A Randomised, Cross-Over, Nicotine Pharmacokinetic and Pharmacodynamic Study of Heated Tobacco Products Compared to Combustible Cigarettes

NCT05459857

Study Protocol - FINAL (v3.0): 29 Oct 2021

A Randomised, Cross-Over, Nicotine Pharmacokinetic and Pharmacodynamic Study of Heated Tobacco Products Compared to Combustible Cigarettes

Sponsor Project No.: NER01/0004

Celerion Project No.: CA35183

Final Protocol (v1.0): 09-Sep-2021
Protocol Amendment 1 (v2.0): 19-Oct-2021
Protocol Amendment 2 (v3.0): 29-Oct-2021

PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
29-Oct-2021 Angela Choi	Final Protocol, Amendment 2, version 3.0 The protocol is amended to address the following changes: 1) At the request of the Research Ethics Committee (REC reference 21/NI/0144), a statement is added in the protocol to indicate that only subjects who are currently smoking or have customarily smoked in the past menthol combustible cigarettes will be eligible to enroll in the study. This will avoid enrolling subjects who will be experiencing menthol cigarettes or nicotine products for the first time while in the study. A new paragraph was added in Section 1.3 (Study Purpose) and it states the following: "The risk to subjects participating in this study is minimized by compliance with the eligibility criteria (Section 4.1 and Section 4.2) and study procedures, adherence to the protocol, as well as close clinical monitoring (i.e., AEs, ECG, vital sign measurements, clinical laboratory tests, and physical examination). The risk that subjects develop clinical symptoms is also low as they will be administered products similar to those that they already use. In addition, menthol-flavoured HTPs will only be given to subjects who are currently smoking menthol combustible cigarettes and/or have customarily smoked them in the past and will not be given to smokers who have had no previous experience of cigarettes or nicotine products containing menthol flavouring." In addition, an exclusion criterion was added in Section 4.2 (Exclusion Criteria) to ensure that only subjects who meet the requirement above may be enrolled. The newly added exclusion criterion states the following: "Has never smoked any menthol cigarettes or cannot tolerate smoking them." 2) Due to a change in the Sponsor representative, the Sponsor Signature Page was revised with the new contact information.

DATE/NAME	DESCRIPTION
	3) For the End-of-study (EOS) serum chemistry sample collection, it was clarified that an 8-hour fast is not required. Thus, footnote "e" in the Study Events Flow Chart and footnote "1" in Section 6.4.4.5 (Clinical Laboratory) were revised (with new text in bold font): "Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken. **For the samples collected at EOS, an 8-hour fast is not required.**" 4) In Section 4.3.1 (Food and Beverages), the last bullet was removed as it is inconsistent with the third bullet, which correctly states that food and beverages containing grapefruit will be restricted for 14 days prior to Check-in and throughout the study. Thus, the section was updated as follows (with deleted text in strikethrough font): "Foods and beverages containing the following substances should not be consumed as indicated below: • Alcohol should be avoided for 48 hours prior to Screening and Check-in to avoid exclusion for a positive alcohol test and throughout the study. • Foods containing poppy seeds should be avoided for 48 hours prior to Screening and Check-in to avoid exclusion for a positive urine drug test and throughout the study. • Food and beverages containing grapefruit for 14 days prior to Check-in and throughout the study. • Caffeinated beverages will be restricted throughout confinement. • ~~No food or beverages containing grapefruit for 14 days prior to Check-in or during confinement.~~" 5) In Section 6.4.5.3 (Serious Adverse Events), the first paragraph was removed as it is inconsistent with the second paragraph, which correctly defines a serious adverse event. Thus, the section was updated as follows (with deleted text in strikethrough font and new text in bold font):

DATE/NAME	DESCRIPTION
	"~~A serious adverse event (SAE) is any AE that in the view of either the Investigator (or designee) or Sponsor, results in any of the following outcomes: death, a life threatening AE, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered serious when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.~~ A **serious adverse event (**SAE**)** is any untoward medical occurrence that ~~at any dose~~ (WHO and ICH definitions): • results in death • is life threatening • results in permanently disabling or incapacitating • requires inpatient hospitalisation • prolongs inpatient hospitalisation • is a congenital anomaly / birth defect • may jeopardise the subject or may require intervention to prevent one or more of the other outcomes listed above. All SAEs, whether or not considered study-related, must be reported by telephone and by fax or e mail to the Sponsor within 24 hours of the CRU's learning of the SAE or, at the latest, on the following workday. The Sponsor's representative to contact about this study is provided in the list of study contacts. The Investigator must also inform the EC, in compliance with GCP reporting guidelines, and the site monitor of any SAE."

DATE/NAME	DESCRIPTION
19-Oct-2021 Angela Choi	Final Protocol, Amendment 1, version 2.0 The protocol is amended to address the following changes: 1) Due to a change in the Sponsor representative, the Sponsor Signature Page was updated with the new contact information. 2) An inclusion criterion was added for male subjects requiring them to use an appropriate method of contraception from Check-in until at least 90 days after the final product use. Another criterion was added to restrict male subjects from donating sperm during the same time frame. The duration of contraception use for female subjects was also extended to at least 28 days after the final product use. Thus, Section 4.1 (Inclusion Criteria) was updated accordingly. 3) Use of the SPA-M topography device during the 2-hour topography session was clarified to state that the device will be stopped and restarted with the use of each new stick or cigarette. Thus, in the Synopsis (Study Design), the Study Events Flow Chart (footnote s), Section 2.2 (Study Endpoints - Puff Topography), Section 3.1 (Design and Procedures), and Section 6.4.3 (Puff Topography), the following changes were made (with deleted text in strikethrough font and new text in bold font): " […] ~~The SPA-M topography device will be reset at 60 minutes in order to collect 2 hours of data.~~ **The topography session will span a 2-hour period and the SPA-M topography device will be stopped and restarted with each new stick or cigarette during that time.** […]" 4) Miscellaneous typographical errors and inconsistencies that do not impact the conduct of the study were also addressed.
09-Sep-2021 Brian Nordskog	Final Protocol, version 1.0

SPONSOR SIGNATURE PAGE

A Randomised, Cross-Over, Nicotine Pharmacokinetic and Pharmacodynamic Study of Heated Tobacco Products Compared to Combustible Cigarettes

Sponsor Representative:

[redacted]
Senior Clinical Research Manager
Imperial Brands PLC
121 Winterstoke Road
Bristol
BS3 2LL
United Kingdom
[redacted]

[redacted]
Signature

_____
Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

A Randomised, Cross-Over, Nicotine Pharmacokinetic and Pharmacodynamic Study of Heated Tobacco Products Compared to Combustible Cigarettes

Clinical Site and Principal Investigator:

Celerion

22-24 Lisburn Road
Belfast, Northern Ireland, BT9 6AD
Tel.: +44 (0) 28 90 554040

[redacted]
S

29 Oct 2021
Date

[redacted]
Printed Name

STUDY CONTACTS

Medical Monitor	To be provided separately
Clinical Laboratory	Celerion 22-24 Lisburn Road Belfast, Northern Ireland BT9 6AD Tel.: +44 (0) 28 90 554040 Fax: +44 (0) 28 90 554141
Bioanalytical Laboratory	Celerion 621 Rose Street Lincoln, Nebraska 68502, USA Contact: Kirk Newland Tel.: +1 402 437-4719

SYNOPSIS

Study Objectives	Primary: 1. To evaluate and compare the maximum plasma concentration (C_{max}) and the area under the concentration-time curve at the last time point measured (AUC_t) of nicotine after the use of each Heated Tobacco product or cigarette comparator. Secondary: 1. To evaluate other pharmacokinetic (PK) parameters of nicotine after the use of each Heated Tobacco product or cigarette comparator. 2. To evaluate the reduction in smoking urges observed after the use of each Heated Tobacco product or cigarette comparator. 3. To evaluate product perception and preference by use of subjective assessments. 4. To evaluate the tolerability and safety of each of the products used. 5. To investigate usage behaviour for each product using measurements of topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter puff interval) for each product.
Study Design	This will be a randomised, cross-over, open-label, confinement study conducted in 24 adult male or female smokers of combustible cigarettes (CCs). The study will investigate combustible and heated tobacco (HT) products in a cross-over design, incorporating PK evaluation, subjective questionnaire assessments, usage behaviour, puff topography, as well as safety evaluation. Subjects will perform a screening visit and 1 study visit, including a 5-day confinement period and finally a follow-up telephone call approximately 7 days after the final product use. *Visit 1 (Screening)* Screening procedures will be performed within 27 days prior to study procedures on Day -1 and will include an eligibility check, review of health status and assessment of nicotine consumption habits. Medical and tobacco-use histories and demographic data will be collected. Other screening procedures include a physical examination (including oral cavity and oropharynx), vital signs, electrocardiogram (ECG), body mass index (BMI), clinical laboratory tests (hematology, serum chemistry, urinalysis), serology, urine/saliva drug, urine/breath alcohol, cotinine screen, exhaled carbon monoxide (CO), and pregnancy and follicle-stimulating hormone (FSH) tests (for females as appropriate). If required, subjects will be offered smoking cessation advice and contact information for a smoking cessation support service.

	Visit 2 (In-clinic period, Day -1 to Day 4) At Visit 2, subjects who successfully complete the screening procedures and meet all the inclusion criteria and none of the exclusion criteria will be eligible to check in to the clinical research unit (CRU) on Day -1 and will remain at the clinic until Day 4 for daily study product use, PK sampling, subjective questionnaire assessments, puff topography (as applicable), and safety assessments. On Day -1, following eligibility confirmation, subjects will undertake a familiarisation session of the study products and questionnaires. The clinical team will explain how the HT products will be used. Subjects will have the opportunity to see the products/devices and packaging and will participate in a Product Trial where they will consume one HT stick (flavour chosen by subject). All products/devices used in the trial session will not be used in the clinical study but will be retained as demonstration samples for accountability purposes. An explanation of how the questionnaires will be administered to the subjects will be given. After the familiarisation session and completion of check-in procedures, subjects will be allowed to smoke their own cigarettes *ad libitum* but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of the morning controlled product use session on Day 1. In the morning of Day 1, after pre-use assessments and confirmation of eligibility, the subjects will be randomised to 1 of 4 product sequences and then provided a single product of the study product in the sequence to which they have been randomised. On Days 1 through 4, subjects will use the assigned study product under controlled conditions (i.e., completely use a single unit of the assigned study product, with puffs taken at 30-second intervals and puffs 3 seconds in duration). PK samples will be collected within 5 minutes pre-study product use and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 120, and 240 minutes following the start of study product use. Questionnaires will be administered to the subject at defined intervals throughout the day. Safety will be monitored throughout the day. On Days 1 through 4, following the 4-hour PK blood collection, subjects will start a 4-hour *ad libitum* product use session (no limits on cigarette or HT consumption) with the same study product used during the morning controlled use session. On Days 3 and 4, puff topography will be performed during the last 2 hours of the 4-hour *ad libitum* product use session. The Sodim Smoking Puff Analyzer Mobile (SPA-M) topography device will collect data (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter-puff interval) for 2 hours. The topography session will span a 2-hour period and the SPA-M topography device

	will be stopped and restarted with each new stick or cigarette during that time. The *ad libitum* product use session on Days 1 through 4 will start at approximately the same time each day, with lunch served at the start of the *ad libitum* product use session, at approximately the same time each day. After completion of the *ad libitum* use session, subjects will be allowed to smoke their own cigarettes (*ad libitum*) but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of the morning controlled product use scheduled on the following day. A new/unused device will be provided to the subjects on each day of HT product use (i.e., the same device will be used for the morning controlled product use and *ad libitum* product use sessions on the same day). On Day 4, following completion of study assessments, subjects will be allowed to use their own cigarettes and will leave the CRU after completing all final check out requirements. *Visit 3 (Follow-up phone call)* A follow-up telephone call (Visit 3) will be made by the CRU in an attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 7 days after the final product use to determine if any adverse event (AE) has occurred since the last study visit.
Study Population	The study population will be comprised of healthy, adult male and female smokers, who are between 21 and 65 years of age (inclusive). Each subject must self-report smoking an average of 10 or more manufactured combustible cigarettes per day (CPD) for at least 12 months prior to Screening. Twenty-four (24) subjects will be enrolled.
Duration of Study Conduct	Subjects will participate in the study for up to 35 days, including an up to 28-day screening period.
Study Products and Administration	Details of the study products are presented as follows: **Product Designation** — **Study Product Name** A — [redacted] HT device with [redacted] stick B — [redacted] HT device with [redacted] stick C — [redacted] HT device with [redacted] stick

	D Subject's own brand combustible cigarette (OBCC)
Endpoints, Key Assessments, and Summarisation	Pharmacokinetics: For each morning product use session on Days 1 through 4, plasma nicotine PK parameters (AUC_{inf}, AUC_{0-90}, AUC_{0-240}, AUC_t, C_{max}, C_{last}, T_{max}, $T_{1/2}$) will be computed from the individual plasma concentrations for each study product. Baseline adjustments will be performed. Nicotine concentrations and PK parameters will be listed by subject and summarised using descriptive statistics. Subjective Effects: *Intent to Use (ITU)* Descriptive statistics of the visual analog scale (VAS) will be provided by study product and product use session. Individual responses will be listed by subject. *Urge to Smoke* Responses and derived parameters (E_{max}, TE_{max}, $AUEC_{0-240}$) will be listed by subject and summarised using descriptive statistics. *Product Evaluation Scale* Responses will be considered as a 7-point scale, and will be presented as factors outlined in Section 7.3.2.2. Descriptive statistics of the subscales will be provided by study product and product use session. Individual responses will be listed by subject. Puff Topography: Topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average flow rate, inter-puff interval) will be listed by subject and summarised using descriptive statistics. Product Use Behaviour: All product use data, including the number of HT sticks used and the number of CCs smoked (Days -1 through Day 4) will be summarised using descriptive statistics. Incidence of device malfunction(s) will also be tabulated. Safety: Safety will be monitored in-study through physical examination (symptom-driven), vital signs measurements, ECGs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis).

	Adverse Events (AEs) spontaneously reported by the subjects or observed by the Investigator or other study personnel will be monitored from Screening until the follow-up. AEs will be tabulated and summary statistics for vital signs and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

STUDY EVENTS FLOW CHART

Table 1. Study Events

EVENTS/ASSESSMENTS																		
Days →	**Scr [a]**	**-1**	**1 Through 4**														**EOS**	**FU**
Minutes →			**0**	**2**	**4**	**6**	**8**	**10**	**15**	**30**	**45**	**60**	**120**	**240**	**360**	**480**		
Administrative Procedures																		
Informed Consent	X																	
Check-In [b]		X																
Review of I/E Criteria	X	X																
Medical History and Demographics	X	X [c]																
Tobacco/Nicotine Product Use History	X																	
Usual Brand Documentation	X	X [c]																
Safety Evaluations																		
Full Physical Examination [d]	X																	
Body Weight, Height, and BMI	X																	
Chem [e], Hematology, Urinalysis	X	X															X [f]	
HIV, HBsAg, and HCV Serology	X																	
Serum Pregnancy Test (Females)	X	X																
Serum FSH (Postmenopausal Females Only)	X																	
Urine Drug and Urine/Breath Alcohol Screen	X	X																
12-lead ECG	X	X															X [f]	
Vital Signs (RR and T)	X	X	X [g]															
Vital Signs (BP and HR)	X	X	X [g]														X [f]	
Exhaled CO	X	X																
Urine Cotinine Screen	X	X																
Review of Concomitant Medications	X	X																
Review of AEs	X	X																
Product Use/Study Assessments																		
Randomisation			X [h]															
IP Use		X [i]	X [j]											X [k]				
Product Use Behaviour		X [l]	X [m]											X [l]				

EVENTS/ASSESSMENTS																	
Days →	**Scr [a]**	**-1**	**1 Through 4**													**EOS**	**FU**
Minutes →			**0**	**2**	**4**	**6**	**8**	**10**	**15**	**30**	**45**	**60**	**120**	**240**	**360**	**480**	
Blood Collection for Nicotine PK			X [n]	X	X	X	X	X	X	X	X	X	X	X			
Intent to Use Questionnaire		X [o]												X			
Urge to Smoke Questionnaire		X [o]	X [p]		X [q]		X [q]		X [q]		X [q]	X [q]	X [q]	X [q]			
Product Evaluation Scale Questionnaire		X [o]												X			
Product Trial		X [r]															
Puff Topography															X [s]		
Other Procedures																	
Tobacco Cessation Information	X															X [f]	
Questionnaire Training		X															
Visit	X																
Confinement in the CRU [b]		X															
Phone Call [t]																	X

a: Within 27 days prior to study procedures on Day -1.

b: Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU, and will remain confined until completion of study procedures on Day 4. Subjects may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per CRU requirements. Check-in procedures include: identification, luggage check, questionnaire on study prohibitions, and subject orientation.

c: To be updated at Check-in as necessary.

d: Symptom-driven physical examinations may be performed at other times, at the Investigator or designee's discretion.

e: Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken. For the samples collected at EOS, an 8-hour fast is not required.

f: To be performed prior to discharge or prior to early termination from the study.

g: To be performed prior to the start of each morning product use session.

h: On Day 1, subjects will be randomised to 1 of 4 sequences.

i: Subjects will participate in a Product Trial where they will consume one HT stick (flavour chosen by subject).

j: Subjects will use the assigned study product under controlled conditions (i.e., completely use a single unit of the assigned study product, with puffs taken at 30-second intervals and puffs 3 seconds in duration), with Hour 0 as the start time of product use.

k: On Days 1 through 4, subjects will use their randomised product (same product as the morning session) *ad libitum* for 4 hours starting after the 4-hour PK blood draw.

l: The number of cigarettes smoked, as appropriate, will be documented from Check-in until beginning of smoking abstinence (Day -1, until at least 12 hours prior to the start of morning controlled product use on Day 1; Days 1 through 3, 8 hours post morning controlled use session IP start until at least 12 hours prior to the start of morning controlled product use scheduled on the following day). The number of cigarettes smoked and the number of HT sticks used will be documented during each 4-hour *ad libitum* product use session (Days 1 through 4).

m: The number of inhalations and reasons for missed puffs will be documented.

n: To be performed approximately 5 minutes prior to the start of the product use session.

o: Subjects will be familiarised with the questionnaires. An explanation of how the questionnaires will be administered to the subjects will be given. Responses will not be recorded.

p: To be performed approximately 10 minutes prior to the start of the product use session.

q: To be performed approximately 30 seconds prior the scheduled PK blood draws.

r: On Day -1, subjects will participate in a Product Trial period where subjects will consume one HT stick (flavour chosen by subject).

s: On Days 3 and 4 only, puff topography measurements will be performed for 2 hours during the last 2 hours of the 4-hour *ad libitum* product use session. The topography session will span a 2-hour period and the SPA-M topography device will be stopped and restarted with each new stick or cigarette during that time.

t: The CRU will attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 7 days after the final product use to determine if any AE has occurred since the last study visit.

Abbreviations: AE = Adverse event, BMI = Body mass index, BP = Blood pressure, Chem = Serum chemistry, CO = Carbon monoxide, CRU = Clinical research unit, ECG = Electrocardiogram, EOS = End-of-study, FSH = Follicle-stimulating hormone, FU = Follow-up, HBsAg = Hepatitis B surface antigen, HCV = Hepatitis C virus, HIV = Human immunodeficiency virus, HR = Heart rate, HT = Heated tobacco, I/E = Inclusion/exclusion, IP = Investigational product, PK = Pharmacokinetic(s), RR = Respiratory rate, Scr = Screening, SPA-M = Sodim Smoking Puff Analyzer Mobile, T = Temperature, OBCC = Own brand combustible cigarette.

ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC_{0-90}	Area under the nicotine concentration-time curve from time 0 to 90 minutes
AUC_{0-240}	Area under the nicotine concentration-time curve from time 0 to 240 minutes
AUC_{inf}	Area under the nicotine concentration-time curve from time 0 to infinity
AUC_t	The area under the concentration time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
$AUEC_{0-240}$	Area under the change from baseline score versus time curve from time 0 to 240 minutes
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
°C	Degree Celsius
CC	Combustible cigarette
CFR	Code of Federal Regulations
CI	Confidence interval
C_{last}	Plasma concentration at last time point
C_{max}	Maximum measured plasma concentration
CO	Carbon monoxide
CPD	Cigarette(s) per day
CRF	Case report form
CRU	Clinical research unit
EC	Ethics committee
ECG	Electrocardiogram
E_{max}	Maximum change from baseline score
EOS	End-of-Study
°F	Degree Fahrenheit

FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HR	Heart rate
HT	Heated tobacco
HTP	Heated tobacco product
ICF	Informed consent form
ICH	International Council for Harmonisation
ITU	Intent to Use
K_2-EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
ln	Natural logarithm
m^2	Meters squared
mAh	Milliampere hour
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
ng	Nanogram
NGP	Next generation product(s)
OBCC	Own brand combustible cigarette
PK	Pharmacokinetic(s)
ppm	Parts per million
PPS	Product Preference Scale
QA	Quality Assurance
RCF	Relative centrifugal force
REC	Research Ethics Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure
SPA-M	Sodim Smoking Puff Analyzer Mobile

SUSAR	Suspected unexpected serious adverse reaction
TE_{max}	Time of the Emax
T_{max}	Time to reach the maximum measured plasma concentration
US or USA	United States of America
USB	Universal serial bus
V	Volt
VAS	Visual analog scale

DEFINITION OF TERMS

Check-in	Check-in is defined as the time when the subject arrives at the CRU to start confinement
Concomitant medication	Concomitant medication refers to all medication taken during the study conduct period from 28 days prior to Screening through End-of-Study. Medications started prior to Screening but which the subject continues to take during the study, are considered to be concomitant medications
Randomisation	Assignment of subjects to a specific sequence
Screening	Screening is defined as the 27-day period prior to study procedures on Day -1, during which subjects will undergo screening assessments
Screening failure	Any subject who does not meet the entry criteria at Screening or Day -1 for study enrollment will be considered a Screening failure
Sponsor	'Sponsor' refers to Imperial Brands PLC
Subject	'Subject' refers to an individual who participates in the clinical study

TABLE OF CONTENTS

List of Appendices

List of Tables

List of Figures

1. INTRODUCTION AND BACKGROUND

1.1 Background

Smoking is a cause of serious diseases in smokers, including lung cancer, heart disease and emphysema. Despite the well characterised health risks, smoking rates in adult populations worldwide remain at 15% to 25%. In addition to methods of helping people quit, investigations are ongoing into the health benefits of reducing exposure to toxicants in people who continue to use tobacco and nicotine, in the absence of combustion. This is being done through the development of new non-combustible tobacco and nicotine products, often referred to as next generation products (NGP).

Tobacco-related health risks are assumed to be due to repeated and sustained exposure to a range of smoke toxicants at high levels. Smoke from conventional cigarettes (CC) is a complex and dynamic mixture of more than 7000 chemical constituents, in both its particulate and vapour phases. Some of these chemicals have been identified as potential contributors to the harmful effects of cigarette smoke and can be evaluated by measuring the levels of these chemicals themselves, or their metabolites, in urine.

Nicotine is an addictive chemical present in combustible cigarette smoke. Nicotine is rapidly absorbed into the bloodstream during cigarette smoking, from where it is rapidly distributed causing both systemic and central effects. In the central nervous system, nicotine acts at neuronal nicotinic receptors and this interaction may underpin its effects on mood and relaxation. The pharmacokinetic (PK) profile of nicotine during cigarette smoking is a rapid rise and fall in plasma nicotine concentrations. Correspondingly, the delivery of nicotine to the brain, and the consequent pleasurable effects experienced by the smoker, are also rapid.

Imperial Brands PLC aim to increasingly transition adult smokers, who would otherwise continue to smoke, to NGPs that are potentially less harmful than CC. Heated tobacco (HT) and electronic cigarettes (E- cigarettes) are two platforms that are being increasingly recognised by public health bodies and regulators as having the potential to reduce the risk of continued smoking. HT products also offer greater optionality in parts of the world where vaping is not permitted or where smokers prefer HT. Imperial Brands have therefore added the Pulze heated tobacco product (HTP) device and iD stick HT consumables to a growing repertoire of NGP.

1.2 Pulze HT Previous Clinical Experience

No clinical studies have been conducted for the Pulze HT products. Pulze was commercially available following a city pilot launch in Fukuoka, Japan, in May 2019.

1.3 Study Purpose

This study is being conducted to evaluate the overall performance of Imperial Brands' Pulze HT device and three flavoured iD HT consumable (sticks) and compare to CC. It will provide data on nicotine PK, product perception and preference, product usage as measured by topography and tolerability and safety of each of the products compared to OBCC. Along with other pre-clinical in vitro studies, clinical and behavioural and population studies, the

results of this study are intended to contribute to a body of evidence to assess the harm reduction potential of Pulze HT and will support regulatory submissions as required. The endpoints to be assessed are based on Section 910 of the Federal Food, Drug, and Cosmetic Act - Application for Review of Certain Tobacco Products (FDA 2019), and the data may also be included in future premarket tobacco application submissions to the Center for Tobacco Products.

The risk to subjects participating in this study is minimized by compliance with the eligibility criteria (Section 4.1 and Section 4.2) and study procedures, adherence to the protocol, as well as close clinical monitoring (i.e., AEs, ECG, vital sign measurements, clinical laboratory tests, and physical examination). The risk that subjects develop clinical symptoms is also low as they will be administered products similar to those that they already use. In addition, menthol-flavoured HTPs will only be given to subjects who are currently smoking menthol combustible cigarettes and/or have customarily smoked them in the past and will not be given to smokers who have had no previous experience of cigarettes or nicotine products containing menthol flavouring.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

Primary

1. To evaluate and compare the C_{max} and AUC_t of nicotine after the use of each Heated Tobacco product or cigarette comparator.

Secondary

1. To evaluate other PK parameters of nicotine after the use of each Heated Tobacco product or cigarette comparator.

2. To evaluate the reduction in smoking urges observed after the use of each Heated Tobacco product or cigarette comparator.

3. To evaluate product perception and preference by use of subjective assessments.

4. To evaluate the tolerability and safety of each of the products used.

5. To investigate usage behaviour for each product using measurements of topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter puff interval) for each product.

2.2 Study Endpoints

Pharmacokinetics:

For each morning product use session on Days 1 through 4, plasma nicotine PK parameters (AUC_{inf}, AUC_{0-90}, AUC_{0-240}, AUC_t, C_{max}, C_{last}, T_{max}, $T_{1/2}$) will be computed from the individual

plasma concentrations for each study product. Baseline adjustments will be performed.

Nicotine concentrations and PK parameters will be listed by subject and summarised using descriptive statistics.

Subjective Effects:

Intent to Use (ITU)

Descriptive statistics of the visual analog scale (VAS) will be provided by study product and product use session. Individual responses will be listed by subject.

Urge to Smoke

Responses and derived parameters (E_{max}, TE_{max}, $AUEC_{0-240}$) will be listed by subject and summarised using descriptive statistics.

Product Evaluation Scale

Responses will be considered as a 7-point scale, and will be presented as factors outlined in Section 7.3.2.2.

Descriptive statistics of the subscales will be provided by study product and product use session. Individual responses will be listed.

Puff Topography:

Puff topopgraphy will be assessed using a SPA-M topography device. The topography session will span a 2-hour period and the SPA-M topography device will be stopped and restarted with each new stick or cigarette during that time. Topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average flow rate, inter-puff interval) will be listed by subject and summarised using descriptive statistics.

Product Use Behaviour:

All product use data, including the number HT sticks used and the number of CCs smoked (Days -1 through Day 4), will be summarised using descriptive statistics.

Incidence of device malfunction(s) will also be tabulated.

Safety:

Safety will be monitored in-study through physical examination (symptom-driven), vital signs measurements, ECGs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis).

AEs spontaneously reported by the subjects or observed by the Investigator or other study personnel will be monitored from Screening until the follow-up.

AEs will be tabulated and summary statistics for vital signs and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

3. SUMMARY OF STUDY DESIGN

3.1 Design and Procedures

This will be a randomised, cross-over, open-label, confinement study conducted in 24 adult male or female smokers of CCs. The study will investigate combustible and HT products in a cross-over design, incorporating PK evaluation, subjective questionnaire assessments, usage behaviour, puff topography, as well as safety evaluation.

During the study, subjects will perform a screening visit and 1 study visit, including a 5-day confinement period and finally a follow-up telephone call approximately 7 days after the final product use.

Visit 1 (Screening)

Screening procedures will be performed within 27 days prior to study procedures on Day -1 and will include an eligibility check, review of health status and assessment of nicotine consumption habits. Medical and tobacco-use histories and demographic data will be collected. Other screening procedures include a physical examination (including oral cavity and oropharynx), vital signs, ECG, BMI, clinical laboratory tests (hematology, serum chemistry, and urinalysis), serology, urine/saliva drug, urine/breath alcohol, cotinine screen, exhaled CO, and pregnancy and FSH tests (for females as appropriate). If required, subjects will be offered smoking cessation advice and contact information for a smoking cessation support service.

Visit 2 (In-clinic period, Day -1 to Day 4)

At Visit 2, subjects who successfully complete the screening procedures and meet all the inclusion criteria and none of the exclusion criteria will be eligible to check in to the CRU on Day -1 and will remain at the clinic until Day 4 for daily study product use, PK sampling, subjective questionnaire assessments, puff topography (as applicable), and safety assessments.

On Day -1, following eligibility confirmation, subjects will undertake a familiarisation session of the study products and questionnaires. The clinical team will explain how the HT products will be used. Subjects will have the opportunity to see the products/devices and packaging and will participate in a Product Trial where they will consume one HT stick (flavour chosen by subject). All products/devices used in the trial session will not be used in the clinical study but will be retained as demonstration samples for accountability purposes. An explanation of how the questionnaires will be administered to the subjects will be given. After the familiarisation session and completion of check-in procedures, subjects will be allowed to smoke their own cigarettes *ad libitum* but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of the morning controlled product use session on Day 1.

In the morning of Day 1, after pre-use assessments and confirmation of eligibility, the subjects will be randomised to 1 of 4 product sequences and then provided a single product of the study product in the sequence to which they have been randomised. On Days 1 through 4, subjects will use the assigned study product under controlled conditions (i.e., completely use a single unit of the assigned study product, with puffs taken at 30-second intervals and puffs 3 seconds in duration). PK samples will be collected within 5 minutes pre-study product use and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 120, and 240 minutes following the start of study product use. Questionnaires will be administered to the subject at defined intervals throughout the day. Safety will be monitored throughout the day.

On Days 1 through 4, following the 4-hour PK blood collection, subjects will start a 4-hour *ad libitum* product use session (no limits on cigarette or HT consumption) with the same study product used during the morning controlled use session.

On Days 3 and 4, puff topography will be performed during the last 2 hours of the 4-hour *ad libitum* product use session. The SPA-M topography device will collect data for 2 hours. The topography session will span a 2-hour period and the SPA-M topography device will be stopped and restarted with each new stick or cigarette during that time.

The *ad libitum* product use session on Days 1 through 4 will start at approximately the same time each day, with lunch served at the start of the *ad libitum* product use session, at approximately the same time each day. After completion of the *ad libitum* use session, subjects will be allowed to smoke their own cigarettes (*ad libitum*) until at least 12 hours prior to the start of the morning controlled product use session scheduled on the following day.

A new/unused device will be provided to the subjects on each day of HT product use (i.e., the same device will be used for the morning controlled product use and *ad libitum* product use sessions on the same day). A new HT stick will be provided at the start of the morning controlled product use session. During the *ad libitum* product use session, subjects will have access to the assigned HT sticks for *ad libitum* use, but a new HT stick will be provided at the start of puff topography.

On Day 4, following completion of study assessments, subjects will be allowed to use their own cigarettes and will leave the CRU after completing all final check out requirements.

Visit 3 (Follow-up phone call)

A follow-up telephone call (Visit 3) will be made by the CRU in an attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 7 days after the final product use to determine if any AE has occurred since the last study visit.

Subjects will not be forced to use any tobacco/nicotine products at any time during the study.

The overall study design is depicted in Figure 1.

Safety will be monitored through physical examination (symptom-driven), vital signs measurements, ECGs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis).

Device malfunctions will also be recorded.

The safety monitoring practices employed by this protocol (i.e., vital signs, 12-lead ECGs, clinical laboratory tests, AE questioning, and physical examinations) are adequate to protect the subjects' safety and should detect all expected emergent AEs.

Discontinued subjects may be replaced at the discretion of the Sponsor.

Figure 1. Overall Study Design

Screening [a]	Check-In Procedures [b]	PK based on Randomization Schedule [c]			Follow-up [d]

Study Days	-1	1	2	3	4
Check-In	X				
Product Trial	X				
Randomization		X			
PK Blood Sampling		X	X	X	X
Subjective Questionnaires	X	X	X	X	X
Puff Topography				X	X

a: To be performed within 27 days prior to study procedures on Day -1.

b: At Check-in, baseline study assessments, questionnaire training and Product Trial will be performed on Day -1.

c: Subjects will be randomised on Day 1 and start study product use and study assessments.

d: A follow-up telephone call will be made by the CRU in an attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 7 days after the final product use to determine if any AE has occurred since the last study visit.

Study Products:

A	[redacted] HT device with [redacted] stick
B	[redacted] HT device with [redacted] stick
C	[redacted] HT device with [redacted] stick
D	Subject's OBCC

3.2 Confinement and Follow-Up

Subjects will be housed at the CRU on Day -1, at the time indicated by the CRU, until after completion of all study procedures on Day 4. Subjects may be admitted earlier than Day -1 of for COVID-19 testing not related to study protocol as per CRU requirements. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee (i.e., for ongoing AE management).

The CRU will attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 7 days after the final product use to determine if any AE has occurred since the last study visit.

3.3 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure as outlined in the Study Events Flow Chart (Table 1).

4. STUDY POPULATION

Subjects selected for this study will be identified via standard recruitment methods.

4.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 21 to 65 years of age, inclusive, at Screening.

2. Reports smoking an average of at least 10 manufactured combustible (menthol or non-menthol) CPD for at least 12 months prior to Screening. Brief periods of non-smoking (e.g., up to ~7 consecutive days due to illness, participation in a study where smoking was prohibited) within 60 days prior to Check-in will be permitted at the discretion of the Investigator.

3. Has a positive urine cotinine ($\geq$ 500 ng/mL) at Screening.

4. Has an exhaled CO > 10 ppm at Screening.

5. A female subject of childbearing potential must have been using 1 of the following forms of contraception and agree to continue using it through completion of the study and for at least 28 days after the final product use:
   - hormonal (e.g., oral, vaginal ring, transdermal patch, implant, or injection) consistently for at least 3 months prior to Check-in;
   - double barrier method (e.g., condom with spermicide, diaphragm with spermicide) consistently for at least 14 days prior to Check-in;
   - intrauterine device for at least 3 months prior to Check-in;
   - a partner who has been vasectomised for at least 4 months prior to Check-in;
   - abstinence beginning at least 28 days prior to Check-in.
6. A female subject of non-childbearing potential must have undergone one of the following sterilisation procedures at least 6 months prior to Check-in:
   - hysteroscopic sterilisation;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to Check-in and FSH levels consistent with postmenopausal status.
7. A non-vasectomised, male subject must agree to use a condom with spermicide or abstain from heterosexual intercourse from Check-in until at least 90 days after the final product use. No restrictions are required for a vasectomised male provided his vasectomy has been performed 4 months or more prior to Check-in. A male who has been vasectomised less than 4 months prior to Check-in must follow the same restrictions as a non-vasectomised male.
8. A male subject must agree not to donate sperm from Check-in until at least 90 days after the last final product use.
9. Is willing to comply with the requirements of the study, including a willingness to use the HT products.
10. Provides voluntary consent to participate in this study documented on the signed informed consent form (ICF).

4.2 Exclusion Criteria

Subjects may be excluded from the study if there is evidence of any of the following criteria at Screening, Check-in, or during the study as noted, in the opinion of the Investigator:

1. Has a history or presence of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, urologic, pulmonary (especially

bronchospastic diseases and asthma), immunologic, psychiatric, or cardiovascular disease, or any other condition that, in the opinion of the Investigator, would jeopardise the safety of the subject or impact the validity of the study results.

2. Has a clinically significant abnormal finding on the physical examination, medical history, vital signs, ECG, or clinical laboratory results, in the opinion of the Investigator.

3. Has a positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) at Screening.

4. Has previously been diagnosed with any form of cancer, except for basal cell or squamous epithelial carcinomas of the skin that have been resected at least 1 year prior to Screening.

5. Has diabetes mellitus that is not controlled by diet/exercise alone, in the opinion of the Investigator.

6. Has had an acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 14 days prior to Check-in.

7. Has a fever (> 100.5°F/38.05°C) at Screening or Check-in.

8. Has a body mass index (BMI) > 30.0 kg/m^2 or < 18.0 kg/m^2 at Screening.

9. Has a history or presence of drug or alcohol abuse within 24 months of Check-in, as determined by the Investigator.

10. Has a systolic blood pressure < 90 mmHg or > 150 mmHg, diastolic blood pressure < 40 mmHg or > 95 mmHg, or heart rate < 40 bpm or > 99 bpm at Screening.

11. Has an estimated creatinine clearance < 70 mL/minute (using the Cockcroft-Gault equation) at Screening.

12. Has a positive urine/breath screen for alcohol or positive urine screen for drugs of abuse at Screening or Check-in.

13. Drinks alcohol in excess of 21 glasses/units per week for males or 14 glasses/units per week for females, with one unit = 150 mL of wine or 360 mL of beer or 45 mL of 45% alcohol.

14. If female, the subject is pregnant, lactating, or intends to become pregnant during the time period from Screening through the end of study.

15. Has taken medication for depression or asthma within 12 months prior to Check-in and throughout the study.

16. Has used prescription anti-diabetic medication and/or insulin therapy within 12 months prior to Check-in and throughout the study.

17. Has used medications known to interact with cytochrome P450 (CYP) 2A6 (including, but not limited to, amiodarone, desipramine, isoniazid, ketoconazole, miconazole, phenobarbital, rifampin, tranylcypromine, methoxsalen) within 3 months prior to Check-in and throughout the study.

18. Has used prescription drugs within 7 days prior to Check-in and throughout the study. Medication listed as part of acceptable birth control methods, hormonal replacement therapy, and occasional or seasonal use of over-the-counter products such as analgesics, antihistamines, nasal decongestants, and dietary supplements are permitted at the discretion of the Investigator (refer to Section 4.3.2).

19. Has used inhalers to treat any medical condition within 3 months prior to Check-in and throughout the study.

20. Use of prescription or over-the-counter bronchodilator medication (e.g., inhaled or oral β-agonists) for treatment of any illness within 12 months prior to Check-in and throughout the study.

21. Is allergic to or cannot tolerate menthol flavouring agents.

22. Has never smoked any menthol cigarettes or cannot tolerate smoking them.

23. Has used other nicotine-containing products other than manufactured combustible cigarettes (e.g., e-cigarettes, roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 14 days prior to Check-in.

24. Has used any prescription smoking cessation treatments, including, but not limited to, varenicline (Chantix®) or bupropion (Zyban®) within 3 months prior to Check-in.

25. Is a self-reported puffer (i.e., adult smoker who draws smoke from the cigarette into the mouth and throat but does not inhale).

26. Is planning to quit smoking during the study or within the next 3 months or is postponing a quit attempt in order to participate in the study.

27. Has donated blood or blood products (including plasma), had significant blood loss, or received whole blood or a blood product transfusion within 90 days prior to Check-in.

28. Donation of bone marrow within the last 6 months prior to Check-in.

29. Has participated in a previous clinical study for an investigational drug, device, biologic, or tobacco product within 90 days prior to Check-in.

30. Is or has a first-degree relative (i.e., parent, spouse, sibling, child) who is a current or former employee of the tobacco or vaping industry or a named party or class representative in litigation with the tobacco or vaping industry.

31. Is or has a first-degree relative (i.e., parent, spouse, sibling, child) who is a current employee of the CRU.

32. In the opinion of the Investigator, the subject should not participate in this study.

4.3 Study Restrictions

4.3.1 Food and Beverages

Foods and beverages containing the following substances should not be consumed as indicated below:

- Alcohol should be avoided for 48 hours prior to Screening and Check-in to avoid exclusion for a positive alcohol test and throughout the study.
- Foods containing poppy seeds should be avoided for 48 hours prior to Screening and Check-in to avoid exclusion for a positive urine drug test and throughout the study.
- Food and beverages containing grapefruit for 14 days prior to Check-in and throughout the study.
- Caffeinated beverages will be restricted throughout confinement.

4.3.2 Medications

Medication use will be assessed to satisfy the inclusion and exclusion criteria. All medications (and reasons for their use) taken from 30 days prior to Check-in through the end-of-study will be recorded. Except for those medications noted in the exclusion criteria (Section 4.2), prescription or over-the-counter medications required to treat a disease or condition are permitted at the discretion of the Investigator. Hormonal contraceptives (e.g., oral, vaginal ring, transdermal patch, implant, injection) and hormonal replacement therapy are permitted. Occasional or seasonal use of over-the-counter products such as analgesics (e.g., acetaminophen), antihistamines, nasal decongestants, and dietary supplements are permitted at the discretion of the Investigator. Other medications may be permitted at the discretion of the Investigator, providing the medication in question would have no impact on the study. Use of any medication will be documented.

Decisions to use concomitant medications during the study will be made in the best interest of the health of the subject. If use of a prohibited medication is required during the study, a decision will be made by the Investigator-to continue or discontinue the subject. Any required medications that might impact study endpoints should be considered during interpretation of the study results.

4.3.3 Meals/Dietary Considerations

For all subjects, meals and snacks will be provided at the appropriate times during confinement at the CRU. Each meal and/or snacks served at the CRU will be standardised and will be similar in caloric content and composition and will be taken at approximately the same time on each day. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Subjects will fast for at least 1 hour prior to and for at least 4 hours after the start of each controlled morning product use session on Days 1, 2, 3, and 4. Lunch will be served at approximately the same time on Days 1 through 4, at the start of the 4-hour *ad libitum* product use session (after collection of the 4-hour PK blood sample). After lunch, subjects will fast for the remainder of the 4-hour *ad libitum* product use session.

During confinement, water will be allowed *ad libitum*, except that subjects may not consume beverages of any kind (including water) during the morning product use sessions on Days 1, 2, 3 and 4. An exception to the water restriction can be made if a subject starts coughing uncontrollably while smoking or using the study products.

4.3.4 Activity

Subjects will be instructed to refrain from abnormal strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from 48 hours prior to Screening and Check-in, and during confinement.

4.3.5 Tobacco Use/Considerations

Except as allowed by the study, consumption of tobacco- or nicotine-containing products will not be permitted from Check-in through discharge. On Days -1 through 4, subjects will be allowed to use their OBCCs, *ad libitum*, after completion of study assessments and after the 4-hour *ad libitum* product use session, but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of morning controlled product use session scheduled on the following day.

4.4 Subject Early Discontinuation or Withdrawal

Subjects will be advised that they are free to withdraw from the study at any time. In addition, subject participation in this study may be discontinued for any of the following reasons:

- AE
- Lost to follow-up
- Non-compliance with study procedures
- Protocol violation
- Study terminated by Sponsor or other regulatory authorities
- Withdrawal of consent
- Investigator's discretion, including a severe laboratory abnormality or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject

Protocol deviations/violations should not lead to subject withdrawal unless they indicate a significant risk to the subject's safety or jeopardise the scientific integrity of the study.

If premature withdrawal from the study occurs for any reason, the Investigator must determine the primary reason and record this information in the case report form (CRF). Additionally, subjects withdrawing after study product administration will undergo all discharge safety procedures as feasible and as deemed necessary by the Investigator.

A subject withdrawn from the study due to any AE or clinically significant abnormal laboratory test values will be evaluated by the Investigator or other qualified individual and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels or until lost to follow-up, as appropriate in the opinion of the Investigator.

Subjects withdrawing or removed from this study cannot re-enter.

4.5 Subject Randomisation

Subjects who complete the study screening assessments and meet all the eligibility criteria and are randomised will be assigned a unique randomisation identification number on Day 1 and will receive study products according to the randomisation scheme generated by Celerion.

The sequences to be used in the randomisation will be ABCD, BDAC, CADB, and DCBA.

If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., Subject No. 101 will replace Subject No. 1).

5. STUDY PRODUCTS/MATERIALS

5.1 Description of Study Products

All subjects will use Products A through D.

The following study products will be used in this study:

Product Designation	Study Product Name
A	[redacted] HT device with [redacted] stick
B	[redacted] HT device with [redacted] stick
C	[redacted] HT device with [redacted] stick
D	Subject's own brand combustible cigarette (OBCC)

5.1.1 Usual Brand Combustible Cigarette

Subjects will be required to bring with them to the CRU a sufficient supply (i.e., 5-day supply [unopened packs]) of their OBCCs for personal use throughout confinement.

5.1.2 [redacted] HT Device with Stick

[redacted] works by the user inserting a specially designed consumable ([redacted]) into the handheld device which contains an electronically controlled heater (Figure 2). The handheld device heats the tobacco using an electronically controlled heating rod. The rod can be set to 2 temperatures: Eco mode (315°C) or Standard mode (345°C). The handheld device supplies heat to the tobacco using the heating rod for 4 minutes. The heating device must be recharged after 20 consecutive uses.

The inclusion of a foil wrap around the tobacco portion of the rod prevents the [redacted] stick from being lit and combusted like a CC (Figure 3).

Figure 2. Heated Tobacco Product Diagram

A

B

Figure 1A. [redacted] device features; Figure 1B. Assembly of the [redacted] device

Figure 3. [redacted] Stick Assembly

5.2 Study Product Accountability and Dispensing

All [redacted] HT Devices and tobacco [redacted] sticks will be provided by the Sponsor. The CRU staff will coordinate shipping of products and devices from the Sponsor. The staff will document the date each shipment was received and recorded in the inventory records. The CRU staff will document and reconcile the total number of products shipped to the CRU, the total number of products dispensed during the study, and the total number of products remaining at the end of clinical conduct. Subjects will bring a 5-day supply (unopened packs) of their OBCCs for personal use at designated times throughout confinement in the CRU.

For each day of HT product use, subjects will be provided with a new/unused device to be used for the morning controlled product use and *ad libitum* product use sessions. A fresh tobacco stick will be provided at the start of the morning controlled product use session and at the start of puff topography.

All products will be stored in a locked, limited-access area at the CRU and kept at controlled room temperature (defined as 20 - 25°C [68 - 77°F], with excursions permitted to 15 - 30°C [59 - 86°F]). Humidity is recorded but not controlled.

Study products for dispensing (including OBCC) to subjects will be prepared by the study staff according to instructions provided by the Sponsor. Individual study product dispensing records will be maintained by the CRU staff for each subject. Care should be taken when repackaging the study products for use at the CRU to avoid exposure to air and moisture to the extent possible. The pharmacy will maintain records of the number of cigarettes dispensed for each subject.

The study staff will document the start time and stop time of each product use session. The number of HT sticks used and cigarettes smoked will be documented during each *ad libitum* product use session on Days 1 through 4. The number of cigarettes smoked will be

documented on Day -1 prior to smoking abstinence (at least 12 hours prior to the start of morning controlled product use session on Day 1), and on Days 1 through 3 following the 4-hour *ad libitum* product use session until at least 12 hours prior to the start of morning controlled product use session scheduled on the following day.

Subjects will smoke their OBCC and use each assigned product only in designated areas of the CRU.

Opened and unopened packages of [redacted] HT devices and sticks will be returned to the Sponsor or destroyed at the direction of the Sponsor. Opened and unopened packages of subject's OBCC will be returned to the subjects at the end of the study. All returns or destruction of study products will be documented.

[redacted] HT device has two power settings: standard mode (345°C temperature) and Eco (315°C temperature). **Subjects should use the device set on the standard mode.**

6. STUDY PROCEDURES

6.1 Screening

Potential subjects will undergo Screening procedures to ensure that they meet the requirements for inclusion in the study within 27 days prior to study procedures on Day -1.

Screening procedures will be performed as delineated in the Study Events Flow Chart (Table 1).

6.1.1 Informed Consent

All prospective subjects will have the study explained by the Investigator or his/her designee and will be required to read, sign, and date an ethics committee (EC)-approved ICF prior to completion of screening or other study procedures. This consent form will provide the subjects in non-technical terms with the purpose of the study, procedures to be carried out, and potential hazards. The subjects will be assured that they may withdraw from the study at any time without jeopardising medical care related to or required as a result of study participation. Subjects will be given a copy of their signed ICF.

6.1.2 Medical History/Demographic Data/Record of Concomitant Medication

Medical history and socio-demographic data, including name, sex, age (each subject must show proof of age with government-issued identification [e.g., driver's license]), race, ethnicity, address, and phone number will be recorded at Screening for each subject.

Additional data including National Insurance Number, as applicable, will be recorded at Check-in.

Any concomitant medications taken from 30 days prior to Check-in through discharge will be recorded in the CRF and source document.

6.1.3 Tobacco/Nicotine Product Use History

Subjects will be required to report previous tobacco-product and nicotine-product use histories to satisfy the study inclusion and exclusion criteria.

Details of the subject's OBCC, including the brand, brand style, flavour, cigarette length, and amount of daily use will be recorded at Screening and updated at Check-in as necessary. A color photocopy or photograph of the subject's OBCC package (including the branding and the UPC code) will be taken by the CRU staff at Check-in.

6.1.4 Exhaled Carbon Monoxide

Exhaled CO levels will be measured using a Bedfont Micro+ Smokerlyzer or similar device, at Screening and at Check-in.

6.2 Check-in and Confinement

Subjects will check in to the CRU on Day -1 at a time specified by the CRU. Check-in procedures will be performed as delineated in the Study Events Flow Chart (Table 1).

After check-in, subjects will complete one set of questionnaires for the purpose of familiarisation with subjective effects questions, appropriate use of the VAS, and use of the computerised tablet system. Data collected from the training session will not be used for any analysis.

The clinical team will explain how the HT products will be used. Subjects will have the opportunity to see the products/devices and packaging and will participate in a Product Trial where they will use the [redacted] device with the HT stick (flavour) of their choice. The HT stick flavour will be recorded; however, no assessments will be made. The purpose of the Product Trial is to familiarise subjects to the [redacted] device and HT stick prior to PK assessments. All products/devices used in the trial session will not be used in the clinical study but will be retained as demonstration samples for accountability purposes.

Subjects will have their personal belongings thoroughly checked during Check-in. All subjects will be required to shower and will receive clean articles of clothing prior to the start of each morning controlled product use (i.e., during the 12-hour abstinence) on Days 1, 2, 3 and 4.

Subjects will be confined from Check-in on Day -1 through completion of scheduled study events on Day 4.

A subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

6.2.1 Baseline Assessments (Day -1)

Subjects will continue to smoke their OBCC from Check-in (after completion of the Product Trial and check-in procedures) through Day -1, but will abstain from use of any tobacco- or

nicotine-containing products for at least 12 hours prior to the start of morning controlled product use session on Day 1.

The number of OBCC smoked per day will be documented.

Baseline assessments will be performed as delineated in the Study Events Flow Chart (Table 1).

6.3 Product Use (Days 1 Through 4)

On Days 1, 2, 3, and 4, subjects will use the study product they are assigned to use according to the randomisation scheme.

In the morning of each day, subjects will use the assigned study product under controlled conditions (i.e., completely use a single unit of the assigned study product, with puffs taken at 30-second intervals and puffs 3 seconds in duration). Following the 4-hour PK blood collection, subjects will start a 4-hour *ad libitum* product use session (no limits on cigarette or HT consumption) with the same study product used during the morning controlled use session.

Each subject will be provided with a new/unused [redacted] HT device for each day of HT product use (i.e., the same device will be used for the morning controlled product use session and the *ad libitum* product use session on the same day). Subjects will be provided the assigned HT stick (based on randomisation sequence) or OBCC on each day. The clinic staff will document the time each product is dispensed. **The Pulze HT device should be used on the Standard Mode Setting**. Products that stop functioning should be replaced as soon as possible, with the failure documented.

6.4 Study Assessments

All study assessments will take place at the times delineated in the Study Events Flow Chart (Table 1) unless otherwise noted below.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.4.1 Nicotine Pharmacokinetics

On each of Days 1, 2, 3 and 4, a 4 mL blood sample for plasma nicotine analysis will be drawn into a plastic K_2-EDTA (lavender top) vacutainer tube at the time points delineated in the Study Events Flow Chart (Table 1). Allowable deviation windows for PK sampling are: ± 30 seconds for samples collected from 3 - 15 minutes, ± 1 minute for samples collected from 30 - 60 minutes, and ± 3 minutes for all other samples.

PK blood samples will be collected by direct venipuncture or through an intravenous catheter port as determined by the clinical staff.

Additional blood (typically up to approximately 1 mL) may be drawn between blood draws for the purpose of keeping the needle patent, if required. The blood from the 1 mL draws will be discarded. In total, approximately 250 mL of blood will be drawn from each subject during the entire study for nicotine PK analysis.

The blood samples collected for plasma nicotine analysis may be kept at room temperature prior to centrifugation, and will be centrifuged at approximately 1000 to 1300 RCF at ~5°C for approximately 10 minutes, within 60 minutes from collection. After centrifugation, the plasma will be transferred to two methanol prewashed 3.5 mL polypropylene screw cap tubes, properly labeled, and then stored at -20°C (± 10°C) or below (within 120 minutes from collection) until analysis.

Samples will be analyzed using a validated liquid chromatography coupled to tandem mass spectrometry detection analytical method with the appropriate quality controls in accordance with FDA Good Laboratory Practice regulations (Title 21 Code of Federal Regulations [CFR] Part 58). Additionally, processing of samples will completed by a non-tobacco user.

6.4.1.1 Future Research

No additional analysis is planned to be performed on the blood samples for possible future research.

6.4.2 Subjective Effects Questionnaires

The Intent to Use (VAS), Urge to Smoke (VAS), and Product Evaluation Scale (7-point scale) questionnaires will be completed using a computerised tablet device. All relevant software and staff training specific to the electronic questionnaires will be provided by IVRCC ePro. Any electronic device used must meet all regulatory requirements, including FDA 21 CFR Part 11.

All questionnaires will be completed at the time points delineated in the Study Events Flow Chart (Table 1).

When scheduled at the same time as a PK blood draw, the Urge to Smoke questionnaire will be completed approximately 30 seconds prior to the scheduled blood draw (except for the one scheduled at Time 0, which will be performed approximately 10 minutes prior to the start of the product use session), and all other questionnaires will be completed within approximately 2 minutes after the last scheduled blood draw.

6.4.3 Puff Topography

Puff topography will be evaluated over the last 2-hour period during the 4-hour *ad libitum* product use session on Days 3 and 4 as indicated in the Study Events Flow Chart (Table 1). Following the 4-hour PK blood collection and at the start of their meal, subjects will be allowed to use their assigned study product *ad libitum* for 4 hours. During the last 2 hours of the *ad libitum* session, topography measurements will be taken. The topography session will span a 2-hour period and the SPA-M topography device will be stopped and restarted with each new stick or cigarette during that time. Puff parameters will be recorded using SPA-M

devices (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter puff interval) for each product.

The *ad libitum* product use session on Days 1 through 4 will start at approximately the same time each day, with lunch served at the start of the *ad libitum* product use session, at approximately the same time each day. After completion of the *ad libitum* use session (i.e., approximately 8 hours after the start of the morning controlled product use), subjects will be allowed to smoke their own cigarettes (*ad libitum*) but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of morning controlled product use session scheduled on the following day.

The topography device will be monitored to ensure the device is actively recording during each session.

Additional details and instructions for puff topography procedures will be provided separately.

Depending on the availability of topography equipment, puff topography may not be performed for some or all assigned subjects.

6.4.4 Safety Assessments

Safety assessments in addition to those below may be obtained as necessary at the discretion of the Investigator. In the case of an early subject withdrawal, discharge safety assessments should be collected to the extent possible.

6.4.4.1 Physical Examination

A standard physical examination assessing the general physical well-being will be performed at Screening. A symptom-driven physical examination will be conducted at other times as deemed appropriate by the Investigator (Table 1).

6.4.4.2 Body Weight, Height, and BMI

Body weight and body height will be measured as delineated in the Study Events Flow Chart (Table 1). BMI will be recorded as kg/m^2.

6.4.4.3 Electrocardiogram

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Table 1). ECGs will be taken following resting in the supine position for at least 5 minutes. All ECG tracings will be reviewed by the Investigator or a qualified designee.

6.4.4.4 Vital Signs

Single measurements of vital signs (respiratory rate, HR, BP, and oral temperature) will be performed as outlined in the Study Events Flow Chart (Table 1). Additional vital signs may be taken at any other times, if deemed necessary.

BP and HR measurements will be taken following a rest period of at least 5 minutes in a seated position. Vital signs are to be measured at least 15 minutes after the last tobacco- or nicotine-containing product used.

On Days 1, 2, 3 and 4, vital signs measurements will be taken within 2 hours prior to the start of the morning product use session.

6.4.4.5 Clinical Laboratory

All clinical laboratory tests will be conducted by an accredited laboratory. Values for the clinical laboratory parameters are to be within the laboratory normal ranges or deemed not clinically significant in the opinion of the Investigator. All tests listed below will be performed as delineated in the Study Events Flow Chart (Table 1). Up to approximately 38 mL of blood will be drawn from each subject during the entire study for clinical laboratory tests.

Serum Chemistry [1]
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Bicarbonate
- Blood urea nitrogen
- Creatinine
- Glucose
- Potassium
- Sodium
- Total protein
- Uric acid

Urinalysis [2]
- Bilirubin
- Blood
- Glucose
- Ketones
- Leukocyte esterase
- Nitrite
- pH
- Protein
- Specific gravity
- Urobilinogen

Additional Tests
- Serology
  - HIV
  - HBsAg
  - HCV
- Serum pregnancy test [3]
- Serum FSH [4]
- Urine cotinine
- Urine drug screen
  - Amphetamines
  - Cannabinoids
  - Cocaine
  - Opiates
- Urine/breath alcohol

Hematology
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- White blood cell count with differential

[1] Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken. For the samples collected at EOS, an 8-hour fast is not required.
[2] A microscopic examination for red blood cells, white blood cells, bacteria, and casts will be performed if an abnormality is noted in leukocyte esterase, protein, blood, or nitrite.
[3] Human chorionic gonadotropin (females only).
[4] For postmenopausal females only.

6.4.5 Adverse Events

An AE is any untoward medical occurrence associated with the use of the study product, whether or not considered study product-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, whether or not related to the study product.

6.4.5.1 Monitoring

The subjects will be instructed to inform the Investigator or staff of any AEs and intercurrent illnesses experienced during the study (i.e., from Screening until follow-up). Additionally, a specific inquiry regarding AEs will be conducted prior to each product use and at discharge (or upon early withdrawal). The inquiry will be posed in a non-specific manner using open-ended questions so as not to bias the response (e.g., How are you feeling today?).

A subject who has any clinically significant AE or clinically significant abnormal laboratory test value will be evaluated by the Investigator or other qualified individual and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels (as appropriate in the opinion of the Investigator), or until the subject is lost to follow-up. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

6.4.5.2 Reporting

All AEs occurring during this clinical trial after the subject has received the first study product (i.e., at the Product Trial) must be recorded on the CRF, including the date and time of onset, action taken, outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up), duration, relationship to product administration, and severity for each event. AEs will be listed.

Events captured between Screening and the first study product use will be documented as baseline signs and symptoms.

The Investigator will review each event and assess its relationship to product administration as unrelated, unlikely, possibly, probably, or likely.

In addition, each sign or symptom reported will be graded on a 3-point severity scale using mild, moderate, or severe.

6.4.5.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that (WHO and ICH definitions):

- results in death
- is life-threatening

- results in permanently disabling or incapacitating
- requires inpatient hospitalisation
- prolongs inpatient hospitalisation
- is a congenital anomaly / birth defect
- may jeopardise the subject or may require intervention to prevent one or more of the other outcomes listed above.

All SAEs, whether or not considered study-related, must be reported by telephone and by fax or e-mail to the Sponsor within 24 hours of the CRU's learning of the SAE or, at the latest, on the following workday. The Sponsor's representative to contact about this study is provided in the list of study contacts. The Investigator must also inform the EC, in compliance with GCP reporting guidelines, and the site monitor of any SAE.

6.4.5.4 Suspected Unexpected Serious Adverse Reactions

In accordance with the European Clinical Trial Directive (Directive 2001/20/EC), the Sponsor must ensure that the Ethics Committee, the appropriate Competent Authority, and the licensing authority are informed of all suspected "unexpected" serious adverse reactions (SUSARs) within 15 days of the event. All SUSARs leading to death, or which are life-threatening should be reported by the Sponsor to the ethics committee, the appropriate Competent Authority, and the licensing authority within 7 days of the event. The Sponsor should present all SUSARs to the appropriate Competent Authority once a year, or on request. Reporting of relevant events to ethics committee, the appropriate Competent Authority, and the licensing authority will be delegated by the Sponsor to the CRO (Celerion).

6.4.5.5 Pregnancy

A pregnancy occurring in a female study subject during the study will be documented in the clinical conduct study report to the EC. Pregnancy itself is not an AE. The Investigator or designee will discontinue the pregnant subject from the study and will advise her to seek prenatal care and counseling from her primary care provider. Advice given will be documented in the subject's source document.

The CRU staff will request the pregnant subject to notify the CRU of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the CRU staff will follow up with the subject until the end of pregnancy, if in compliance with the CRU's standard operating procedures (SOPs) and with the subject's consent. This request and the subject's response will be documented in the subject's source document.

6.4.5.6 Smoking Cessation Information

At Screening and prior to discharge from the study (or upon early termination), all subjects will be advised that to reduce the health effects of smoking, the best thing to do is to quit, and

will be encouraged to contact a qualified medical professional for advice on smoking cessation.

7. DATA ANALYSIS

Data will be handled and processed according to Celerion SOPs, which are written based on the principles of GCP. A brief description of the statistical analysis is included below, detailed methodology for all summary and statistical analyses of the data collected in this trial will be documented in a statistical analysis plan (SAP) prepared by Celerion and agreed upon by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints and/or their analysis will also be reflected in a protocol amendment. If deemed appropriate, additional statistical analyses other than those described in this section may be performed and included in the plan.

7.1 Sample Size Estimation

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives.

7.2 Analysis Populations

7.2.1 Safety Population

The Safety Population will include all subjects who have successfully completed eligibility requirements after checking in to the CRU and used at least one study product.

7.2.2 Outcomes Population

The Outcomes Population is a subset of the safety population and will consist of subjects who used a study product and have evaluable PK, subjective effects, or topography data. This population will be used in the summary and analysis of PK, subjective effects, topography, and product use, and all available data will be included in the summary tables to the extent possible.

7.3 Data Analysis, Summarisation, and Statistical Methods

SAS software (version 9.4 or higher, Cary, North Carolina) will be used for all data presentation and summarisation including summary tables, graphs, and data listings. In general, all data will be listed by subject and time point and summarised by study product, time point, product use session (as applicable), and sex using descriptive statistics appropriate for the endpoint. Figures will be used to display the data graphically.

Missing data will not be imputed. Where individual data points are missing because of dropouts or other reasons, the data will be considered missing at random and summarised based on reduced denominators.

7.3.1 Nicotine Pharmacokinetic Analysis

Individual nicotine concentrations will be adjusted for baseline nicotine ("baseline-adjusted") and all PK parameters will be calculated based on the adjusted concentrations. Baseline adjustment will be performed by subtraction of the pre-existing nicotine concentration from each nicotine concentration obtained after test product administration in that period/day for each subject using the following equation:

$$C_t = C_{t\ unadjusted} - [C_0 \cdot e^{-Kel \cdot t1}]$$

where C_t is the adjusted concentration at time t, $C_{t\ unadjusted}$ is the observed concentration at time t, C_0 is the pre-product use concentration (-5 minutes), $Kel = \frac{\ln(2)}{t½}$, t½ is 2 hours (average nicotine half-life), t is the actual sampling time since product administration, and t1 is the actual sampling time since the time of the pre-product use sample. Any resulting negative concentration values following the baseline adjustment will be set to 0.

Nicotine PK parameters will be determined from the adjusted individual subject plasma concentration-time profiles by applying a non-compartmental approach using appropriate validated PK software (e.g., Phoenix® WinNonlin® version 8.1 or higher).

For each morning product use session on Days 1, 2, 3 and 4, the following PK parameters will be calculated from the baseline-adjusted nicotine concentration-time data:

AUC_{0-90}	Area under the baseline-adjusted nicotine concentration-time curve from time 0 (defined as the start of the product use session) to the 90-minute time point as calculated by the linear trapezoidal method
AUC_{0-240}	Area under the baseline-adjusted nicotine concentration-time curve from time 0 (defined as the start of the product use session) to the 240-minute time point as calculated by the linear trapezoidal method
AUC_t	Area under the baseline-adjusted nicotine concentration-time curve from time 0 (defined as the start of the product use session) to time t.
AUC_{inf}	Area under the baseline-adjusted nicotine concentration-time curve from time 0 (defined as the start of the product use session) extrapolated to infinity (represents the total nicotine exposure across time).
C_{max}	Maximum baseline-adjusted plasma concentration.
C_{last}	Plasma baseline-adjusted nicotine concentration at last time point measured
T_{max}	Time to reach the maximum baseline-adjusted plasma concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
$T_{1/2}$	Terminal elimination half-life.

Plasma concentrations below the limit of quantitation will be set to one-half of the lower limit of quantitation for the calculation of descriptive statistics of unadjusted plasma nicotine concentrations and for the calculation of baseline-adjusted nicotine concentrations.

Nicotine concentrations and PK parameters will be listed by subject and summarised by study product, by sex and overall using descriptive statistics.

7.3.1.1 Analysis of Variance

A linear mixed model for analysis of variance will be performed on the log-transformed PK parameters C_{max} and AUC following the morning product use session on each of Days 1, 2, 3, and 4. The model will include sequence, study product, and study day as fixed effects and subject-nested-within-sequence as a random effect. Sequence will be tested using subject-nested-within-sequence as the error term. Geometric least-squares means (LSM) and 95% confidence intervals (CIs) will be provided for the PK parameters of C_{max} and AUC by study product. Geometric LSM ratio, 95% CIs of geometric LSM ratio, and p-values will be provided for the study product comparisons in C_{max} and AUC. The comparisons of interest will include each of the study products compared to each other.

The above statistical analyses will be performed using the appropriate SAS procedure.

Non-parametric analysis (Wilcoxon Signed Rank test) will be performed for the comparisons of T_{max}.

Details of the statistical methods will be provided in the SAP.

7.3.2 Subjective Effects

7.3.2.1 Urge to Smoke Parameters

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

Emax	The maximum change from baseline VAS score (VASpre-use - VASpost-use).
TEmax	Time of the Emax. If the maximum value occurs at more than one time point, TEmax will be defined as the first time point with this value.
$AUEC_{0-240}$	The area under the change from baseline VAS score versus time curve from time 0 to 240 minutes.

Responses and derived parameters will be listed by subject and summarised by study product, by sex and overall using descriptive statistics.

An appropriate statistical method, similar to the PK analysis detailed above, will be used to compare Urge to Smoke parameters (no data transformation).

7.3.2.2 Product Evaluation Scale

Product Evaluation will be considered as a 7-point scale. Responses will be presented as the following factor scores:

a) Satisfaction: average of the response scores from questions 1, 2, 3, and 12;

b) Psychological reward: average of the response scores from questions 4 to 8;

c) Aversion: average of the response scores from questions 9, 10, 16, and 18;

d) Relief: average of items 11, 13, 14, 15, and reversed for item 20 (i.e., not at all = 7, extremely = 1);

e) Items 17, 19, 21 will be summarised as individual item scores.

Descriptive statistics of the subscales will be provided by study product, by sex and overall. Individual responses will be listed by subject.

7.3.2.3 Intent to Use

Descriptive statistics of the VAS will be provided by study product. Individual responses will be listed by subject.

7.3.3 Puff Topography

The following topography parameters will be assessed:

- Puff count
- Puff duration
- Puff volume
- Peak puff flow rate
- Average puff flow rate
- Inter-puff interval

Topography parameters will be listed by subject and summarised by study product, study day, overall and by sex, usual brand cigarette flavour (non-menthol or menthol), age, number of years smoking, CPD, and time point using descriptive statistics.

An appropriate statistical method, similar to the PK analysis detailed above, will be used to compare topography parameters.

7.3.4 Product Use Behaviour

The number of HT sticks used (*ad libitum* product use session), the number of CCs smoked (Days -1 through 4), and the number of puffs (morning controlled product use session) will

be listed by subject and summarised by study product, product use session, study day and overall using descriptive statistics.

7.3.5 Safety

Safety data including single vital signs assessments, ECGs, and clinical laboratory results will be listed and summarised by subject and time point as appropriate.

All AEs captured in the database will be listed in by-subject data listings. However, only study product use-emergent AEs will be summarised. A study product use-emergent AE is defined as an AE that is starting or worsening at the time of or after the first study product use.

Frequencies of subjects with study product use-emergent AEs, regardless of relationship to study product will be summarised and sorted by system organ class. Frequencies of subjects with study product use-emergent serious AEs will be likewise summarised. Frequencies of study product use-emergent AEs will be summarised by severity and relationship to study product.

Changes in physical examinations (if any) will be described in the text of the final report.

All concomitant medications recorded will be listed by subject.

Incidence of device malfunction(s) will be tabulated.

8. STUDY ADMINISTRATION

8.1 Ethics

8.1.1 Institutional Review Board

This protocol, ICFs, and any amendments to the protocol will be reviewed by a Research Ethics Committee (REC) prior to initiation. The study will not be initiated without the approval from the REC. Notice that the protocol and informed consent that have been reviewed and approved by the REC will be in the final study report.

8.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol and in accordance with the relevant articles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in 1964 and as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Edinburgh (2000); Notes of Clarification added Washington (2002) Tokyo (2004), South Korea (2008), and Brazil (2013).

8.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out, and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign, and

date an ICF summarising the discussion prior to Screening, and will be assured that they may withdraw from the study at any time without jeopardising their medical care.

Subjects will be given a copy of their signed ICF.

8.2 Confidentiality

All clinical sites and vendors will have signed confidentiality agreements with Celerion. By signing this protocol, the Investigator and Celerion staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

Neither the clinical site nor Celerion will supply to the Sponsor any subject names, initials, date of birth (except year), or other personal identifiers (HIPAA 2015). All such information appearing on any study document must be redacted before a copy of the document is supplied to the Sponsor. The photocopied government-issued ID to verify subject age will be kept separate from other source documentation and not provided to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information i.e., full name, National Insurance Number details etc. may be released to the Sponsor. The subjects will be informed during the consenting process that representatives of the Sponsor, EC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection laws.

8.3 Termination of the Study

The Investigator reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

8.4 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

8.5 Direct Access to Source Data/Documents

All clinical sites and vendors will ensure that the Sponsor, EC and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6][R2] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

8.5.1 Monitoring the Study

The responsible study monitor or Sponsor's designee will contact and visit the Investigator as necessary, and he/she will be allowed, upon request, to inspect and verify all records of the study (e.g., source document, ICFs, CRFs, regulatory documents) in a manner consistent with GCP and all other applicable state and federal law.

It will be the study monitor's responsibility to inspect the source documents to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the CRF. The monitor will verify that each subject has consented in writing prior to any study procedures being performed. Where the terms of the Informed Consent, GCP, and all other applicable state and federal law permit, the monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator (or his/her designee) agrees to cooperate with the monitor to ensure that any issues detected in the course of these monitoring visits are resolved.

In addition, the Sponsor's internal auditors (or designee) and government inspectors may evaluate the study and must be allowed access to CRFs, source documents, and other study files.

The Investigator must notify the Sponsor (or designee) promptly of any inspections of the study or activities related to the study scheduled by regulatory authorities, allow the Sponsor (or designee) to be present, and promptly forward copies of inspection reports to the Sponsor (or designee).

8.6 Reporting for the Study

8.6.1 Case Report Forms

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the Investigator. The final signed CRFs are provided to the Sponsor in the format as decided upon between Celerion and the Sponsor (e.g., compact disc, flash drive, secure file transfer protocol). This will be documented in the Data Management Plan (if applicable).

8.6.2 Data Coding

AEs will be coded using MedDRA®. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Each dictionary version will remain the same throughout the trial. Coding will be completed by qualified members of the Celerion staff.

8.6.3 Report Format

According to the ICH Harmonised Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

8.6.4 Record Keeping

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

8.7 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor’s written consent to publish the information.

9. REFERENCES

Food and Drug Administration: Section 910 of the Federal Food, Drug, and Cosmetic Act - Application for Review of Certain Tobacco Products (May 2019). Available at: https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/section-910-federal-food-drug-and-cosmetic-act-application-review-certain-tobacco-products.

Hatsukami DK, Zhang Y, O'Connor RJ, Severson HH. Subjective responses to oral tobacco products: scale validation. Nicotine Tob Res. 2013;15(7):1259-64.

U.S. Department of Health and Human Services. National Institutes of Health. HIPAA Privacy Rule. Information for Researchers. Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (06Nov2015). Available at: https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html.

10. APPENDICES

Appendix 1. Demographics Questionnaire

Appendix 2. Urge to Smoke Questionnaire

Appendix 3. Product Evaluation Scale (PES)

Appendix 4. Intent to Use Questionnaire

Appendix 1: Demographics Questionnaires

Screening Demographics Questionnaire

1. What is your date of birth?

   _____

2. What is your sex?

   ☐ Male
   ☐ Female

3. Which one of these groups would you say best describes your race?

   ☐ White/Caucasian
   ☐ Black/African American
   ☐ Asian
   ☐ Native Hawaiian or other Pacific Islander
   ☐ American Indian or Alaska Native
   ☐ Other (SPECIFY): _____

4. Are you Hispanic or Latino?

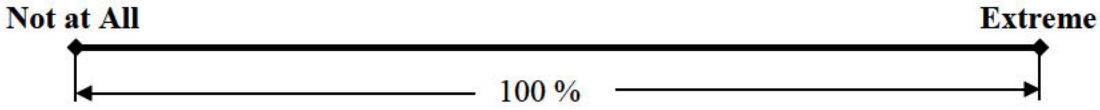
   ☐ Yes
   ☐ No

Appendix 2: Urge to Smoke Questionnaire

Note: The following question will be paired with a VAS. The VAS will be anchored with "Not at All" on the left and "Extreme" on the right.

Please respond to the question by making a vertical mark anywhere along the horizontal line.

How strong is your urge to smoke right now?



Appendix 3: Product Evaluation Scale (PES)

(Hatsukami 2013)

Please mark the number that best represents how using the product made you feel.

1. Was it satisfying?
2. Did it taste good?
3. Did you enjoy the sensations in your mouth?
4. Did it calm you down?
5. Did it make you feel more awake?
6. Did it make you feel less irritable?
7. Did it help you concentrate?
8. Did it reduce your hunger for food?
9. Did it make you dizzy?
10. Did it make you nauseous?
11. Did it immediately relieve your craving for a cigarette?
12. Did you enjoy it?
13. Did it relieve withdrawal symptoms?
14. Did it relieve the urge to smoke?
15. Was it enough nicotine?
16. Was it too much nicotine?
17. Was it easy to use?
18. Were there bothersome side effects?
19. Were you comfortable using the product in public?
20. Did you still have a craving for a cigarette after using the product?
21. Are you concerned that you would become dependent on this product?

Scale: 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 "Satisfaction" (items 1, 2, 3, and 12); "Psychological Reward" (items 4 through 8); "Aversion" (items 9, 10, 16, and 18); and "Relief" (items 11, 13, 14, 15, and reversed for item 20) and single items 17, 19, and 21 will be summarised.

Appendix 4: Intent to Use Questionnaire

Note: The following question will be paired with a VAS. The VAS will be anchored with "Not at All" on the left and "Extremely" on the right.

Please respond to each phrase by making a vertical mark anywhere along the horizontal line.

1. If available, how likely are you to buy your assigned study product in the future?