AN EXPLORATORY PET-STUDY OF DEPOSITION, DISPOSITION AND BRAIN UPTAKE OF [^{11}C]NICOTINE AFTER INHALATION OF 2 NICOTINE FORMULATIONS VIA THE *MY*BLUTM E-CIGARETTE IN SMOKERS

NCT# NCT04780815

Statistical analysis plan – FINAL v1.0; 14DEC2020

CLINICAL TRIAL CONSULTANTS AB

CONFIDENTIAL

Statistical analysis plan (SAP)

Sponsor:	*Nerudia Ltd.*
Study code:	*NER 03/001*
CTC project no:	*270-82-2019*
Study title:	*An exploratory PET-study of deposition, disposition and brain uptake of [^{11}C]nicotine after inhalation of 2 nicotine formulations via the myblu™ e-cigarette in smokers*
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2 VERSION HISTORY

This statistical analysis plan (SAP) for study NER 03/001 is based on the protocol dated 30JAN2020.

Table 1 SAP version history summary

SAP version	Approval Date	Changes	Rationale
0.1	05DEC2020	-	Version ready for internal review
0.2	07DEC2020		Version ready for Sponsor review
1	14DEC2020	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 NER 03/001. 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	
Part A: **1. To measure the amount of nicotine deposited in the lungs and the oral cavity during 40 minutes after administration of 11C-labelled nicotine via the *my*blu™ e-cigarette system using PET**	Part A 1.1 Dynamic PET Digital Imaging and Communications in Medicine (DICOM) images over the lungs and oral cavity 0-40 minutes after administration. 1.2 Radioactivity vs. time profiles for the lungs and oral cavity 0-40 minutes after administration
Secondary	
Part A **2.1 To describe the single-dose pharmacokinetics of 11C-labelled nicotine, given via the *my*blu™ e-cigarette system, by measuring the radioactivity in arterial blood in discrete samples up to 30 minutes following administration.** **2.2 To evaluate safety and tolerability of ^{11}C-labelled nicotine inhaled via the *my*blu™ e-cigarette system**	Part A 2.1.1 Radioactivity vs. time profiles for arterial blood at 2, 4, 6, 8, 10, 15, 20 and 30 minutes after administration of [^{11}C]nicotine inhalation. 2.2.1 Frequency, intensity and seriousness of adverse events (AEs). 2.2.2 Clinically significant changes in vital signs. 3.2.2
Tertiary/Exploratory	
Part B **3.1 To measure the amount of nicotine deposited in the brain during 30 minutes after administration of ^{11}C-labelled nicotine via the myblu™ e-cigarette system using PET.** **3.2 To describe the single-dose pharmacokinetics of 11C-labelled nicotine, given via the *my*blu™ e-cigarette system, by measuring the radioactivity in arterial blood in discrete samples up to 30 minutes following administration.** **3.3 To evaluate safety and tolerability of ^{11}C-labelled nicotine inhaled via the *my*blu™ e-cigarette system**	Part B 3.1.1 Dynamic PET DICOM images over the brain 0-30 minutes after administration. 3.2.1 Radioactivity vs. time profiles for arterial blood at 2, 4, 6, 8, 10, 15, 20 and 30 minutes after administration of [^{11}C]nicotine inhalation. 3.3.1 Frequency, intensity and seriousness of AEs. 3.3.2 Clinically significant changes in vital signs.

4.2 Clinical study design

This was a single centre, exploratory PET-study of deposition, disposition and brain uptake of [^{11}C]nicotine when given to smokers as two different formulations via the *my*blu™ ecigarette system.

The study was divided in two parts:

PART A: PET 1 and PET 2 (including 5 subjects/formulation, total 10 subjects)

PART B: PET 3 (including 2 subjects/formulation + 3 optional subjects, total 4-7 subjects).

4.3 Statistical hypotheses

Not applicable.

4.4 Number of subjects

A total of 16 subject were included in the study, 11 in part A and 5 in part B.

4.5 Randomisation

Not applicable.

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 received at least one dose of IP and who has at least one post-baseline assessment data.

5.2.2 Safety analysis set

The Safety Analysis Set will comprise all subjects who received at least one dose of the IP.

5.2.3 Per protocol analysis set

The Per Protocol Set (PPS) will consist of all subjects who have been randomised and completed the study without any major protocol deviations that are judged to compromise the analysis of the data. All protocol violations will be judged as major or minor prior to database lock.

5.2.4 Use of analysis set

The FAS population will be used for both of efficacy and safety evaluation. The PPS will be used for the efficacy evaluations and the safety analysis set will be use for safety 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, dose group, and assessment time, where applicable. Subject data listings will be sorted by treatment, subject, and timing of assessments.

5.5 Significance level

Not applicable.

5.6 Multiple comparisons/multiplicity

Not applicable.

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. No imputation of data will be performed.

5.8 Adjustment for covariates

Not applicable.

5.9 Multicenter studies

Not applicable. This is a single centre study.

5.10 Examination of subgroups

Not applicable.

5.11 Blind review

Not applicable. This is an open-label study.

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 14.

6.2 Baseline characteristics and demographics

The following baseline characteristics will be summarised by treatment:

- 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 STATISTICAL METHODOLOGY

All parameters will be presented by treatment and assessment timepoint using summary statistics. Additional statistical analyses are specified below.

8.1 Primary endpoint(s) analysis

8.1.1 Definition of endpoint(s)

See section Clinical study objectives and endpoints above.

8.1.1.1 PET endpoints (Part A)

This section refers to the primary objective #1, endpoint 1.1 and 1.2.

The PET Centre will be responsible for evaluation of PET data, and present time activity data on deposition during the dynamic scans in PET-scan 1 and 2. For the evaluation of [^{11}C]nicotine kinetics in the lung, primary bronchi, oral cavity and airways, volumes of interest (VOIs) will be delineated, and time activity data generated utilising PET-image analysis software. The VOIs will be delineated based on the anatomical information from the low dose CT-images combined with the uptake seen in the PET images. Deposition in the lungs will be measured and presented for one large VOI covering the entire lung.

Furthermore, a small VOI may be delineated to be representative for deep lung tissue, however this VOI will not include the entire deep lung tissue. Even though alveolar tissue cannot be identified in detail on the ULDCT or PET images, the highest density of alveolar tissue, combined with lowest density of bronchi and major blood vessels, will be found in the peripheral part of the lung and a small VOI will be delineated at a position representative for deep lung tissue.

8.1.2 Sensitivity analysis

Not applicable.

8.1.3 Supplementary analyses

Not applicable.

8.2 Secondary endpoint(s) analysis

8.2.1 Definition of endpoint(s)

This section refers to the secondary objective #2.1 and endpoint 2.1.1.

See section Clinical study objectives and endpoints above.

8.2.2 PET endpoints (Part A)

See section PET endpoints above.

8.2.2.1 Adverse events (part A and B)

This section refers to the secondary objective #2.2, endpoint 2.2.1,and to the exploratory objective #3.3, endpoint 3.3.1.

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 and study part and overall.

All AE data will be listed subject and include the verbatim term entered by the Investigator.

8.2.2.2 Vital signs (Part A and B)

This section refers to the secondary objective #2.2, endpoint 2.2.2, and to the exploratory objective #3.3, endpoint 3.3.2.

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

All data will be listed by subject.

8.2.3 Sensitivity analysis

Not applicable.

8.2.4 Supplementary analyses

Not applicable.

8.3 Tertiary/exploratory endpoint(s) analysis

8.3.1.1 PET endpoint (part B)

This section refers to exploratory objective #3.1 and #3.2, endpoints 3.1.1 and 3.1.2.

For PET-scan 3 acquired over the brain, the amount of nicotine distributed to the brain will be estimated. A whole brain VOI will be delineated on the T1-MR images overlaid on the brain PET-image. This part of the study is explorative and dependent on the time course of the [^{11}C]nicotine uptake to the blood and the time activity uptake for brain nicotine may be difficult to measure with a sufficient signal-to-noise ratio. The uptake data will be stored in spreadsheet format and sent to study sponsor to enable further data analysis. Furthermore, and as an exploratory part of the PET-image analysis, other regions may be delineated and analysed, if visual inspection of overlaid PET and ULDCT images shows substantial uptake in other tissues or regions.

8.3.1.2 Physical examinations (Part A and B)

Clinically significant and non-clinically significant abnormal findings will be specified and presented by subject and summarised by treatment and study part.

All data will be listed by subject.

8.3.1.3 ECG resting 12-lead (Part A and B)

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

All data will be listed by subject.

8.3.1.4 Safety laboratory analyses (Part A and B)

Clinical laboratory data will be summarised by treatment and study part.

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

All data will be listed by subject.

8.4 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.

8.5 Other analyses

Not applicable.

8.6 Interim analysis

Not applicable.

9 CHANGES FROM THE CSP

None.

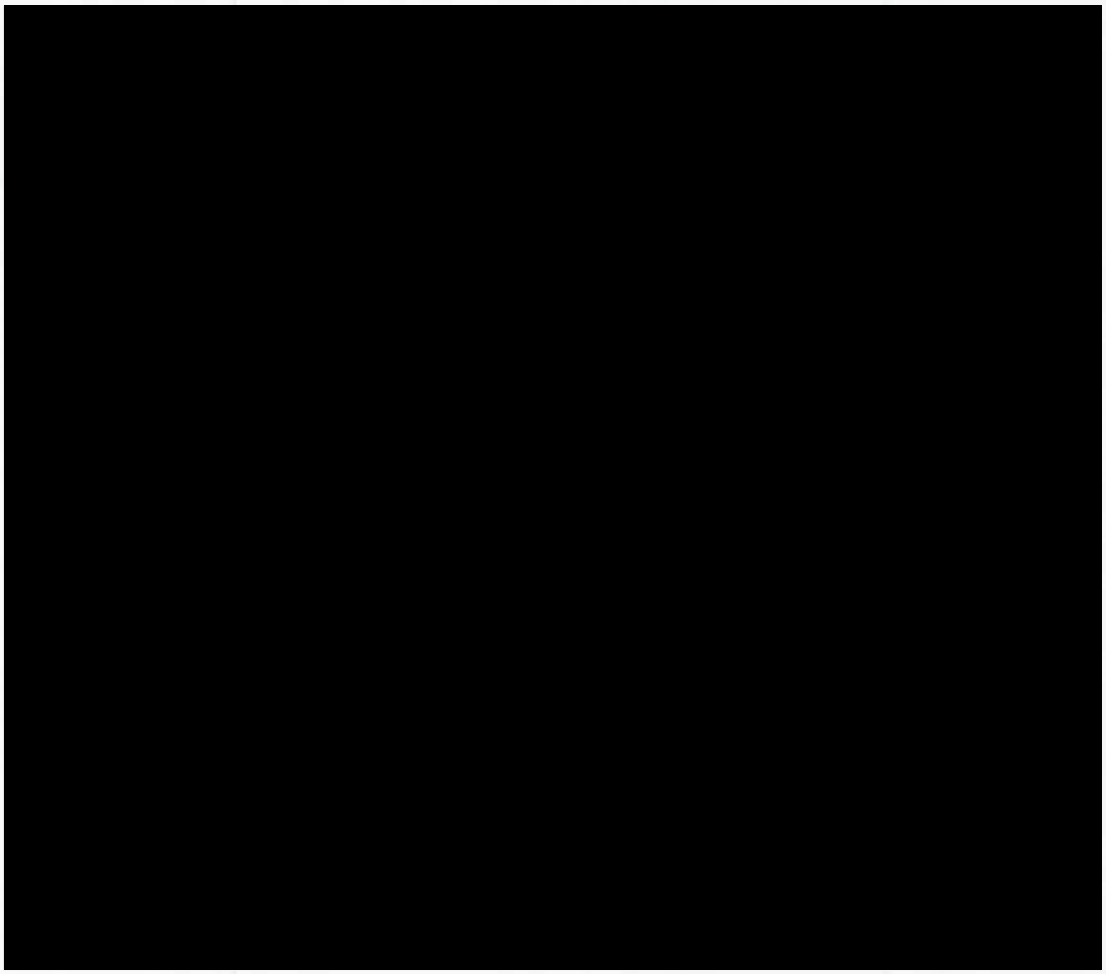
10 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
- Statistical analyses and summary tables and Listings.

11 SOFTWARE

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



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Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	12/15/2020 5:04:33 AM
Certified Delivered	Security Checked	12/15/2020 5:04:47 AM
Signing Complete	Security Checked	12/15/2020 5:05:45 AM
Completed	Security Checked	12/15/2020 5:05:45 AM

Payment Events	Status	Timestamps

13 SUPPORTIVE DOCUMENTATION

13.1 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
ECG	Electrocardiogram
FAS	Full analysis set
IP	Investigational product
MedDRA	Medical Dictionary for Regulatory Affairs
PPS	Per protocol set
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
WHO	World Health Organization

13.2 Appendix 2 – changes to protocol-planned analyses

14 STATISTICAL OUTPUT LAYOUT

14.1Template tables

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

14.1.1 Descriptive statistic table – continuous variables

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

14.1.2 Descriptive statistic table – discrete variables

Assessment	Assessment timepoint	Result	PART A FORMULATION 1	PART A FORMULATION 2	PART B FORMULATION 1	PART B FORMULATION 2	[Total]
[Parameter 1]	[Assessment timepoint 1]	[RESULT 1]	x(x.x%)/X	x(x.x%)/X	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	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	x(x.x%)/X	x(x.x%)/X
		[RESULT 2]	x(x.x%)/X	x(x.x%)/X	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]

14.2Tables

Table 14.1.1 Baseline characteristics and demographics (Full analysis set)

		PART A FORMULATION 1 (N=X)	PART A FORMULATION 2 (N=X)	PART B FORMULATION 1 (N=X)	PART B FORMULATION 2 (N=X)	Total (N=X)
Age (years)	n/nmiss	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)
	Median (Min, Max)	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
	Mean (SD)	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)
Height (cm)	n/nmiss	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)
	Median (Min, Max)	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
	Mean (SD)	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)
Sex	Female	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)

		PART A FORMULATION 1 (N=X)	PART A FORMULATION 2 (N=X)	PART B FORMULATION 1 (N=X)	PART B FORMULATION 2 (N=X)	Total (N=X)
	Male	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%)
	Not Hispanic Or Latino	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%)
	Asian	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%)
	Native Hawaiian or other Pacific Islander	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%)

```
[STUDYID] Summarised demographics data.
Data based on the [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
- Part A Formulation 1	x
- Part A Formulation 2	x
- Part B Formulation 1	x
- Part B Formulation 2	x
Withdrawn subjects	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
Completed subjects	x
- Part A Formulation 1	x
- Part A Formulation 2	x
- Part B Formulation 1	x
- Part B Formulation 2	x
Included in full analysis set	x
Included in safety analysis set	x
Included in per protocol analysis set	x
Subjects at VISIT 1	x

	Total
Subjects at VISIT 2	x
Subjects at VISIT 3	x

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

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

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

Table 14.1.4.1 Concomitant medications (Full analysis set)

	Part A Formulation 1 N=X		Part A Formulation 2 N=X		Part B Formulation 1 N=X		Part B Formulation 2 N=X		Total N=X	
ATC Name Level 4 ATC Name Level 5	n(%)	m	n(%)	m	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.x%)	x
Proton pump inhibitors	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
etc.										

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the Full analysis set
NER_03-001_14_01_04_01_FULLSET.rtf Concomitant medications, SAS program: CM_summary.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2020-12-03T19:52:49. Data extracted at: 2020-12-02T09:09:59

Table 14.1.4.2 Prior medications (Full analysis set)

See template for Table 14.1.4.1 Concomitant medications (Full analysis set) above.

Table 14.1.6 Exposure to 11C-Nicotine by dose group (Full analysis set)

See template for Descriptive statistic table – continuous variables above.

Table 14.3.1.1 Overview of adverse events (Full analysis set)

	PART A FORMULATION 1 N=X		PART A FORMULATION 2 N=X		PART B FORMULATION 1 N=X		PART B FORMULATION 2 N=X		Total N=X	
	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
Any SAE	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
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
Causality										
Possibly Related	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
Unlikely Related	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
Moderate	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
Life-threatening	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

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

Table 14.3.1.2 Adverse events by system organ class and preferred term (Full analysis set)

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

Table 14.3.2 Physical Examination (Full analysis set)

See template for Descriptive statistic table – discrete variables above.

Table 14.3.3 Vital signs measurements (Full analysis set)

See appendix table – 14.1.1 Descriptive statistic table – continuous variables

Table 14.3.4.1 ECG interpretation (Full analysis set)

See appendix table – 14.1.2 Descriptive statistic table – discrete variables

Table 14.3.4.2 ECG measurements (Full analysis set)

See appendix table – 14.1.1 Descriptive statistic table – continuous variables

Table 14.3.5.1 Safety laboratory Measurement: Clinical Chemistry (Full analysis set)

See appendix table – 14.1.1 Descriptive statistic table – continuous variables

Table 14.3.5.2 Safety laboratory Measurement: Haematology (Full analysis set)

See appendix table – 14.1.1 Descriptive statistic table – continuous variables

14.3 Listings

Listing 16.2.1.1. Discontinued subjects (All subjects)

Listing 16.2.2.1 Protocol deviations (All subjects)

Listing 16.2.3.1 Subject excluded from PPS (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 history (Full analysis set)

Listing 16.2.4.3 Baseline events (Full analysis set)

Listing 16.2.5.1 Prior and concomitant medications (Full analysis set)

Listing 16.2.5.2 Exposure to 11C-Nicotine (Full analysis set)

Listing 16.2.6.1 Adverse events, part 1 (Full analysis set)

Listing 16.2.6.2 Adverse events, part 2 (Full analysis set)

Listing 16.2.7.1. Serious adverse events, part 1 (Full analysis set)

Listing 16.2.7.2 Serious adverse events, part 2 (Full analysis set)

Listing 16.2.7.3 Serious adverse events, seriousness criteria (Full analysis set)

Listing 16.2.8.1 Vital signs - height, weight and BMI (Full analysis set)

Listing 16.2.8.2 Vital signs (Full analysis set)

Listing 16.2.8.3 Vital signs - abnormal findings (Full analysis set)

Listing 16.2.9 ECG (Full analysis set)

Listing 16.2.10.1 Safety laboratory - clinical chemistry (Full analysis set)

Listing 16.2.10.2 Safety laboratory - haematology (Full analysis set)

Listing 16.2.10.3 Safety laboratory - other measurements (Full analysis set)

Listing 16.2.10.4 Safety laboratory - abnormal findings (Full analysis set)

Listing 16.2.11 Physical examinations (Full analysis set)

Listing 16.2.12 Disposition (All subjects)

Listing 16.2.13 Subject visits (All subjects)

Listing 16.2.14 Subject elements (All subjects)