Nicotine uptake and abuse liability assessments of 5 blu disposable electronic cigarettes in comparison to a combustible cigarette

NCT05457634

Statistical analysis plan - Original 02/Aug/2021

STATISTICAL ANALYSIS PLAN

Clinical Site Name:	LA Clinical Trials, LLC
Protocol Number and Title:	Fontem-PK-01 Nicotine uptake and abuse liability assessments of 5 blu disposable electronic cigarettes in comparison to a combustible cigarette
Protocol Version and Date:	Original Version: 13-Jul-2021
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STATISTICAL ANALYSIS PLAN Original Version Approvals

Nicotine uptake and abuse liability assessments of 5 blu disposable electronic cigarettes in comparison to a combustible cigarette

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Name: [redacted] (on behalf of Fontem US LLC) Signature: [redacted]	Date: 17 Aug 2021

REVISION HISTORY

VERSION	DATE	DESCRIPTION OF REVISIONS	REVISED BY
0	02-AUG-2021	Original Version	Not applicable

1. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the baseline-adjusted nicotine concentration-versus-time curve
BMI	Body mass index
Cavg	Average plasma concentration
Cmax	Maximum plasma concentration
CRF	Case report form
CV	Coefficient of variance
CSR	Clinical study report
ECG	Electrocardiogram
eCO	Expired carbon monoxide
Emax	Maximum response
ENDS	Electronic nicotine delivery systems
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliters
PES	Product Evaluation Scale
ppm	Parts per million
PK	Pharmacokinetic(s)
PMTA	Premarket Tobacco Product Applications
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class
TFL	Tables, figures, and listings
Tmax	Time of maximum plasma concentration
TEmax	Time to maximum response
US	United States
VAS	Visual analog scale

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2. INTRODUCTION TO THE STATISTICAL ANALYSIS PLAN

This statistical analysis plan (SAP) is based on Study Fontem-PK-01 'Nicotine uptake and abuse liability assessments of 5 blu disposable electronic cigarettes in comparison to a combustible cigarette,' original version, dated 13 July 2021. It details the methodology to be used in analyzing the data and outlines the specifications in the Tables, Figures, and Listings (TFLs) for data to be included for executing the final statistical analyses for this study.

The analyses specified in this document supersede the high-level analysis plan described in the protocol. Study measurements and assessments, planned statistical methods, and critical derived variables are summarized in this plan. Planned tables, figures and listings are specified.

The final pharmacokinetic (PK) and statistical analysis will proceed according to the SAP approved by Fontem US LLC as well as Xyzagen Inc. and CPAN Inc. Any deviations in final analyses from this SAP will be documented in the clinical study report (CSR).

3. INTRODUCTION TO THE STUDY

3.1. BACKGROUND AND RATIONALE OF STUDY

Fontem US LLC is undertaking clinical studies to evaluate electronic nicotine delivery systems (ENDS) to provide an alternative to combustible cigarettes for smokers. Upon user inhalation, an e-liquid solution containing nicotine, glycerol, propylene glycol, and flavor agents is heated and delivered into the lungs via an aerosol.

The objective of ENDS products is to provide sufficiently satisfying alternatives to cigarette smoking. According to the National Academies of Sciences, Engineering, and Medicine, "There is conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes."

This study is being conducted to assess the abuse liability and puffing topography of blu disposable e-cigarettes in adult combustible cigarette smokers. Nicotine uptake, subjective effects, and puff topography will be evaluated and compared with subjects' usual brand combustible cigarette. It is anticipated that the results from this study will provide evidence that the blu disposable e-cigarettes relative to subjects' usual brand combustible cigarettes are appropriate for the protection of the public health, and will therefore support a Premarket Tobacco Product Application (PMTA) submission to the Center for Tobacco Products at the Food and Drug Administration (FDA). The FDA's PMTA guidance for ENDS (FDA 2019) suggests that applicants include, in addition to other information, results from studies addressing topography and use patterns and an assessment of abuse liability.

3.2. STUDY OBJECTIVES

3.2.1. Primary Objectives

- To determine the PK of nicotine absorption into the blood of subjects when they use the blu disposable e-cigarette with varying flavors in each study arm compared to when they smoke a combustible cigarette.
- To characterize subjective effects after use of the study products and a combustible cigarette.

3.2.2. Secondary Objectives

- To compare puff topography when subjects smoke a combustible cigarette versus use of the blu disposable e-cigarette.
- To evaluate overall safety in subjects using the blu disposable e-cigarette.

3.3. STUDY ENDPOINTS

3.3.1. Primary Endpoints

- Baseline-adjusted plasma nicotine $Cmax_{0\text{-}120}$, $Cavg_{0\text{-}120}$, $Tmax_{0\text{-}120,}$ $AUC_{0\text{-}120,}$ $Cmax_{120\text{-}180}$, $Tmax_{120\text{-}180,}$ $AUC_{120\text{-}180}$, $Cavg_{120\text{-}180,}$ $AUC_{0\text{-}180}$
- Subjective effects measures:
  - Product liking assessment
  - Intent to Use Product Again assessment
  - Urge to Smoke Questionnaire
  - Product Evaluation Scale (PES)
- Mass change of blu disposable e-cigarette during puffing

3.3.2. Secondary Endpoints

- Puff topography (e.g., count, duration, volume, flow rate, and inter-puff interval)

3.3.3. Safety Endpoints

- Heart rate and blood pressure during product use sessions
- Adverse events (AE)/Serious adverse events (SAE)

3.4. STUDY DESIGN

This will be a part-randomized, open-label abuse liability assessment and puffing topography study of nicotine-containing products carried out in 20 healthy adult volunteers who smoke combustible cigarettes. The schedule of events is presented in Section 10.

After screening, subjects will attend the study site 6 times (Visits 2-7). Prior to each visit, subjects will be required to refrain from using any nicotine-containing products for a period of at least 12 hours before study product use.

During their second visit (Visit 2), the subjects will smoke their usual brand cigarette during 2 use sessions. In the first session, subjects will smoke a single combustible cigarette of their usual brand by taking 10 puffs, 30 seconds apart. Blood samples (5 mL) will be obtained for plasma nicotine analysis at -5, 3, 5, 7, 10, 15, 20, 30, 45, 60, 90, and 120 minutes relative to the first puff on the cigarette. Blood pressure and heart rate will be recorded at -10 (baseline), 8, 60, and 120 minutes. Subjects will be asked to complete several subjective effects questionnaires at various points either before, during, or after product use.

In the second session, which will begin immediately after the 120 minute blood draw and after all questionnaires have been completed, subjects will be allowed to take *ad libitum* puffs on their usual brand cigarette for a period of 60 minutes (1 hour) while puffing topography measurements are made with a CReSS Pocket device. Subjects may use as many cigarettes as they like. Blood samples for nicotine PK analysis will be drawn at 135, 150, 165, and 180 minutes relative to the first puff on the cigarette at the visit (i.e., at 15, 30, 45, and 60 minutes of the *ad lib* session). Blood pressure and heart rate will be recorded at 180 minutes. Subjective effects questionnaires will also be completed at specified time points.

At the end of Visit 2, subjects will be randomized into a product use sequence for testing the investigational products (blu disposable e-cigarettes).

Subjects will then visit the study site on 5 subsequent occasions (Visits 3-7); at each visit, the subjects will use their assigned blu disposable e-cigarette during 2 use sessions (standardized and *ad lib*, same as at Visit 2). Study procedures during the 2 use sessions will be the same as at Visit 2.

All blu disposable e-cigarettes (Table 1) will be provided by the sponsor. At Visit 2, subjects will smoke their own brand of combustible cigarette.

Table 1 Study Products

Product	Flavor	Nicotine Strength	Figure and Table Code
A	[redacted]	2.4%	A
B	[redacted]	2.4%	B
C	[redacted]	2.4%	C
D	[redacted]	2.4%	D
E	[redacted]	2.4%	E
F	Subject's Usual Brand Combustible Cigarette		F

4. RANDOMIZATION AND BLINDING

4.1. RANDOMIZATION

Eligible subjects at Visit 2 will be assigned a randomization number beginning with 2001. The randomization will determine the order in which the subjects will test the study products at Visits 3 to 7. The randomization code for the study products will be produced using a computer-generated Latin-square procedure.

4.2. BLINDING

It is not possible to blind the study products.

5. DEFINITION OF ANALYSIS POPULATIONS

5.1. Safety Population

The Safety Population will include all subjects who have successfully completed eligibility requirements and using at least one study product.

The Safety Population will be used to summarize subject disposition, demographics and baseline characteristics, and safety data.

5.2. Outcomes Population

The Outcomes Population is a subset of the Safety Population and will consist of subjects who use a study product and have evaluable PK, subjective effects, or topography data.

The Outcomes Population will be used in the summary and analysis of PK, subjective effects, topography, and product use.

5.3. Pharmacokinetic Subpopulation

The PK Subpopulation is a subset of the Outcomes Population and will consist of subjects who appear to have met the pre-exposure smoking abstinence period (Section 8.9.2).

The PK Subpopulation will be used in the summary of PK parameters.

6. SAMPLE SIZE CALCULATION

Since this study is the first to examine the nicotine PK in subjects using these blu disposable e-cigarettes, no formal power calculations were performed. The sample size is typical of other studies reported in literature examining the PK and subjective effects of different tobacco/nicotine products. A sample size of 20 subjects has been determined adequate to meet the study objectives.

7. GENERAL STATISTICAL CONSIDERATIONS AND DEFINITIONS

7.1. BASELINE AND VISIT WINDOWS

Unless otherwise specified in this section, baseline, which is defined as the last non-missing assessment prior to the first product use within a visit, will be used in baseline and change from baseline analyses. Baseline adjustment will be performed by subtraction of the baseline nicotine concentration from each nicotine concentration obtained after test product use on that day for each subject.

The summary tables by visit will use the values from the scheduled visit.

7.2. SUMMARY STATISTICS

Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation (SD), minimum and maximum values of the raw data, coefficient of variance (CV; PK concentration and PK parameters), geometric mean, and geometric CV (%) (PK parameters only). Means and medians will be reported to one more significant digit than the raw data values being analyzed. Standard deviations will be reported to two more significant digits, and the minimum and maximum will be reported to the same number of significant digits as the raw data values being analyzed.

Categorical variables will be summarized as the number and percentage of subjects per category. All percentages will be rounded to one decimal point. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects had a response in a particular category. Denominators for each analysis will be based on the population of interest (e.g., Safety Population; subjects with non-missing data) unless otherwise noted.

In general, all data will be listed by subject and time point.

SAS software (version 9.3 or higher, Cary, NC) will be used for data presentation and summarization including summary tables, graphs, and data listings not associated with the nicotine concentration or PK parameters.

7.3. DATA HANDLING RULES

7.3.1. Missing Data

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 summarized based on reduced denominators.

7.3.2. Interim Analysis

No interim analysis is planned for this study.

8. STATISTICAL ANALYSES

8.1. SUBJECT DISPOSITION AND WITHDRAWALS

A disposition table will summarize the number of subjects screened, screen failed, randomized, Safety Population, Outcomes Population, PK Subpopulation, completed the study, discontinued early, and reasons for discontinuation. Percentages will be based on the Safety Population.

The reason for discontinuation will be summarized using the categories specified in the case report form (CRF) page.

Subjects excluded from the Outcomes Population and PK Subpopulation will be listed.

8.2. PROTOCOL DEVIATIONS

All deviations related to safety, informed consent, eligibility, and protocol compliance will be listed by subject.

8.3. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics (age, sex, race, ethnicity, body weight, height, body mass index [BMI]) and baseline characteristics (heart rate, systolic and diastolic blood pressure, and eCO results) will be summarized descriptively.

8.4. MEDICAL HISTORY

Abnormalities identified from any physical examinations at the Screening visit, if required by the study physician, will be recorded in the CRF as Medical History. Any medical conditions with a start time prior to first use of study product will be recorded as part of the subject's medical history.

Medical history data will be coded with MedDRA Version 22.0 or later and will be listed by System Organ Class (SOC) and Preferred Term (PT).

8.5. TOBACCO/NICOTINE PRODUCT USE HISTORY AND FTND

Results from the Nicotine Use History Questionnaire will be summarized descriptively for each question.

Fagerström Test for Nicotine Dependence (FTND) responses will be summarized descriptively for each question. In addition, the total score will be calculated and included in the summary. Total FTND score will be the total of the scores to each question as follows:

Fagerstrom Test for Nicotine Dependence

PLEASE TICK (✓) ONE BOX FOR EACH QUESTION			
How soon after waking do you smoke your first cigarette?	Within 5 minutes	☐	3
	6-30 minutes	☐	2
	31-60 minutes	☐	1
	After 60 minutes	☐	0
Do you find it difficult to refrain from smoking in places where it is forbidden? e.g. Church, Library, etc.	Yes	☐	1
	No	☐	0
Which cigarette would you hate to give up?	The first in the morning	☐	1
	Any other	☐	0
How many cigarettes a day do you smoke?	10 or less	☐	0
	11 - 20	☐	1
	21 - 30	☐	2
	31 or more	☐	3
Do you smoke more frequently in the morning?	Yes	☐	1
	No	☐	0
Do you smoke even if you are sick in bed most of the day?	Yes	☐	1
	No	☐	0
	Total Score		

SCORE		
	1- 2 = low dependence	5 - 7= moderate dependence
	3-4 = low to mod dependence	8 + = high dependence

8.6. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be listed, and prior medications will be flagged.

8.7. SUBJECTIVE MEASURES

Response to product liking, urge to smoke, and intent to use product again questionnaires are recorded as VAS scores or Likert scales and will be treated as continuous variables.

The PES is 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 Questions 11, 13, 14, 15, and reversed for Questions 20 (i.e., not at all = 7, extremely = 1);

e) Questions 17, 19, & 21 will be summarized as individual item scores.

For the Urge to Smoke questionnaire, the maximum response (Emax), defined as the maximum absolute value of change from baseline and time to maximum response (TEmax) will be determined. In the case of multiple values considered as Emax, the earliest time point associated will be used in calculating TEmax.

8.8. PUFF TOPOGRAPHY

Puff duration, volume, peak flow, and average flow rate will be summarized by study product.

8.9. PHARMACOKINETIC ANALYSIS OF NICOTINE PLASMA CONCENTRATION

PK parameters of plasma nicotine levels will be calculated using noncompartmental methods with the Phoenix WinNonlin version 8.3 software platform (Certara, Princeton, NJ). Plasma concentrations and the computed plasma PK parameters will be listed for each study product and subject.

The following PK parameters will be calculated; all parameters will be baseline-adjusted using the value at time -5 minutes:

- $Cmax_{0-120}$ = Maximum plasma concentration during defined use session
- $Tmax_{0-120}$ = Time of maximum plasma concentration during defined use session
- AUC_{0-120} = Area under the plasma concentration-time curve from time 0 to 120 minutes during defined use session
- $Cavg_{0-120}$ = Average concentration from 0 to 120 minutes defined as AUC_{0-120}/120 minutes
- $Cmax_{120-180}$ = Maximum plasma concentration during the *ad libitum* puffing session
- $Tmax_{120-180}$ = Time of maximum plasma concentration during the *ad libitum* puffing session
- $AUC_{120-180}$ = Area under the plasma concentration-time curve from time 120 minutes to 180 minutes during the *ad libitum* puffing session
- $Cavg_{120-180}$ = Average concentration from 120 to 180 minutes defined as $AUC_{120-180}$/60 minutes
- AUC_{0-180} = Area under the plasma concentration-time curve from time 0 minutes to 180 minutes during both puffing sessions
- RCmax = Ratio of $Cmax_{120-180}/Cmax_{0-120}$
- RCavg = Ratio of $Cavg_{120-180}/Cavg_{0-120}$

A one-way or repeated measures analysis of variance will be conducted on the Outcomes Population $Cmax_{0-120}$ and AUC_{0-120} to assess for statistical differences between the Usual Brand combustible cigarette and the blu disposable e-cigarettes. Significance based on a Dunnett's multiple comparison assessment will be reported.

8.9.1. Concentration Values Below the Limit of Quantitation

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.

8.9.2. Elevated Baseline

Upon review of the bioanalytical data, subjects with baseline nicotine levels that are higher than their 120-minute values will be considered as not meeting the pre-exposure smoking abstinence criteria and will be considered for exclusion from the PK Subpopulation. Subjects who do not meet the abstinence criteria in ≥50% of their visits will be excluded from the PK Subpopulation.

8.9.3. Baseline-Adjusted Nicotine Concentration

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 baseline nicotine concentration from each nicotine concentration obtained after test product use on that day for each subject.

8.10. SAFETY ANALYSES

8.10.1. Mass Change (Product Use)

The blu disposable e-cigarette weight difference of before and after use in both use sessions will be summarized descriptively.

The amount of liquid consumed in the controlled product use session will not be combined with the amount consumed in the *ad libitum* session.

8.10.2. 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.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 22 or higher.

AEs will be reported under the product last used when the onset of AE occurred or when the severity of an existing AE changes.

The following AE summaries will be presented.

- Overall Summary of AEs: the number of events, number and percent of subjects who experienced AEs, SAEs, severe AEs, related AEs, and AEs leading to study discontinuation; summarized by study product and overall.
- Incidence of AEs by MedDRA SOC and PT: AEs will be summarized by SOC and PT. If a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject under the SOC in which it was categorized.
- Incidence of AEs by PT and maximum severity will be presented for each level of severity by PT and product use. When a subject experiences the same AE (PT) at more than one level of severity, only the most severe one will be counted.

Additionally, listing of AEs will be presented including all data collected in the CRF, along with the derived variable, duration of AE, and the coded variables, SOC and PT.

8.10.3. Laboratory Tests

Clinical biochemistry, hematology, and urinalysis laboratory results from screening visit will be listed.

8.10.4. Vital Signs

Vital signs (systolic and diastolic blood pressure and pulse rate) will be summarized descriptively by time point. Change from baseline values will be calculated and summarized similarly.

8.11. OTHER DATA

Other data including urine drug screen, urine cotinine, pregnancy test, expired carbon monoxide breath test, and randomization data will be listed.

9. CHANGES TO THE PLANNED ANALYSES

None.

10.SAP APPENDICES

APPENDIX 1 STUDY EVENTS FLOW CHART

	Screening Visit 1	Product use phase (Visits 2 to 7)	Follow-up phone call/visit
Informed consent	X		
Socio-demographic data	X		
Biochemistry, hematology, and urinalysis	X		
Urine drugs of abuse screen	X		
Urine cotinine level (must be >200 ng/mL)	X		
Alcohol breath test	X		
Inclusion/exclusion criteria	X	X	
Urine pregnancy test[1]	X	X	
Electrocardiogram[2]	X		
Prior/concomitant medications	X	X	X
COVID-19 screening[3]	X	X	
SARS-CoV-2 (coronavirus) rapid (10 minute) antigen test	X		
Nicotine use history[4]	X		
Exhaled carbon monoxide level (must be >10 ppm)	X		
Medical history	X		
Vital signs, height, and weight[5]	X		
Study product trial use session	X		
Randomization		X (Visit 2 only)	
Test product use		X[6]	
At-home familiarization period[7]		X	
Compliance check[8]		X	
Blood draws for nicotine pharmacokinetics		X[9]	
Heart rate and blood pressure measurements		X[10]	
Product liking, urge to smoke, intent to use product again questionnaires, and Product Evaluation Scale (PES)		X	
Puff topography assessments		X	
Mass change measurements		X	
Adverse events		X	X
Post-study assessments			
Telephone call to subjects[11]			X
Safety assessments (vital signs, biochemistry, hematology, and urinalysis) and physical exam[12]			X

[1]Female subjects of child-bearing potential, at Visit 1 and before any product use.
[2]Single 12-lead ECG will be taken following resting in the supine position for at least 5 minutes.
[3]Subjects will be queried for symptoms of COVID-19 at each encounter (both in person and telephone reminder calls for visits). In addition, at each study site visit, body temperature will be assessed before allowing the subject to enter the clinic. If the subject has a COVID-19 vaccination card, a copy of it will be obtained for the subject's study record; however, being vaccinated is not a requirement to enter the study.
[4]Fagerström Test for Nicotine Dependence and nicotine use history questionnaires.
[5]Blood pressure and heart rate.
[6]Subjects must abstain from any nicotine-containing products for at least 12 hours prior to product use visits.
[7]The day prior to their study site visit to use that product; for blu disposable only.
[8]Exhaled CO <15 ppm.
[9] -5, 3, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 135, 150, 165, and 180 minutes.
[10]Before any product use; during and after product use sessions.
[11]Between 5 and 7 days after the last study site visit.
[12]Symptom driven, if indicated and requested by the study physician following post-study telephone call.

APPENDIX 2 QUESTIONNAIRES

APPENDIX 2.1 NICOTINE USE HISTORY QUESTIONNAIRE

1. Do you currently smoke cigarettes? Yes____ No____ (If no, exclude)

2. If yes:
    a. Average number of cigarettes smoked per day during the past 3 months? _____
        i. What brand do you smoke?_____ menthol or tobacco flavor?_____
        ii. Full flavor_____ Medium____ Light____ Ultralight_____
        iii. Filter____ Non filter____
        iv. Commercially rolled_____ roll your own_____ (exclude if roll your own)

3. Age started smoking? _____

4. Maximum CPD smoked on average during any one year since started smoking? _____

5. Have you used any nicotine containing products other than cigarettes or e-cigarettes in the past 14 days?
    a. No____ Yes____ (exclude if yes)

6. Number of serious quit attempts? _____

7. If >0:
    a. Longest time quit smoking? Years____ Months_____ Days_____
    b. Methods used to quit smoking:
        i. Counseling Yes____ No____
        ii. Nicotine gum Yes____ No____
        iii. Nicotine lozenge Yes____ No____
        iv. Nicotine patch Yes____ No____
        v. Nicotine inhaler Yes____ No____
        vi. Nicotine nasal spray Yes____ No____
        vii. Chantix Yes____ No____
        viii. Zyban Yes____ No____
        ix. Electronic Cigarette Yes____ No____
    c. Did you use an electronic cigarette in your most recent attempt to quit smoking? Yes____ No____

8. Length of time you have used the following types of electronic cigarettes?
    a. Cigalike: Years_____ Months_____ Days_____ Never used_____
    b. Cartridge/Pod type: Years_____ Months_____ Days_____ Never used_____
    c. Vape pen: Years_____ Months_____ Days_____ Never used_____
    d. Large tank: Years_____ Months_____ Days_____ Never used_____

e. Mod unit: Years_____ Months_____ Days_____ Never used_____

9. Are you currently using (within the past 7 days) any of the following types of electronic cigarettes:
   a. Cigalike: Yes____ No____
   b. Cartridge/Pod type:: Yes____ No____
   c. Vape pen: Yes____ No____
   d. Large tank: Yes____ No____
   e. Mod unit: Yes____ No____

10. Use of other tobacco products. Have you ever used:
   a. Chewing tobacco Yes_____ No_____
   b. Pipe Yes_____ No_____
   c. Hookah Yes_____ No_____
   d. Small Cigar Yes_____ No_____
   e. Large Cigar Yes_____ No_____
   f. Snus Yes_____ No_____

APPENDIX 2.2 FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE

1. How soon after you wake up do you smoke your first cigarette? (Check one)	Within 5 minutes ☐ 6-30 minutes ☐ 31-60 minutes ☐ After 60 minutes ☐
2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in cinema, etc.? (Check one)	Yes ☐ No ☐
3. Which cigarette would you hate most to give up? (Check one)	The first one in the morning ☐ Any other ☐
4. How many cigarettes/day do you smoke?	10 or less ☐ 11-20 ☐ 21-30 ☐ 31 or more ☐
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes ☐ No ☐
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes ☐ No ☐

APPENDIX 2.3 PRODUCT LIKING QUESTIONNAIRE

Please indicate on the line below how much you liked the combustible cigarette/e-cigarette you have just used.

Not at all ——————————————— A great deal

Appendix 2.4 Urge To Smoke Questionnaire

How strong is your current urge to smoke your usual brand cigarette?

———————————————

No Urge Very Strong Urge

APPENDIX 2.5 Intent To Use Product Again Questionnaire

How likely are you to use the cigarette/e-cigarette you have just used in the future?

———————————————

Definitely would not Definitely would

APPENDIX 2.6 Product Evaluation Scale Questionnaire

	1 Not at all	2 Very Little	3 A little	4 Moderately	5 A lot	6 Quite a lot	7 Extremely
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?							