A RANDOMISED, CROSS-OVER, RELATIVE BIOAVAILABILITY STUDY OF NICOTINE DELIVERY AND NICOTINE EXTRACTION FROM ORAL TOBACCO PRODUCTS (TRADITIONAL SNUS, CONVENTIONAL CIGARETTE AND THREE ORAL TOBACCO-FREE NICOTINE DELIVERY PRODUCTS)

NCT# NCT04891406

Statistical analysis plan - FINAL version 1.0 02FEB2021

CONFIDENTIAL

Statistical analysis plan (SAP)

Sponsor:	*Imperial Tobacco Ltd*
Study code:	*IB-OND-PKZX-01*
CTC project no:	[redacted]
Study title:	*A randomised, cross-over, relative bioavailability study of nicotine delivery and nicotine extraction from oral tobacco products (traditional snus, conventional cigarette and three oral tobacco-free nicotine delivery products)*
SAP version and date:	*FINAL version 1.0 02FEB2021*

1 TABLE OF CONTENTS

2 VERSION HISTORY

This statistical analysis plan (SAP) for study IB-OND-PKZX-01 is based on the protocol dated 26AUG2021.

Table 1 SAP version history summary

SAP version	Approval Date	Changes	Rationale
0.1	11JAN2021	-	Version ready for internal review
0.2	25JAN2021	-	Version ready for Sponsor review
1	02FEB2021	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-PKZX-01.* 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

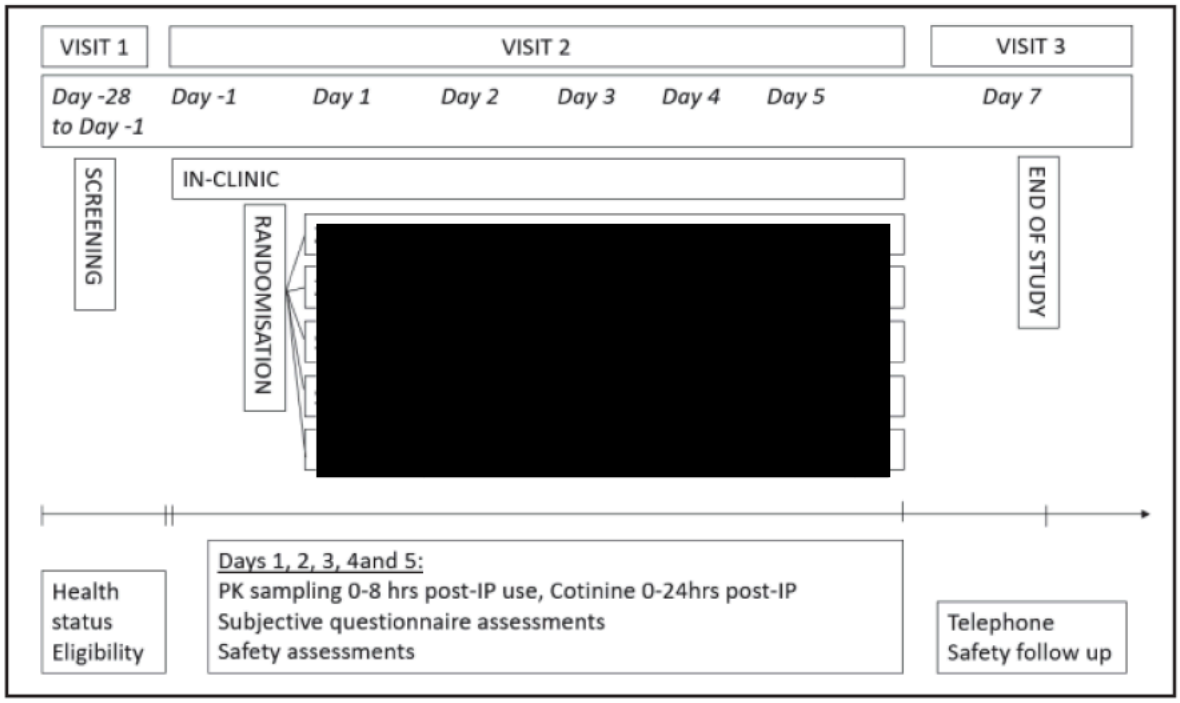
Objects	Estimands/Endpoints
Primary	
1. To evaluate and compare the maximum plasma concentration (C_{max}) and the area under the curve at the last timepoint measured (AUC_t) of nicotine after the use of each product.	1.1 Cmax and AUC_t
Secondary	
2.1 To evaluate other pharmacokinetic parameters of nicotine 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 Cmax (T_{max}), plasma concentration at last timepoint measured (Clast), terminal elimination halflife ($T_{1/2}$).
2.2 To evaluate extracted dose of nicotine in used products.	2.2.1 The extracted dose of nicotine from each portion to evaluate the correlation between AUC and extracted dose of nicotine.
2.3 To evaluate product perception and preference by use of subjective assessments.	2.3.1 Subjective assessment endpoints from Heaviness of smoking index (HSI), Product evaluation scale (PES), Modified cigarette evaluation questionnaire (MCEQ), Products preference scale (PPS).
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 ECG.
2.5 To evaluate the total nicotine exposure by measuring cotinine following single and *ad lib* use of each of the products.	2.5.1 Assessment of total nicotine exposure following plasma cotinine levels (concentration and applicable calculated PK parameters) following controlled single use and *ad lib* use of IP.
Tertiary/Exploratory	
NA	NA

4.2 Clinical study design

This will be a randomised cross-over, open-label, confinement study conducted in 24 male or female snus and cigarette consumers. The study will investigate 5 different nicotine containing products in a cross-over fashion. Cross-over in design, the study will incorporate pharmacokinetics evaluation, nicotine extraction evaluation, subjective questionnaire assessments as well as safety evaluation.

During the study participation, subjects will come for 2 visits to the clinic, including a 5-day confinement period and finally a follow up end-of-study telephone call within a week of product use.

The following figure gives an overview of the study design:



4.3 Statistical hypotheses

The primary objective will be examined by the following statistical comparisons for AUC_t and Cmax:

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

Log transformed nicotine Cmax and AUC_t estimates will be evaluated separately in a linear mixed-effects repeated meassurments analysis of variance model with fixed effects for period, sequence, and product. Repeated effect will be period and a random effect for subject. Kenward-Rogers degrees of freedom approximation will be used. Covariance structures (SAS abbreviated terminology) VC, UN, CS, AR(1), ARMA(1,1) and TOEP(q) for the repeated meassurements will be tested and the structure with the highest adjusted Akaike criteria will be used in the final analysis. The estimated product differences will be back-transformed to present the ratios of geometric least squares (LS) means and 95% CIs of each test product versus each other from the same model.

4.4 Number of subjects

Approximately 48 subjects will be screened to achieve a total of 24 randomised subjects.

4.5 Randomisation

On Day 1, subjects will be randomised to one of 5 treatment sequences. The five different products are:

A: ZoneX #2, OND, white tobacco-free nicotine pouch, 5.8 mg nicotine/pouch

B: ZoneX #3, OND, white tobacco-free nicotine pouch, 10.1 mg nicotine/pouch

C: Skruf snus fresh slim white, 10.9 mg nicotine/pouch

D: [redacted]

E: Marlboro Gold, conventional cigarette, 0.8 mg nicotine/cigarette

The 5 randomisation sequences are described in the table below:

Order					
Sequence 1	A	B	C	D	E
Sequence 2	B	C	D	E	A
Sequence 3	C	D	E	A	B
Sequence 4	D	E	A	B	C
Sequence 5	E	A	B	C	D

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

4.6 Blinding

Not applicable.

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. The FAS population will be used to assess safety.

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 PK analysis will be based on the PK analysis set. The FAS population will be used for all other evaluations.

5.3 Definition of baseline

The baseline measurement is defined as the latest non-missing measurement prior to first dose of the IP.

5.4 Summary statistics

In general, all data collected will be presented with summary statistics. Summary statistics will include at least number of subjects, mean, standard deviation, median, minimum, and maximum for continuous data whereas frequency and percentage will be provided for categorical data. Tables with summary statistics will be divided by treatment group, sequence, and assessment time, where applicable. Subject data listings will be sorted by treatment, subject, and timing of assessments.

5.5 Significance level

All hypothesis testing will use a 5% significance level (α=0.05).

5.6 Multiple comparisons/multiplicity

Both unadjusted and Tukey-Kramer adjusted p-values will be provided for product comparisons in the mixed effects repeated meassurements model. Otherwise no adjustment for multiple comparisons will be made.

5.7 Handling of dropouts, missing data and outliers

Please see the last section under Pharmacokinetic Analysis below.

For all other data – outliers will be included in summary tables and listings, and will not be handled separately in any analyses. No imputation of data will be performed.

5.8 Multicenter studies

Not applicable.

5.9 Examination of subgroups

Not applicable.

5.10 Blind review

Not applicable.

6 SUBJECTS

6.1 Subject disposition

The subject disposition table will include the number of screened subjects, reasons for withdrawal prior to treatment with the IP, number of subjects for each IP, reasons for withdrawal and the number of completed subjects in the study. The table will also summarise the number of subjects in each study population. See tables and listings in the statistical output layout, section 15.

6.2 Baseline characteristics and demographics

The following baseline characteristics will be summarised by sequence:

- Gender
- Age
- Weight
- Height
- BMI
- Ethnicity
- Race

7 TREATMENT INFORMATION AND EXTENT OF EXPOSURE

7.1 Active treatment

The number of subjects on each IP will be tabulated with start time and stop time. Duration of application will be tabulated using listings and summary statistics.

7.2 Prior and concomitant medications

Prior and concomitant medication data will be listed and tabulated by Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant medications will be coded according to the World Health Organization (WHO) ATC classification system.

8 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 reach C_{max}
- C_{last} - The last observed plasma concentration
- AUC_{0-90} - 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

Analysis will be based on the actual sampling times recorded during the study. 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} and T_{max} 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 infitity 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:

• Lambdaz 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}).

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 ($lambda_z$) and observed pre-dose concentration (considered to have been collected at time 0). Baseline adjustments will be calculated according to the formula:

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

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

If there is a confirmed dosing error during the study, the pharmacokinetic 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.

9 STATISTICAL METHODOLOGY

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

9.1 Primary endpoint(s) analysis

9.1.1 Definition of endpoint(s)

9.1.1.1 Pharmacokinetic parameters C_{max} and AUC_t and baseline adjusted 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 and analysed using the model described under Statistical hypotheses above.

9.1.2 Sensitivity analysis

Not applicable.

9.1.3 Supplementary analyses

Not applicable.

9.2 Secondary endpoint(s) analysis

9.2.1 Definition of endpoint(s)

9.2.1.1 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, endpoint 2.1.1.

All pharmacokinetic parameters will be summarised descriptively.

9.2.1.2 Extracted dose of nicotine

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

Extracted dose of nicotine will be assessed by the formula:

(A*B)/C – D

where

A = Reference value of nicotine as assessed by the average of extracted nicotine i unused reference pouches
B = Weight of the unused pouch
C = Reference weight value as assessed by the average of weight för unused reference pouches
D = Extracted nicotine of the used pouch

Extracted dose of nicotine will be summarised descriptively and analysed using a Wilcoxon rank sum test to assess differences between IPs for each assessment timepoint.

A correlation ratio to AUC_{inf}, AUC_t, baseline adjusted AUC_{inf} and AUC_t divided with the derived extracted dose of nicotine (attained via the formula above) will be calculated and presented using descriptive statistics.

9.2.1.3 Extracted flavour

Extracted flavour transfer will be assessed by the formula:

(A*B)/C – D

where

A = Reference value of flavour as assessed by the average of extracted flavour in unused reference pouches
B = Weight of the unused pouch
C = Reference weight value as assessed by the average of weight för unused reference pouches
D = Extracted flavour of the used pouch

Extracted flavour will be summarised descriptively and analysed using a Wilcoxon rank sum test to assess differences between IPs for each assessment timepoint.

9.2.1.4 Product perception and preference

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

Self-assessed Heaviness of smoking index (HSI) will be summarised descriptively by sequence.

Products evaluation scale (PES), Modified cigarette evaluation questionnaire (MCEQ) and Products preference scale (PPS) will be summarised descriptively by treatment, sub-question and assessment timepoint.

In addition, sub-category and the total score of PES will be tabulated using descriptive statistics and a graph of the product mean at each time point will be produced.

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

9.2.1.5 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 SOC and PT.

Incidence of AEs and SAEs will be summarised by SOC and PT by treatment, assessment time point and overall.

9.2.1.6 Vital signs

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

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

9.2.1.7 ECG resting 12-lead

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

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

Changes over time will be presented using shift tables, if considered appropriate.

9.2.1.8 Safety laboratory analyses

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

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

Abnormal, clinically significant values will be summarised separately, if considered appropriate.

9.2.1.9 Total nicotine exposure

This section refers to the secondary objective #2.5, endpoint 2.5.1.

Plasma cotinine levels will be analysed descriptively.

9.2.2 Sensitivity analysis

Not applicable.

9.2.3 Supplementary analyses

Not applicable.

9.3 Tertiary/exploratory endpoint(s) analysis

Not applicable.

9.4 Discontinuation

Patients who discontinue from IP treatment will be tabulated. The reason for discontinuation will be given. For discontinuation due to AE, the AEs will be given.

9.5 Other analyses

Not applicable.

9.6 Interim analysis

Not applicable.

10 CHANGES FROM THE CSP

11 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
- Statistical analyses, summary tables, listings and graphs

12 SOFTWARE

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

14 SUPPORTIVE DOCUMENTATION

14.1 Appendix 1 – list of abbreviations

Abbreviation of term	Explanation
AE	Adverse event
ATC	Anatomical-therapeutic-chemical
APTT	Activated partial thromboplastin time
CF	Clean file
CRF	Case report form
CSP	Clinical study protocol
CTC	Clinical Trial Consultants
ECG	Electrocardiogram
FAS	Full analysis set
HSI	Heaviness of smoking index
IP	Investigational product
MedDRA	Medical Dictionary for Regulatory Affairs
MSEQ	Modified cigarette evaluation questionnaire
PES	Products evaluation scale
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PPS	Products preference scale
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SOC	System organ class
WHO	World Health Organization

14.2 Appendix 2 – changes to protocol-planned analyses

15 STATISTICAL OUTPUT LAYOUT

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

15.1 Template tables

Template tables includes template tables and will be adjusted depending on the collected data.

15.1.1 Descriptive statistic table – continuous variables

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

Data based on [ANALYSIS SET]. Baseline at [Assessment timepoint 1]. ND: Not defined - no evaluable observations. NA: Not available - no non-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], [USER EMAIL] [TIMESTAMP]

15.1.2 Descriptive statistic table – discrete variables

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

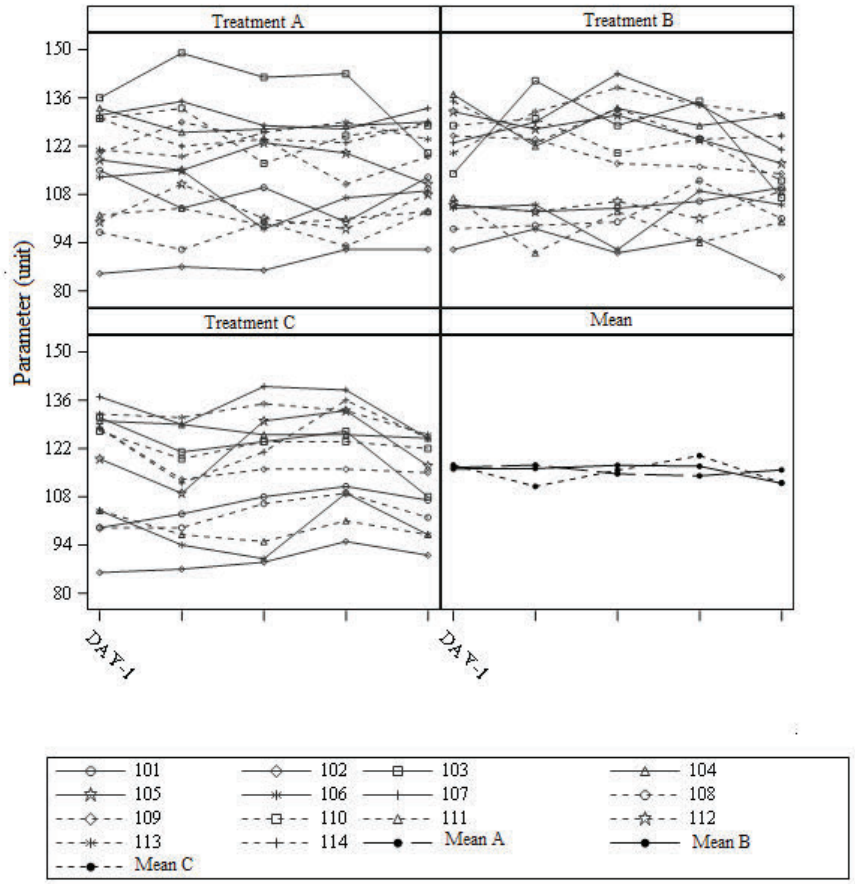
Data based on [ANALYSIS SET].
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: descriptive_stat_tables.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

15.1.3 Shift table

Assessment	Assessment timepoint	Result	NORMAL n (%)	ABNORMAL CS n (%)	ABNORMAL NCS n (%)	MISSING n (%)	TOTAL n (%)
[Parameter 1]	[Assessment timepoint 1]	NORMAL	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
		ABNORMAL CS	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
		ABNORMAL NCS	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
		MISSING	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
		TOTAL	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], [USER EMAIL] [TIMESTAMP]

15.2Template figures



Data based on [ANALYSIS SET].
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: individual_figures.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

15.3Tables

Table 14.1.1 Baseline characteristics and demographics (Full analysis set)

		SEQUENCE 1 (N=X)	SEQUENCE 2 (N=X)	SEQUENCE 3 (N=X)	SEQUENCE 4 (N=X)	SEQUENCE 5 (N=X)	Total (N=X)
Age (years)	n/nmiss	x/x	x/x	x/x	x/x	x/x	x/x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	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)	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	x/x	x/x	x/x
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	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.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)
Height (cm)	n/nmiss	x/x	x/x	x/x	x/x	x/x	x/x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	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)	x.x (x, x)	x.x (x, x)	x.x (x,x)
Weight (kg)	n/nmiss	x/x	x/x	x/x	x/x	x/x	x/x
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	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.x)	x.xx (x.x, x.x)	x.xx (x.x, x.x)	x.xx (x.x,x.x)
Sex	Female	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
	Male	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
Ethnicity	Hispanic Or Latino	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
	Not Hispanic Or Latino	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
Race	American Indian Or Alaska Native	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
	Asian	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
	Black or African American	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
	Native Hawaiian or other Pacific Islander	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
	White	x (x.x%)	x (x.x%)	x (x.x%)	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], [USER EMAIL] [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
--- [trt x]	x
--- [trt y]	x
--- [trt z]	x
Withdrawn subjects	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
Completed subjects	x
--- [trt x]	x
--- [trt y]	x
--- [trt z]	x
Included in [pop x]	x
Included in [pop x]	x
Included in [pop x]	x
Subjects at [VISIT x]	x
Subjects at [VISIT x]	x
Subjects at [VISIT x]	x
Subjects at [VISIT x]	x

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

	SEQUENCE 1 N=X		SEQUENCE 2 N=X		Total N=X	
System organ class Preferred term	n(%)	m	n(%)	m	n(%)	m
Total	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**
SOC 1s	**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
SOC 1 PT 2	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
SOC 2	**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
SOC 2 PT 2	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]
[STUDYID] Medical history events by system organ class and preferred term, [Full analysis set], SAS program: mh_summary_by_soc_and_pt.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.1.4 Concomitant 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: mh_summary_by_soc_and_pt.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.2.1 Heaviness of smoking index (HSI) (Full analysis set)

Question		SEQUENCE 1	SEQUENCE 2	[Total]
[Question 1]	n	x	x	x
	Mean (SD)	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)
	n	x	x	x
	Mean (SD)	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)

Etc…

ND: Not defined - no evaluable observations. NA: Not available - no non-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], [USER EMAIL] [TIMESTAMP]

Table 14.2.2 Products evaluation scale (PES) (Full analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables. No result category column (there is no baseline data). Also include sub-category and total scores.

Table 14.2.3 Products evaluation scale (PES) – Wilcoxon Signed Rank Sum tests comparison of treatments (Full analysis set)

Question sub-category	Assessment timepoint	Test product	Reference product	90% CI lower bound	Estimated difference	90% CI upper bound	P-value
Question sub-category 1	[Assessment timepoint 1]	Treatment 1	Treatment 2	x.xx	x.xxxx	x.xxx	x.xxxx
		Treatment 1	Treatment 3	x.xx	x.xxxx	x.xxx	x.xxxx
		…	…	…	…	…	…

Data based on Full analysis set. ND: Not defined - no evaluable observations. NA: Not available - no non-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], [USER EMAIL] [TIMESTAMP]

The above table should include all available timepoints and all possible product comparisons. In addition to sub-category scores, total PES scores should be evaluated as well.

Table 14.2.4 Modified cigarette evaluation questionnaire (MCEQ) (Full analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables. No result category column (there is no baseline data).

Table 14.2.5 Products preference scale (PPS) (Full analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables. No result category column (there is no baseline data).

Table 14.3.1 Overview of adverse events (Full analysis set)

	ELEMENT 1 N=X		ELEMENT 2 X=X		Total N=X	
	n(%)	m	n(%)	m	n(%)	m
Any AE	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
Any AE leading to withdrawal	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
Causality						
Possibly Related	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
Unlikely Related	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
Moderate	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
Life-threatening	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

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 [ELEMENTS] are omitted from summary.
[STUDYID] Overview of adverse events, [Full analysis set], SAS program: ae_summary_tables.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

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

	ELEMENT 1 N=X		ELEMENT 2 N=X		Total N=X	
System organ class Preferred term	n(%)	m	n(%)	m	n(%)	m
SOC 1s	**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
SOC 1 PT 2	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
SOC 2	**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
SOC 2 PT 2	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 [ELEMENTS] are omitted from summary.
[STUDYID] Adverse events by system organ class and preferred term, [Full analysis set], SAS program: ae_summary_by_soc_and_pt.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.3.3 Safety laboratory measurements (Full analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

Table 14.3.4 Safety laboratory interpretation (Full analysis set)

See appendix table – 15.1.2 Descriptive statistic table – discrete variables

Table 14.3.5 Safety laboratory – shift table (Full analysis set)

See appendix table – 15.1.3 Shift table

Table 14.3.6 Vital signs measurements (Full analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

Table 14.3.7 ECG measurements (Full analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

Table 14.3.8 ECG interpretation (Full analysis set)

See appendix table – 15.1.2 Descriptive statistic table – discrete variables

Table 14.3.9 ECG interpretation – shift table (Full analysis set)

See appendix table – 15.1.3 Shift table

Table 14.3.10 Physical examinations measurements (Full analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

Table 14.4.1 Plasma concentration (Pharmacokinetic analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

Table 14.4.2 PK parameters (Pharmacokinetic analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

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

PK variable	Test formulation	Reference formulation	90% CI lower bound	Ratio of geometric LSMeans	90% CI upper bound	Unadjusted p-value	Tukey-Kramer adjusted p-value
AUCt (unit)	Treatment 1	Treatment 2	x.xxx	x.xxxx	x.xxx	x.xxxx	x.xxxx
	Treatment 1	Treatment 3	x.xxx	x.xxxx	x.xxx	x.xxxx	x.xxxx
	…	…	x.xxx	x.xxxx	x.xxx	x.xxxx	x.xxxx
Cmax (unit)	Treatment 1	Treatment 2	x.xxx	x.xxxx	x.xxx	x.xxxx	x.xxxx
	Treatment 1	Treatment 3	x.xxx	x.xxxx	x.xxx	x.xxxx	x.xxxx
	…	…	x.xxx	x.xxxx	x.xxx	x.xxxx	x.xxxx

Data based on PK analysis set. Pairwise treatment comparisons are based on a repeated meassurement mixed model. The overall significance of the model has p-value of x.xxxx. [STUDYID] Adverse events by system organ class and preferred term, [Full analysis set], SAS program: ae_summary_by_soc_and_pt.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.4.4 Cotinine sampling (Pharmacokinetic analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

Table 14.4.5 Nicotine pouch collection (Pharmacokinetic analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

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

See Table 14.2.3, but without the question sub-category column.

Table 14.4.6 Extracted flavour transfer (Pharmacokinetic analysis set)

See appendix table – 15.1.1 Descriptive statistic table – continuous variables

15.4Figures

Figure 14.2.6 Products evaluation scale (PES) sub-category and total scores over time by treatment (Full analysis set)

See appendix figure – 15.2 Spaghetti plot

Figure 14.2.7 Plasma concentrations over time by treatment (Pharmacokinetic analysis set)

See appendix figure – 15.2 Spaghetti plot

15.5Listings

Listing 16.2.1.1. Discontinued subjects (All subjects)

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)

Listing 16.2.5.1. Prior and concomitant medications (Full analysis set)

Listing 16.2.6.1. Snus/cigarette habits (Full analysis set)

Listing 16.2.7.1. HIV, hepatitis B and C (All subjects)

Listing 16.2.8.1. Other laboratory meassurements (All subjects)

Listing 16.2.9.1. Heaviness of smoking index (HSI) (Full analysis set)

Listing 16.2.9.2. Product evaluation scale (PES) (Full analysis set)

Listing 16.2.9.3. Modified cigarette evaluation questionnaire (MCEQ) (Full analysis set)

Listing 16.2.9.4. Products preference scale (PPS) (Full analysis set)

Listing 16.2.10.1. Plasma concentration (Pharmacokinetic analysis set)

Listing 16.2.10.2. PK parameters (Pharmacokinetic analysis set)

Listing 16.2.10.3. Cotinine sampling (Pharmacokinetic analysis set)

Listing 16.2.11.1. Nicotine pouch collection (Pharmacokinetic analysis set)

Listing 16.2.11.2. Extracted flavour transfer (Pharmacokinetic analysis set)

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

Listing 16.2.12.2. Adverse events, part 2 (Full analysis set)

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)

Listing 16.2.13.1. Safety laboratory (Full analysis set)

Listing 16.2.14.1. Vital signs (Full analysis set)