse events (Full analysis set)

	A N=X		B N=X		C N=X		D N=X		Follow-Up N=X		Total N=X	
	n(%)	m	n(%)	m	n(%)	m	n(%)	m	n(%)	m	n(%)	m
Any AE	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Any SAE	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Any AE leading to withdrawal	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Any AE leading to death	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Causality												
Unlikely Related	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Possibly Related	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Probably Related	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Severity												
Mild	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Moderate	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Severe	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Life-threatening	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Death	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the treatment period included in the [Full analysis set].
Adverse events that occurred during screening are omitted from summary.
[STUDYID] Overview of adverse events, [analysis set], SAS program: ae_summary_tables.sas. Run by: [USERNAME],

Table 14.3.2 Adverse events by system organ class and preferred term (Full analysis set)

	A N=X		B N=X		C N=X		D N=X		Follow-U N=X
System organ class Preferred term	n(%)	m	n(%)	m	n(%)	m	n(%)	m	n(%)
SOC 1s	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**
SOC 1 PT 1	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)
SOC 1 PT 2	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)
SOC 1 PT 3	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)
SOC 2	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**
SOC 2 PT 1	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)
SOC 2 PT 2	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the treatment period included in the Full analysis set
Adverse events that occurred during screening are omitted from summary.
[STUDYID] Adverse events by system organ class and preferred term, [analysis set], SAS program: ae_summary_by
[TIMESTAMP]

Table 14.3.3 Safety laboratory measurements - clinical chemistry (Full analysis set)

See appendix
Template table A Descriptive statistic table – continuous variables
[Note to programmer: Clinical laboratory data will be summarised by IP with absolute and percent change from baseline]

Table 14.3.4 Safety laboratory interpretations - clinical chemistry (Full analysis set)

See appendix
Template table B Descriptive statistic table – discrete variables..

Table 14.3.5 Safety laboratory measurements - haematology (Full analysis set)

See appendix
Template table A Descriptive statistic table – continuous variables
[Note to programmer: Clinical laboratory data will be summarised by IP with absolute and percent change from baseline]

Table 14.3.6 Safety laboratory interpretations - haematology (Full analysis set)

See appendix
Template table B Descriptive statistic table – discrete variables..

Table 14.3.7 Vital signs measurements (Full analysis set)

See appendix
Template table A Descriptive statistic table – continuous variables. Include all parameters except those includ
[Note to programmer: Vital signs will be summarised by IP with absolute and percent change from baseline]

Table 14.3.8 Vital signs interpretations (Full analysis set)

See appendix
Template table B Descriptive statistic table – discrete variables. Include all parameters except those included

Table 14.3.9 ECG measurements (Full analysis set)

See appendix
Template table A Descriptive statistic table – continuous variables

Table 14.3.10 ECG interpretations (Full analysis set)

See appendix
Template table B Descriptive statistic table – discrete variables

Table 14.3.11 Physical examinations (Full analysis set)

See appendix
Template table B Descriptive statistic table – discrete variables

Table 14.3.12 Physical examinations interpretations (Full analysis set)

See appendix
Template table B Descriptive statistic table – discrete variables

Table 14.3.13 Plasma concentrations (Pharmacokinetic analysis set)

See appendix
Template table A Descriptive statistic table – continuous variables

Table 14.4.1 PK parameters (Pharmacokinetic analysis set)

See appendix
Template table A Descriptive statistic table – continuous variables.
PK parameters to be included in the table (in the following order):

- Non- baseline adjusted: T_{max}, C_{max}, AUC_{0-90}, AUC_t, AUC_{inf}, C_{last} and $T_{1/2}$.
- Baseline adjusted: T_{max}, C_{max}, AUC_{0-90}, AUC_t, AUC_{inf}, C_{last} and $T_{1/2}$.

Table 14.4.2 PK parameters – Normalised by dose (Pharmacokinetic analysis set)

See appendix
Template table A Descriptive statistic table – continuous variables.

Table 14.4.3 PK parameters – Treatment comparisons (Pharmacokinetic analysis set)

Assessment (unit)	Test formulation	Reference formulation	90% CI lower bound	Ratio of geometric LSMeans	90% CI upper bound	p-value
AUCt (unit)	A	D	x.xxx	x.xxxx	x.xxx	x.xxxx
	B	D	x.xxx	x.xxxx	x.xxx	x.xxxx
	C	D	x.xxx	x.xxxx	x.xxx	x.xxxx
Cmax (unit)	A	D	x.xxx	x.xxxx	x.xxx	x.xxxx
	B	D	x.xxx	x.xxxx	x.xxx	x.xxxx
	C	D	x.xxx	x.xxxx	x.xxx	x.xxxx
…	…	…	…	…	…	…

```
Data based on PK analysis set. Pairwise treatment comparisons are based on a repeated measurement mixed model
model has p-value of x.xxxx. [STUDYID], [PK analysis set], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [
```

Table 14.4.4 Extracted dose of nicotine - normalised by weight and relative amount (Full analysis

[Note to programmer: Derivations in Section 8.2.1.2]

		A	B	C	D
Assessment (unit)					
NICOTINE (mg/pouch)	n	x	x	x	x
	Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
	Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)
NICOTINE (%)	n	x	x	x	x
	Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
	Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)

Data based on Full analysis set.[STUDYID] Adverse events by system organ class and preferred term, [analysis
Run by: [USERNAME], [TIMESTAMP]

Table 14.4.5 Extracted dose of nicotine – Wilcoxon Signed Rank tests comparison of treatments (

Parameter (unit)	Test product	Reference product	95% CI lower bound	Estimated difference	95% CI upper bound	p-value
NICOTINE (mg/pouch)	A	D	x.xx	x.xxxx	x.xxx	x.xxxx
	B	D	x.xx	x.xxxx	x.xxx	x.xxxx
	C	D	…	…	…	…
NICOTINE (%)	A	D	x.xx	x.xxxx	x.xxx	x.xxxx
	B	D	x.xx	x.xxxx	x.xxx	x.xxxx
…	…	…	…	…	…	…

Data based on PK analysis set.[STUDYID], SAS program: [PROGRAM NAME]. Run by: [USERNAME], [TIMESTAMP]

Table 14.4.6 Extracted dose of nicotine – Pearson correlations to PK parameters (Pharmacokineti

PK Parameter (unit)	Extracted dose of nicotine (mg/unit) for Product	Pearson correlation	p-value
Baseline-adjusted AUC_{inf}	A	x.xxx	x.xxxx
Baseline-adjusted AUC_{inf}	B	x.xxx	x.xxxx
…	…	…	…

Correlations close to 1 indicates a strong correlation. Data based on PK analysis set.[STUDYID], SAS program: [TIMESTAMP]

14.4Figures

Figure 14.2.1 Products evaluation scale (PES) sub-category and total scores individual graphs (Fu

See appendix
Template figure B Treatment measurements over time by subject figure

Figure 14.2.2 Products evaluation scale (PES) sub-category and total scores mean graphs (Full an

See appendix Template figure C Measurements over time by treatment with confidence interval bars figure

Figure 14.2.3 Urge to use (VAS score) individual graphs (Full analysis set)

See appendix
Template figure B Treatment measurements over time by subject figure

Figure 14.2.4 Urge to use (VAS Score) mean graphs (Full analysis set)

See appendix Template figure C Measurements over time by treatment with confidence interval bars figure

Figure 14.4.1 Individual plasma concentrations over time (lin-log) (Pharmacokinetic analysis set)

See appendix Template figure A Subject measurements over time by treatment figure

Figure 14.4.2 Individual plasma concentrations over time (lin-lin) (Pharmacokinetic analysis set)

See appendix Template figure A Subject measurements over time by treatment figure

Figure 14.4.3 Mean plasma concentrations over time (lin-log) (Pharmacokinetic analysis set)

See appendix
Template figure B Treatment measurements over time by subject figure

Figure 14.4.4 Mean plasma concentrations over time (lin-lin) (Pharmacokinetic analysis set)

See appendix
Template figure B Treatment measurements over time by subject figure

14.5 Listings

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Listing 16.2.2.1. Protocol deviations (All subjects)

Listing 16.2.3.1 Subjects excluded from PKAS (All subjects)

Listing 16.2.3.2 Population definitions (All subjects)

Listing 16.2.3.3. Non-eligible subjects (All subjects)

Listing 16.2.4.1. Demography (Full analysis set)

Listing 16.2.4.2 Medical/surgical history (Full analysis set)

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Listing 16.2.12.1. Adverse events, part 1 (Full analysis set)

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Listing 16.2.12.3. Serious adverse events, part 1 (Full analysis set)

Listing 16.2.12.3. Serious adverse events, part 2 (Full analysis set)

Listing 16.2.12.4. Serious adverse events, seriousness criteria (Full analysis set)

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Listing 16.2.16.1. Physical examinations (Full analysis set)

Listing 16.2.17.1. Disposition (All subjects)

Listing 16.2.18.1. Subject visits (All subjects)

Listing 16.2.19.1. Subject elements (All subjects)